DENTAL CONSIDERATIONS IN MINIMIZING OSTEO RADIONECROSIS IN HEAD AND NECK CANCER PATIENTS: DELPHI-DERIVED FACTORS FOR A DECISION ANALYSIS

by

CARL KIMBERLY CRAMER
B.Sc. (Hons.) 1974, D.M.D. 1979
University of British Columbia, Vancouver, B.C., Canada

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Department of \underline{Health Care and Epidemiology}, Faculty of Medicine, Grad. Studies.

The University of British Columbia
Vancouver, Canada

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ABSTRACT

Osteoradionecrosis (ORN), a potential complication in head and neck cancer patients irradiated at high doses, can have severe consequences on patient quality of life and costs of treatment. Teeth can never be extracted from irradiated bone without the risk of osteoradionecrosis, but diseased teeth carry a greater ORN risk. The management of teeth so as to minimize the occurrence of ORN, while preserving maximal quality of life for all patients at risk, is a day-to-day problem for dental staff in many oncology treatment centers. Guidelines for the extraction of teeth prior to radiotherapy published by the National Institute of Health and elsewhere in the literature are not exact, so additional information, ideally a validated clinical decision analysis on the dental minimization of ORN, or an algorithm or clinical policy deriving from it, would be highly useful. This thesis is a step towards these clinical goals, producing data of immediate clinical interest in addition to data specially suited to ORN epidemiology and decision analysis.

[i.e., they do not fully explain the decision process or the weighting of the factors related to the decisions] (Barker and Barker 1990).

References cited in the Abstract are


The thesis is also justified on methodological grounds. Formal, traditional clinical decision tree analysis of complicated dental treatment dilemmas are very rarely found in the literature, and the incorporation of survey research is uncommon. Thus, this research is exploratory with respect both to the survey process used and its proposed outcomes.

Official and semi-official documents indicating appropriate oral management of patients at risk for osteoradionecrosis (NIH 1990; ADA 1989; Barker, Barker, and Gier 1992) do not appear to have utilized formal consensus methodologies to reach their conclusions, and none appeared to provide an opportunity for anonymous dissent from the positions initially presented. This study does not, however, seek to duplicate the implied objective of NIH (1990) (to produce in a living document, general guidelines for clinicians). It primarily seeks, using formal consensus methodology, to examine systematically the assumptions made during preradiotherapy dental intervention decisions, point out weaknesses, indicate considerations relevant to a theoretical decision analytic framework, suggest a theoretical clinical decision analysis, and indicate research necessary to quantify further the decision process. By achieving consensus, the way to create validated decision analyses useful for clinician and patient education and decision support is made clear. Measures proposed in this research are also a step toward validated patient-derived utilities that would facilitate the implementation of decision analysis, cost-benefit, and quality control frameworks.

The focus of the eventual theoretical decision analysis, and primary research question for which data are to be identified using a modified Delphi technique, is: "Under what conditions should teeth be extracted within the high dose radiation volume in order to minimize the frequency and severity of ORN?" The Delphi consensus approach was chosen for the Survey because it permitted analysis of responses from a...
select group of experts, provided anonymity required to minimize intimidation, and it did not require simultaneous geographical proximity of the experts and involvement of a trained panel-discussion facilitator. Open- and close-ended items, scenarios, and rating scales for agreement with Delphi statements and confidence in responses were presented to volunteer experts. 12 of 22 experts solicited from the U.S. and Canada (55%) participated in the Delphi survey, and 4 of 16 in Europe and Australia. (In other words, 28 of 38 experts (74%) solicited for participation in the Delphi Survey agreed to participate. 16 of the 38 (42%) actually returned the 60-page long survey.)

The inclusion of the close-ended items in the survey was made practical by the body of literature on the clinical problem. This permitted combination of Delphi rounds one and two and useful comparison of responses; the comparisons generally implied high content validity for the close-ended items.

Expert opinion consensus revealed that major risk factors for ORN were Radiation (particularly dose, dose per fraction, the timing of radiation, the osseous volume irradiated to high dose, and the presence or absence of interstitial therapy); Periodontal Status (as assessed using conventional static indicators, e.g. pocket depth); and Endodontic status. Anatomical site { a) mandible; b) posterior part of mandible; perhaps c) proximity of roots to surgical cuts} also were considered by respondents to be highly relevant to ORN risk. The oral hygiene status of the dentition, projected caries rate, patient compliance, and salivary status were considered relevant to ORN risk but are presumed to be mathematically dependent and to need to contribute to the decision analysis as a multifactorial integral indicating their combined ORN risk.
Surgical trauma, particular metabolic states, anticipated mandibular perfusion capability, and mucosal friability were considered by respondents to be relevant to ORN risk or the decision to extract, but either they, or their effects, were regarded as difficult to quantify. {Factors proposed for inclusion in the decision analysis were assessed and characterized as to their suitability (i.e., quantifiability, controllability, and degree of independence). This approach was indicated by the natures of the dental variables potentially relevant to the clinical problem.}

Only a minority of respondents indicated that hyperbaric oxygen or chemotherapy affected ORN prognosis. These findings may be significant, or artifacts of the survey's design. Close-ended items were not present to prove the reliability of these responses.

A decision analysis on ORN-prophylactic tooth extraction should include factors related to the desirability of retaining particular teeth irradiated at high dose. Factors proposed as relevant to this proposed multifactorial utility sub-variable included caries rate, tooth mechanical soundness/restorability, and tooth functionality.

The median minimum expert-recommended extraction healing time prior to radiotherapy was 7 days; the median desired time, 14 days (mean, 11.6).

Factors integrated in the scales proposed in this study for ORN-associated pain and function were supported as related to quality of life. Pain was regarded the most important factor affecting quality of life, function and pathological fracture were regarded as secondary. (Other factors were suggested and merit further investigation.) Function levels in various ORN categories clearly appear to be associated negatively with pain, suggesting that quality of life utilities could, if only validated pain data were available at some particular time in the future, be related (as an approximation) to pain alone, at first.
The clinimetric scale outcome measures suggested in this thesis could be incorporated in frameworks for quality improvement or cost-benefit analysis, although conclusions drawn would be limited by their ordinality and lack of validation.

Although all data reported are subject to reliability and validity constraints outlined in the thesis, qualitative data supplied on important topics were quite consistent from item to item, and relatively few (and non-critical) items were associated with low consensus or other proposed indicator of poor data quality. Most quantitative estimates of ORN risk were judged to lack adequate quality and validity, but pain and function assessed in two ways for categorized ORN demonstrated consistency, and seemingly remarkable consistency was present in the extreme ORN categories—ORN3b (progressive ORN with jaw fracture,) and ORN0 (patient at risk, no ORN). Cross-impact analysis and other statistical manipulations designed to correct for potential confounders generally were inadvisable due to the small numbers of responses present.

A theoretical, introductory decision analysis on the dental minimization of osteoradionecrosis is presented at the conclusion of the thesis. Further research is required before it can be validated and used clinically. Actions advocated to enable this, and to enhance the data base for all future studies on the dental management of ORN, are:
1. Adoption of an identical definition for osteoradionecrosis of the jaws, in future studies

2. Application to the Canadian Institute of Health Information to recommend the adoption by the "International Classification of Diseases" of a specific diagnostic code for osteoradionecrosis of the jaws.

3. Initiation of ongoing collection of epidemiological data for ORN of the jaws from non-experimental data bases employing such definitions.

4. Initiation of further prospective data gathering in patients at risk for ORN, with detailed recording of the treatments employed and the ORN prognostic factors outlined above, and ORN outcomes.

5. Adoption of a common standard for categorization of ORN outcomes.

6. Integration of existing data on the distribution of categorized ORN severity.

7. Assessing expert consensus on the relationships of chemotherapy and hyperbaric oxygenation to ORN rates and healing, anonymously.


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CHAPTER I. INTRODUCTION

1. THE CLINICAL PROBLEM

"The incidence, predisposing factors, and clinical course of osteoradionecrosis are subject to considerable variability and are dependent on many complex inter-relating factors" (Beumer, Harrison, Sanders and Kurrasch 1984).

Patients treated for oral cancer face a range of consequences. Surgical therapy may directly compromise oral function, while high dosage irradiation may cause complications such as xerostomia (decreased salivation), taste loss, mucositis, dermatitis, trismus (muscle spasm), infections, dental caries, growth and developmental abnormalities, soft tissue necrosis, and osteoradionecrosis (NIH 1990).

Osteoradionecrosis ("ORN") is necrosis of bone that may follow therapeutic irradiation for head or neck cancer in the absence of recurrent or metastatic disease. Diagnosis is primarily based on clinical signs -- ulceration or necrosis of the mucous membrane, with sustained exposure to the oral environment of the underlying necrotic bone. Osteoradionecrosis can severely affect patient quality of life (NIH 1990). It may result in severe, constant pain (NIH 1990), pathologic fracture of the mandible in 23% of cases, progressive necrosis in 19%, with resolution only in 15% of cases (Epstein et al 1987b). As ORN can be refractory to treatment (Stevenson-Moore and Epstein 1993), prevention is highly desirable.
Dental pre-radiotherapy interventions have been shown to favorably influence rates of complications, including osteoradionecrosis (NIH 1990). Teeth can never be extracted from irradiated bone without the risk of osteoradionecrosis, but diseased teeth carry a greater ORN risk. The timing of necessary tooth extractions also is important. For instance,

Prophylactic extraction of teeth before radiation therapy has been suggested to prevent the development of dental complications that may require extraction and stimulate the development of osteoradionecrosis. Twice the risk of osteonecrosis is seen in those in whom teeth were extracted after irradiation (2.2 vs. 1.1%). A comparison of the number of cases of necrosis in relation to the number of patients who had teeth removed shows a higher percentage (7.1 vs. 5.4%) of necrosis in patients with teeth extracted after radiotherapy. These findings demonstrate a reduced risk of developing necrosis when selected teeth are extracted before radiotherapy...” (Epstein et al 1987a, 52).

Societal expectations for retention of teeth (Hand et al 1988) and dental contributions to quality of life noted in the Literature Review section of this thesis underscore the importance and desirability of retention and maintenance of functional teeth in irradiated sites. Thus, there is a day-to-day clinical problem and dilemma whether functional teeth that contribute to quality of life should be sacrificed in order to minimize the small risk of ORN and its much greater diminution in quality of life in the few who eventually develop ORN. The question, "Under what conditions should teeth be

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1 (Epstein, et al 1987b; Murray et al 1980a; Murray et al 1980c; Gehrig 1969)
extracted within the high dose radiation volume in order to minimize the frequency and severity of osteoradionecrosis and its impacts on quality of life?" is a primary focus of the formal theoretical decision analysis for which this study will gather data.

Theoretical decision analysis critically examines the present basis for clinical decision making and furthers the eventual production of a validated clinical decision analysis. The latter will provide a quantitative basis for making the necessary clinical decisions with minimal bias. Decision analyses of the clinical problem do not now exist.3

Discussion of osteoradionecrosis risks and associations with various therapeutic and patient factors, the epidemiology of head and neck cancer, and other aspects of the clinical problem will be found in the Literature Review.

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2 specifically related to native bone. Persons interested in osteoradionecrosis in neovascularized bone or the use of osseo-integrated implants in mandibular reconstruction could consider Mirante et al (1993) as an introduction to these topics.

3 However, head-and-neck cancer treatment-planning "decision analyses" are now available. Weiss, Harrison and Isaacs (1994, "Use of Decision Analysis in Planning a Management Strategy for the Stage N0 Neck") is a conventional decision analysis, apparently of high quality, suggesting for the average patient that when the probability of occult metastasis is greater than 20%, treatment rather than observation becomes preferable, and that of the treatment options considered, elective irradiation appeared to be slightly preferable (as assessed by "folding back" branches) to optional elective neck dissection. In contrast, Coulthard (1993), using a less conventional format, describes in qualitative terms some diagnostic and therapeutic maneuvers appropriate to Stages 1, 2, 3 and 4 carcinomas of the oral cavity. Schein (1989, 48-61) discusses considerations related to decision-making for the management of cancers of the lip, oral pharynx, salivary glands, and paranasal sinus.

4 (e.g., compliance with recommended home care procedures)
2. DECISION ANALYSIS

A. OVERVIEW

Diagnosis and treatment planning are important aspects of the practice of any physician, dentist, or surgeon. The validity with which practitioners are able to identify health problems and treatment options, and the consequences in each case, will help to determine the potential quality of the health care services provided. Support for these diagnostic or treatment planning decision making processes will be provided by the application of formal clinical decision analysis and the data associated with individual clinical decision analyses. Decision analyses, and the clinical algorithms or practice policies incorporating them, could speed the physician decision-making process and assist in quality or cost-benefit ratio assessments of the services provided. They also could assist patient education and informed decision making by patients (Merz 1993).

Figure 1, a reproduction of Figure 1-1, p. 5, of (Weinstein and Fineberg 1980), illustrates "The Decision Analytic Approach".

The scientific basis of decision analysis derives from operations research and game theory (Last 1988). Its formal application in medical science (specifically, medical diagnosis) can be traced to (Ledley and Lusted 1959). All available choices and their potential outcomes in a clinical dilemma are identified (Hagen 1992). Best available sources of data are located for the probabilities and the measure of the desirability ("utility") that will be assigned to each potential outcome.

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5 Simpson et al, quoted by McCreery and Truelove (1991, Part 1), defined clinical decision analysis as a "structured approach to guide a person to workable solutions of a problem, to make plans, and to evaluate data."

6 for instance, the preference of the "average" patient for the outcome
FIGURE 1
"THE DECISION ANALYTIC APPROACH"
after (Weinstein & Fineberg 1980, Figure 1-1, 5)

| I. Identify and Bound the Decision Problem | • Alternative Actions
|   |   • Additional Information Possible
|   |   • Treatment Options
|   |   • Possible Clinical Information Obtained
|   |   • Possible Clinical States of the Patient at Different Points in Time
|   |   • Other Considerations

| II. Structure the Decision Problem | • Decision Tree Representing Logical and Temporal Sequence of Clinical Problem
|   |   • Clinical Starting Point
|   |   • Choices
|   |   • Probabilistic Events
|   |   • Outcomes

| III. Characterize the Information Needed | • Uncertainties
|   |   • Valued Outcomes

| IV. Choose a Preferred Course of Action | • Synthesis of Structures and Available Information
|   |   • Quantification as a Means to this End
|   |   • Sensitivity Analysis of Conclusions
Decision trees are, at the present time, the most popular type of decision analytic framework employed in formal decision analyses (Higgins and Martin 1988). Others proposed have included flow charts, the discrimination net proposed by Feigenbaum (Feigenbaum 1959), and the Markov model (Sonnenberg and Beck 1993). The "decision matrix" technique is mentioned in (Douglass and McNeil 1983), who also provide a good review of basic decision analysis concepts\(^7\) as they apply to dentistry.

Clinical decision analyses are usually based on assessments of clinical risk and non-monetary desirability of clinical outcomes. However, decision analyses also can incorporate cost-benefit analysis, as described methodologically in Sox et al (1988).\(^8\) Schoenbaum, McNeil, and Kavet (1976) "The Swine-Influenza Decision" illustrates an application of decision-analytic cost-benefit evaluation to public health. Both quality of life assessment and economic evaluation is utilized in reference to cancer clinical trials in Morris and Goddard (1993), while Hilden and Habbema (1990) describe "The [statistical] Marriage of Clinical Trials and Clinical Decision Analysis". Fulton (1985) incorporated policy analysis (alluding to probabilities and utilities as beliefs and values.)

Despite any potential limitations in the data for an individual decision analysis (for instance, one ultimately deriving from this thesis, additional research, and the literature), the exercise in clinical reasoning required to frame and explicitly structure the analysis can itself be a valuable exercise exploring the assumptions otherwise informally made by clinicians during the decision making associated with a clinical problem. Thus it highlights the nature of the decision process and areas in need of further research, while the effects of variables that are as yet poorly quantified can be modeled using sensitivity analysis.

\(^7\) and clinical epidemiological principles as these apply to dental diagnosis

\(^8\) Analogously, these also have application in the commercial world (Ungson and Braunstin 1982).
B. DECISION TREES

Barnoon and Wolfe (1972) state that a conventional decision tree representation of the clinical decision process requires for each disease classification:

"a) a list of tests and therapeutic measures which comprise the action space
b) a list of outcomes
c) a probability association associating the outcomes in each stage with the actions leading to these outcomes
d) the utility associated with each of the terminal outcomes"

Examples are illustrated in Figure 2 ("A Generic Medical-Surgical Decision Tree") and Figure 3 ("A Simple ORN-Prophylactic Tooth Extraction Decision Tree").

Formal decision analysis is based on an understanding of the concept of expected value defined as a weighted average of all possible outcomes of a decision (Weinstein 1980b). Given weights of probabilities associated with each outcome and the expected values associated with all the outcomes, the decision maker should choose the option that on average yields the best expected value.

Probabilities and utilities are generally expressed as decimal values between 0 and 1. A health-based quality of life utility of "1.00" would be associated with ideal health; of 0.00, with death; and negative decimal fractions, with fates worse than death, e.g. torture or excruciating, unrelieved, disabling pain.
FIGURE 2
A GENERIC MEDICAL-SURGICAL DECISION TREE
modified after Figure 6-7 (Sox et al 1988, 156)
"The complete decision tree for comparing medical and surgical treatment of a hypothetical disease",

| Decision Node: Where several choices are possible |
| Probability Node: Where chance determines which outcome will occur; probabilities within a branch totaling 1.0. |

![Decision Tree Diagram]

- **Disease Present**: $p = 0.1$
  - **Surgery for Cure**
    - **Survive**: $p = 0.9$
      - **Cure**: Utility = 2
    - **Operative Death**: Utility = 3
  - **Palliate**
    - **Survive**: $p = 0.98$
      - **Cure**: Utility = 5
    - **No Cure**: Utility = 6
  - **Operative Death**: Utility = 7
- **Disease Absent**: $p = 0.99$
  - **Survive**: Utility = 8
- **Treat Medically**
  - **Cure**: Utility = 10
  - **No Cure**: Utility = 11
A SIMPLE
ORN-PROPHYLACTIC TOOTH EXTRACTION
DECISION TREE

FIGURE 3

Average probability of ORN occurrence, given "Yes," = \( a \)

Average probability of ORN occurrence, given "Yes," = \( a \)

Average quality of life, given "Yes" & ORN, = \( b \)

Utility

Utility

"Yes":

Extract

Tooth

Should Tooth Be Extracted?

"No":

Do Not Extract

Utility

Utility

Average probability of ORN occurrence, given "No," = \( c \)

Average probability of ORN occurrence, given "No," = \( c \)

Average quality of life, given "No" & ORN, = \( d \)

Utility

Utility

Average quality of life, given "Yes" & no ORN, = \( b' \)

Average quality of life, given "No" & no ORN, = \( d' \)

where

"a" and "c" are ORN probability variables, and "b" and "d" are utility (i.e., outcome) variables,

and the average relative desirability for the choice "Yes" branch of the decision tree is

\( (a \times b) + [(1-a) \times b'] \)

and for the choice "No" branch of the decision tree is

\( (c \times d) + [(1-c) \times d'] \)

KEY:
after (Sox et al 1988, 152)

Decision Node:
Where several choices are possible

Probability Node:
Where chance determines which outcome will occur
In Figure 3, the only example of a "decision node" is "Extract?" However, with multiple decision nodes, or with multi-attribute frequency or utility variables, the relative desirability of the two "branches" of the "decision tree" may reverse for certain values of the variables \(a, b, c,\) and \(d.\) (Sometimes \(a, b, c,\) and \(d\) themselves may be multi-attribute variables with their values determined in turn by the values of contributory variables.)

Sometimes a single decision can have multiple outcomes that are divorced from any future influence of the care-giver. For instance, the decision "Yes" might generate some chance of death, some chance of survival with unavoidable functional deficit, and some chance of survival with potential for complete prosthodontic rehabilitation. The choice "Yes", having multiple potential outcomes, then would be termed a "probability node."

Each probability node displays all clinically relevant potential events at that particular point in the decision tree. All probabilities at each chance node must add up to one, and thus the consequences or branches at each chance node must be mutually exclusive.

The relative desirability of the branches "Yes" and "No" could reverse if "Yes" and "No" generate different outcome probability distributions. "Sensitivity" and "threshold" analyses (to be discussed later) would permit the identification of the circumstances under which the relative desirability of the two choices for the decision whether to extract teeth in the high dose radiation volume reverses.

Traditional decision trees assume that clinical choices are associated with statistically independent, non-recursive effects that can form mutually exclusive "branches". If clinical states are found to interact to produce different outcomes or probabilities, such interacting states must be considered as assumptions for different decision trees.
C. UTILITIES

Utilities are the preferences or states of desirability associated with each particular outcome. Although various approaches to utility assessment can be considered, decision analyses often pursue patient-derived utilities as the ultimate goal compatible with patient-centered health. (Health-care-provider-chosen measures such as survival times, etc. might not reflect the total concerns of the patient.) For many types of studies, patient-derived utilities ideally can be generated in one of several standard forms: quality of life ("QOL"), health-related quality of life ("HRQOL"), Declining Exponential Approximation of Life Expectancy ("DEALE"), quality adjusted life expectancy/Quality-Adjusted Life Years ("QALY"), etc. (Sox et al 1988; Hagen 1992). Quality-adjusted life years\(^9\) are most often used (Torrance and Feeny 1989). An alternative to quality adjusted life years has been proposed, the healthy-years equivalent ("HYEs")\(^10\). Surrogate scales, e.g. measures associated in some way with quality of life, may be substituted as an interim measure when validated measures for quality of life are lacking.

Patient-derived dental outcome measures of various types are discussed in Slade (1996) and associated articles\(^11\). Patient-centered utility determinations using the scientifically-favored (Mehrez and Gafni 1989) standard reference gamble technique seem to have been reported in only two dental publications, Fyffe (1992) and an abstract on orthodontic tooth extraction decision analysis, Lee and Miller (1993). Bass et al

\(^9\) also proposed as an epidemiologic measure for dentistry in the article Haugejorden and Klock (1992)

\(^10\) The advantages and relative complexity and limitations of "HYEs" are discussed by Fryback (1993), its references, and Mehrez and Gafni (1989).

(1994) found that patient-derived standard gamble values were significantly greater than rating scale values.

Methods other than the Standard Reference Gamble for estimating patient-derived utilities exist; these include the time-tradeoff technique (Sox 1988), the willingness-to-pay technique, categorical scaling, and the use of visual analogue or other rating scales. Maas and Stalpers (1992) describe another approach to utility determination, "additive conjoint measurement", in which "the treatment with the higher utility is determined from pair comparisons among outcomes that vary in quality and quantity of life". They advocate this for utility determinations associated with the choices between radiation therapy and laryngectomy in laryngeal cancer patients12.

Patient-derived utilities reflect directly the values and feelings of the person/patient for whom either the care-giver is responsible, or who under an emerging paradigm should be an autonomous decision maker ethically responsible within limits for his/her own fate. An alternative utilizes physician-derived rating-scale values as surrogates for patient quality of life. Physician-derived and patient-derived utilities can be highly correlated. For instance, Boyd et al (1990) found that physicians, and patients involved with colostomies, tended to predict similar and associated utilities for colostomies in comparison to patients who did not themselves have a colostomy.

12 claiming that their method of comparing outcome pairs allows better testing of underlying axioms, and avoids difficulties inherent with, other, "risk-based", assessment procedures.
D. SENSITIVITY ANALYSIS

The values of a particular variable in a decision analysis may not be a constant, or it may be a "constant" that can be determined at the time of analysis only in approximate terms. In such cases

1. the value of this variable of interest should be varied over its entire clinically relevant range\textsuperscript{13}, while the other variables are held at their assumed values;

2. the impact of these variations should be assessed by "folding back" the decision tree branch involved and valuing the branch over the range of variable values

3. a determination should be made as to whether the relative desirability/undesirability of the branch involved, in comparison with other branches associated with the decision node, changes as the variable value is altered. (If this occurs, then the decision recommendations change) (Hughes and Hughes 1990; Sox et al 1988).

The identification of critical values of variables which result in different decision recommendations is termed "threshold analysis".

The purposes of sensitivity analysis are:

1. to determine the variable values over which the decision considered is valid

2. to assist in validating the decision analytic model (particularly important when "'soft data' are used, for instance in subjective estimations of probability and utility"); this also encourages acceptance and utilization by clinicians (Critchfield 1986).\textsuperscript{14}

\textsuperscript{13} The ranges are usually determined by reference to the literature and expert opinion.
\textsuperscript{14} as quoted in Hughes and Hughes (1990)
"In one-way sensitivity analysis, the value for one probability or outcome measure is varied, and the others remain constant. In two-way sensitivity analysis, pairs of variables are changed simultaneously. In three-way sensitivity analysis, two-way sensitivity analysis is repeated for several values of a third variable" (Sox et al. 1988, 303).

"N-way" sensitivity analysis is described as a technique suitable for evaluating decision trees when none of the parameters are known with any degree of certainty (Hughes and Hughes 1990). However Hughes and Hughes (1990) cite Shortliffe (1979) as arguing that such decision analysis is invalid because it depends heavily on subjects' possibly inaccurate probability and utility estimates. Techniques of sensitivity analysis for subjective probabilities described in Weinstein, Fineberg and Elstein (1980, 180-3) explore the stability of decision analysis over a range of estimates.
E. DATA FOR PROBABILITIES AND UTILITIES

The five stages of Cooper's 1982 "Integrative Research Review" described in Smith, Smith and Stullenbarger (1991) are relevant to efforts in gathering data for risk estimate probabilities in decision tree branches:

1. problem formulation
2. data collection
3. data evaluation
4. analysis and interpretation
5. public presentation.

Additional principles of systematic literature review outlined in other references have theoretical relevance but are too lengthy to outline. One also could consider techniques of meta-analysis, i.e. statistical synthesis of related articles.

Evaluation of literature must include an evaluation of its quality. Obviously, data from controlled clinical trials and prospective cohort studies are among the most desirable sources for probabilities that will be assigned to the branches in a decision tree. Types of flaws potentially associated with case series, cohort studies, case control studies, etc. include confounding, non-generalizability, co-intervention biases, diagnostic suspicion biases, and competing risks, etc. (Jaeschke and Sackett 1989).

"Non-experimental" data systems sometimes play a role in clinical epidemiological studies, which in turn can contribute to clinical decision analyses. Roos

15 (Wood-Dauphinee and McPete 1986; Schechter and Leblanc 1986; Jaeschke and Sackett 1989; Burdette and Gehan 1970) -- the latter being particularly relevant to epidemiological studies.

16 (Smith, Smith and Stullenbarger 1991; Eddy, Hasselblad, and Shacter 1990; Droitcour, Silberman, and Chelimsky 1993).
(1989) describes the use of non-experimental data (e.g. hospital data bases, cancer registries) in planning of randomized trials and in clinical decision analysis.

Retrospective analyses can be performed with the goal of estimating probabilities of different outcomes and determining interventions worthy of further research to examine their impact on outcomes and etc. Parenthetically, Roos (1989) advocates the maintenance and improvement of "well organized high quality data bases" as a priority for "funding agencies interested in technology assessment, cost control, and quality of care".

Lacking sufficient high-quality data, the decision analyst, when attempting to provide an analytic framework, to isolate significant criteria, or to quantify inputs and outputs, can face problems similar to those of individual practitioners partly dependent upon clinical impressions and anecdotal reports. This is the case for the clinical problem of the dental management of osteoradionecrosis, for which validated quantitative epidemiological data for the effects of assumed prognostic variables is scant. Validated quality-of-life measures for late oral complications of cancer are essentially nonexistent.\(^{17}\)

When limited research data are available, the decision analyst may utilize formal consensus methodologies (e.g. nominal group technique, Delphi technique) intended to improve the reliability (if not necessarily, the validity) of relevant expert clinical opinion (Fink, Kosecoff, Chassin, Brook 1984). These can then be integrated with data of higher quality to provisionally identify factors and quantify values suitable for a decision analysis. This information can be abstracted into a framework for analysis (e.g. a decision tree), and thus contribute to the decision and sensitivity analyses.

\(^{17}\) For details and references, please see Literature Review.
F. DECISION ANALYSIS AND THE PATIENT

Although both patients and clinicians can benefit from recognition of the treatment alternatives that can be generated by the application of a suitable decision analysis, a question sometimes presents itself: "Is the decision analysis truly applicable to the particular patient at hand?" Decision analyses can create clinical policies, decision rules, protocols, and algorithms that can be applied to classes of patients (Littenberg and Sox 1988); when implemented, these should improve the consistency and overall quality of patient management (Eddy 1990a). However, specialized assumptions may be necessary for particular patients with unusual conditions (e.g. a particular metabolism, family history, or psychological state).

Patient-derived utilities may be individualized to particular patients using validated measures, "chair-side" standard gamble interviews, or other means. The value that clinical decision making places on individual patient preferences fits quite well with recent societal, legal, medical, and dental trends. The current literature recognizes “…the evolution to patient-centered care in many areas of medicine: patient care, health-related law, medical education, research, and quality assessment” (Laine and Davidof 1996), the "shift from clinician-patient paternalism to self-determination…" (Smith 1990), and that the patient now may be regarded as an "informed consumer" (Niessen 1994, 1327) requiring informed consent to an extent perhaps greater than traditionally assumed by the health professions (Canterbury vs. Spence, 1972, cited in Murphy (1976) and Kauffman (1983)).
Kay, Brickley, and Knilljones (1995) conclude that "an over-concentration on the biomedical model of dental health may cause dentists to make decisions which are inappropriate to their patients' values and preferences". Others advocate a move from traditional dental practice based on clinical experience to one based upon an evidence-based approach requiring the use of scientifically unbiased data and "specific rules of evidence to quantify their recommendations" (Levine and Shanaman 1995; McGuire and Newman 1995). Decision analysis can integrate successfully with these trends and in fact has been advocated by Merz (1993) as a new paradigm for treatment planning and legal informed consent. Clancy, Cebul and Williams (1988) concluded from their randomized, controlled trial that individualized decision analysis can influence the clinical decisions taken by "knowledgeable and interested patients".

However, not all patients are willing to participate in clinical decision making. For instance, one study indicated that only 64% of the public thought that they would want to select their own treatment if they developed cancer, while 59% of cancer patients thought similarly (Degner, and Sloan, 1992). Interventions exist, however, to foster patient-involved decision making (Neufeld, Degner, and Dick 1993; Carter 1992).
G. DECISION ANALYSIS AS AN AID TO BAYESIAN REASONING

Several theories of decision making exist. They differ in that some are prescriptive (i.e., how decisions ought to be made) while others are descriptive (i.e., how decisions actually are made). Perhaps the Bayesian approach could fall into the former category. Were a physician to think in Bayesian terms, his or her estimate of the "posterior probability" of a disease being present would be based on knowledge of two factors, the prior probability of the disease, and the true- and false-positive rates of the test(s) involved. New data would be incorporated into reconsiderations of the problem in a manner that would overcome forms of bias perhaps otherwise present (e.g. representativeness, availability, regression to the mean, and anchoring, discussed in the Literature Review).

In essence, decision trees could be considered Bayesian. However, Bayesian logic may not model the way that humans behave during the clinical decision making process.

"In everyday clinical reasoning, levels of risk tend to be treated categorically rather than on a continuous probability scale... Intuitive decision making generally processes risk factors sequentially rather than simultaneously. A case is scanned first for evidence concerning one risk and if that does not yield a decision the second [risk] is evaluated. Decisions may vary depending on which risk is considered first" (Elstein, et al 1992).

Slovic, Rorer and Hoffman (1971) describe three potential categories of reasons why humans may not display Bayesian reasoning: misperception, misaggregation (inability to utilize information presented in a Bayesian format), and artifact (e.g. distortions in the processing of extreme probabilities).\(^{18}\)\(^{19}\)

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\(^{18}\) In contrast, Bergus has proposed that "the Bayesian approach is intuitive to physicians and can mirror their internal diagnostic processes" (Bergus, in press, cited in Murray and Bergus 1995).

\(^{19}\) Further perspectives are offered by (Edwards 1968) and psychological decision theory, heuristics and behavioral decision theories described in (Thomas, Wearing and Bennett 1991, 17-28.) This section cannot detail all concepts and methodology of decision analysis or clinical epidemiology. Readers interested in these may consider (Sackett, Haynes, Guyatt, and Tugwell 1991; Thomas,
Whether or not Bayes' theorem is considered a description of how humans analyze data or how they should analyze data, conventional decision trees do employ Bayesian logic and should enable routine use of Bayesian thinking.

H. DECISION ANALYSIS AND DENTISTRY

Decision analysis has been applied to dentistry in matters of diagnosis, clinical judgment, patient management and treatment, and formation of health policies. Tables 1 through 5 of McCreery and Truelove (1990, Part 2) list dental decision-analysis-related literature on diagnosis, treatment planning, disease prediction, computer applications and policy. Table 2, "Publications on Treatment Planning" lists 25 papers, of which one article in each of restorative dentistry and radiography, endodontics, oral surgery, and oral medicine feature decision trees. (Another in oral medicine involves a Markovian model.)

A good historical overview of decision making in dentistry is provided in the article, "Decision Making in Dentistry. Part I: A historical and methodological overview" (McCreery and Truelove 1991). The Journal of Dental Education did not advocate the incorporation of clinical decision analysis into dental school curricula until December of

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Wearing and Bennett 1991; Sox et al 1988; and a slightly dated, eminently readable and authoritative book written at a higher level, Weinstein and Fineberg 1980).
1992 (Bolender 1992). Although dental decision-related analyses appear to be of relatively high quality, they are relatively few compared to medicine and most fail to approach closely the standard "formal" decision tree protocol advocated in the textbook Sox (1988). For instance, Stockstil, Bowley, and Atinasio (1992) consider fixed prosthodontics decision trees only in non-probabilistic terms, even though Knoebel (1986 advocated the incorporation of probabilistic decision making analyses into clinical practice.

One dental article, (Mileman and Kievit 1992), is structured according to the "traditional" decision tree analysis principles outlined in Sox et al (1988). It applies decision tree and cost-benefit analysis to oral radiology, conducting three-way cost effectiveness sensitivity analysis for variation in the sensitivity and specificity of radiographs. (Radiographs are considered as a diagnostic test, given a varying a priori chance of a peri-apical lesion\(^{20}\).) The article varies from traditional decision analysis, however, in that it does not assign patient-derived utilities to the final outcomes.

The article Brickley, Kay and Shepherd (1995, "Decision Analysis for Lower-third-molar Surgery") is a potentially useful dental example of semi-formal decision tree analysis. It surveys the literature data to ascertain probabilities for various outcomes following extractions of lower third molars, suggests preliminary utility values, determines clinical relevance, and performs sensitivity analyses.\(^{21}\)

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20 A periapical lesion is a lesion around a tooth root tip, e.g. inflammation or infection. It frequently results from pathology of the tooth pulp and root canal soft tissue.

21 However, in this paper bleeding outcomes are not well defined.
3. ORN-PROPHYLACTIC DECISION ANALYSIS AND THIS THESIS

It was noted above that when limited research data are available, the decision analyst may utilize formal consensus methodologies to improve the reliability of relevant expert clinical opinion, subsequently integrating these opinions with other relevant data of higher quality to provisionally identify factors and quantify values suitable for a decision analysis. The goal of the present thesis research is to produce opinion data that can augment data from the literature for a theoretical decision analysis focused on the research question, "Under what conditions should teeth be extracted within the high dose radiation volume in order to minimize the frequency and severity of osteoradionecrosis and its impacts on quality of life?" Toward this goal a highly modified Delphi Survey of suitable content was constructed. The thesis—background, methodology, findings, etc.—assumes the following outline:

Chapter 2: Literature Review
2. Utilities and Outcomes
3. Clinical Problem
   (Oral Cancer Epidemiology, Treatment Strategies; Radiation Effects; ORN Pathogenesis, Definition, etc.; ORN; ORN Epidemiology and Predisposing Factors)

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22 The modifications of traditional Delphi technique employed, and rationale for same, will be discussed in subsequent sections. As described in the beginning of Results, the Delphi survey identifies radiological, dental, and medical potential ORN risk factors, then characterizes their importance, relevance, practicality, and controllability as contributory factors to an ORN-prophylactic dental clinical decision analysis. Factors relevant to extraction of teeth in the high dose radiation volume are considered. Outcome-related-factors (ORN anatomic location associations with clinical presentation, ORN severity associations, factors skewing ORN severity distributions, and ORN pain and function and potential Quality Of Life associations) are then presented.
Chapter 3: Methodology


Chapter 4: Results

1. Identification and Direct Assessment of ORN Risk Factors
   (a. General and Dental; b. Irradiation To High Dose, etc. c. Endodontics; d. Timing of Dental Extractions e. Relation of Oral-surgical, Medical, and Prosthetic Technique to ORN Risk)

2. Assessment of Characteristics of ORN "Risk Factors"
   a. Perceived Relevance to ORN-Prophylactic Treatment Planning Factor Practicality for Decision Analysis, e.g.
   b. Quantifiability, c. Clinical Controllability

3. Factors Relevant to Tooth Extraction


5. Outcomes, and Factors Related to Outcomes
   a. Severity of ORN Lesions
   b. ORN-Associated Factors That May Affect a Patient's Quality of Life
   c. Anatomical Location and ORN Clinical Presentation
   d. Factors Skewing ORN Severity Distributions
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   b. Definition Of Osteoradionecrosis
   c. Respondent Personal and Practice Characteristics
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3. Integration: Factor Suitability for Decision Analysis
4. Reliability
5. Validity Considerations and Limitations
6. Bias, Reliability, and Validity Conclusions and Applications

Chapter 7: Conclusions

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Appendixes:
1. Large Tables
2. Letters and Forms sent to Respondents.
3. Delphi Survey
4. Details: Responses of Low Data Quality
5. Class of Data Generating Undefined Quartiles
CHAPTER II. LITERATURE REVIEW

0. "EXECUTIVE SUMMARY"

I. DELPHI CONSENSUS TECHNIQUE; OPINION DATA

Delphi technique opinion data may be useful but must be accepted with reservations. Significant reliability may be found or developed, but unrecognized sources of bias may persist, and validity will be unproved.

II. UTILITIES AND POTENTIAL OUTCOME VARIABLES

Utilities suited to the proposed decision analysis do not exist at the present time. The basis for the creation of outcome scales for the survey (as described in the Methodology section) are factors related to quality of life, as described in this section; information about the clinical problem, provided in section 3. of the Literature Review; and articles describing the clinical experience of head and neck cancer.¹

III. CLINICAL PROBLEM.

1. ORAL CANCER EPIDEMIOLOGY AND PREDISPPOSING FACTORS

Squamous cell oral cancer tends to be a disease of the elderly and of multifactorial origin and risk factors, slowly declining in incidence from about 2 to 8 (locally \( \pm 3.5 \)) /100,000 persons/year, with about a 50% 5-year post-treatment survival rate.

¹ e.g., Dudgeon, DeLisa, and Miller (1980) and Dhillon, Palmer, Pittam, and Shaw (1982)
2. ORAL SQUAMOUS CELL CARCINOMA LESIONS AND TREATMENT STRATEGIES

90% of all carcinomas of the oral cavity are squamous. Common locations for oral squamous carcinoma are the oral portion of the tongue, the mandibular gingiva, and the floor of the mouth. Treatment often involves irradiation with high doses, and surgery. Irradiation sources may be external or intra-oral. Irradiation with intra-oral sources is termed brachytherapy, and one form of this, "interstitial" therapy, involves placement of the sources within the tissues. All forms of cancer therapy have side-effects, and the approach best suited to balance favorable prognosis with a patient's personal definition of quality of life may be difficult to determine.

3. PATHOLOGY OF RADIATION INJURY

The oral complications of radiotherapy may include injuries to the salivary glands, oral mucosa, oral musculature, alveolar bone, periodontium, and to a lesser extent, teeth. Side-effects may include xerostomia, rampant dental caries, mucositis, taste loss, osteoradionecrosis, infection, dermatitis and trismus (NIH 1990).

4. OSTEORADIONECROSIS PATHOGENESIS, DEFINITION, DIAGNOSIS, CLINICAL PRESENTATION, AND TREATMENT

Osteoradionecrosis follows partial vascular/ microvascular obliteration (a condition to which the mandible is particularly sensitive), relative hypoxia, and cellular death. Although radiography may assist its diagnosis, most authors consider the diagnosis of ORN to be based primarily on clinical signs and symptoms of ulceration or necrosis of the mucous membrane, with exposure of necrotic bone for more than 3 months (Epstein, et al 1987a, 48). Since ORN lesions can have severe consequences on quality of life and can be extremely refractory to treatment, the preferred health
strategy is prevention rather than cure. The use of hyperbaric oxygenation as prophylaxis is good in theory but some question its universal effectiveness.

Conservative therapy of existing ORN lesions usually has far fewer negative consequences than radical, but radical surgery sometimes is necessary.

5. ORN-PROPHYLACTIC DENTAL SCREENING STRATEGIES (STRESS: PERIODONTAL, ENDODONTIC, AND INFECTION STATUS)

Risk for osteoradionecrosis can be reduced by effective pre-irradiation-treatment oral assessment, and interventions affecting ORN prognostic variables (NIH 1990).

6. OSTEORADIONECROSIS EPIDEMIOLOGY

The literature describing osteoradionecrosis (e.g. rates, potential prognostic factors, location, timing, severity, and consequences) is reviewed. ORN rates cited in the literature have ranged from 0 to 100%, reflecting not only clinical experience but artifacts of definition and diagnostic and other types of bias. The comparability (and thus, the external validity) of some ORN literature can be questioned because clinical protocols and patient case distributions differ. The "causes" of osteonecrosis are discussed in the literature, but in some cases these may simply be associations. Causes and variables identified in a few articles have been incorporated into ORN risk rate prediction formulas. If a separate diagnostic code for ORN of the jaws could be created in the International Classification of Diseases", the basis of many registries, this will widen the future ORN data base available for epidemiological analysis.

IV. POTENTIAL FACTORS PREDISPOSING OSTEORADIONECROSIS: SUMMARY

This section gathers most hypothesized ORN risk factors and extraction indications for final review, and complements previous discussions with additional perspectives.
1. DELPHI CONSENSUS TECHNIQUE; OPINION DATA

In the absence of prospective, randomized, controlled scientific studies, analyses and patient care guidelines can be based on consensus methodologies. Four formal consensus methodologies have been described: the nominal group technique (Horton 1980) the Delphi technique, the Glaser "State of the art technique" (Glaser 1980), and a model developed by National Institutes of Health. The "Delphi Technique" and the "Nominal Group Technique" are the two with the longest history (Fink et al 1984). Many consensus methodologies assume that opinions of experts grouped under special circumstances can reveal a closer approximation of the objective truth\(^2\) than would be achieved through conventional pooling of expert opinion, although some question this notion (French 1986).

General characteristics of the Delphi Technique as described in Whitman (1990) and Pill (1971) include anonymity, multiple iterations with controlled feedback, and statistical summaries. Typically, an open-ended survey is sent to empaneled experts who in turn provide responses that allow the Delphi experimenter to frame items for subsequent close-ended surveys. Each subsequent survey will incorporate statistical summaries of item responses from the previous version so that each respondent can compare these with his/her own thoughts. (Each open- or close-ended version of the

\(^2\) (providing guidance, e.g., in decision analyses),
survey is termed an "iteration" or a "round".) Responses to subsequent rounds should tend to converge. Rowe, Wright and Bolger (1991) explain the original concept of Delphi proposed by Dalkey as one in which holdout experts most confident in their opinions tend to move the group median toward the area containing the true answer. They describe Delphi as a two step procedure involving first, an interacting stage seeking to debias individual judgments, and then one or more stages with feedback\textsuperscript{3,4}.

Linstone and Turroff (1975) characterize Delphi as a method for structuring a group communication process such that it is effective in allowing the group to deal with complex problems.

The advantages claimed for the Delphi Technique include:

1. Participation without geographic, and to a lesser extent, temporal, constraints
2. Anonymity during participation, thought to reduce bias from deference to the more prestigious members of the panel
3. Lack of need for a trained interview facilitator (Fink 1984; Millholland 1973).

\textsuperscript{3} as in Rowe, Wright and Bolger (1991, 238 & 243, Figures 1 & 2). (Please Note: "Traditional" Delphi technique is explained particularly well by this article.)

\textsuperscript{4} Although Rowe, Wright and Bolger (1991) state, citing Parente and Anderson-Parente (1987) in particular, that there is a general trend towards more valid judgments with multiple iterations, they also interpret several papers to indicate that panelists "may produce more valid judgments over rounds in the absence of additional information of the other group members' estimates". This is contrary to the just-explained traditional interpretation of why Delphi works. Rowe, Wright and Bolger (1991) conclude that the process of iteration itself may be playing a part in allowing panelists to reconsider their original thoughts and move their own opinions closer to a reconsidered, final position. They also cite Hill and Fowles (1975) as explaining that concurrence may be due to "bandwagon" and "fatigue" effects as well as reasoned consideration of arguments.
Present official and semi-official documents indicating appropriate oral management of patients at risk for osteoradionecrosis do not appear to have utilized formal consensus methodologies to reach their conclusions. The NIH Consensus Conference relied on "consensus panel" experts' reports, as modified by audience input, to create a consensus; it then published the revised papers with recommendations on pretherapy dental interventions, management of complications, and areas needing future research. Thus, the NIH (1990) methodology may involve a theoretical risk that some audience members may have been too intimidated to question the positions presented for their approval.

The Delphi technique is compatible with a Bayesian information processing framework, and is useful when data available are vague or not reliable (Sahal 1975). Delphi studies in health usually predict or prescribe the future. British Columbia Ministry of Health (1991) is a typical Delphi--an initial questionnaire for issue identification, a second questionnaire for future priority setting, and a third questionnaire for final ranking of the issues. A dental example, Kaldenberg, Becker, and Hallen (1990, "Dentistry in the Year 2000: Assessments from a Delphi Panel") differs from classical Delphi Technique in the sense that full scale multiple iteration was not employed.

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5 1) Consensus Development Conference on Oral Complications of Cancer Therapies: Diagnosis, Prevention, and Treatment. (1989; published in 1990 and referenced in this thesis as "(NIH 1990)").

2) ADA (1989): "American Dental Association Oral Health Guidelines Head and Neck Cancer Patients Receiving Radiation Therapy". (This was developed by the ADA "Council on Community Health, Hospital, Institutional and Medical Affairs" "primarily as a resource tool rather than [as] an attempt to set specific standards of care").

3) Barker, Barker, and Gier (1992), representing consensus among the authors, three consultants, and the five members of the "Executive Committee" of the "International Society for Oral Oncology".

6 and ADA (1989) methodology not reviewed here

7 Sahal (1975) also recommends that Delphi studies incorporate cross-impact analyses to ascertain interacting variables.
Milholland, Wheeler, and Heieck (1973, "Medical Assessment by a Delphi Group Opinion Technic") use the Delphi technique in a manner somewhat similar to this thesis research. A related example, in which a Delphi-related consensus methodology is used to produce a list of clinical indications for a surgical procedure, is Merrick, et al (1987). Merrick, et al (1987) "used a two-round consensus panel method to derive and rate the appropriateness of comprehensive sets of detailed clinical indications for performing carotid endarterectomy." It found that ratings derived in this process were reliably reproduced six to eight months after the completion of the process, were consistent with those in the literature, and that a statistical analysis demonstrated that they followed a logical rationale. Merrick, et al (1987) concluded that consensus methods that do not force agreement can be used with panels of physicians to produce detailed, reliable, and valid indications, as well as identifying areas of disagreement appropriate for further study.

Fink, Kosecoff, Chassin, Brook (1984) state that Delphi reliability increases with the number of rounds, and an early school of thought advocated three Delphi close-ended item rounds in addition to an initial open-ended survey of the experts. However, Sweigert and Schabacker (1974, "The Delphi Technique: How Well Does It Work In Setting Educational Goals") concluded that "if ranking is the major concern, one round may be enough". Fink, Kosecoff, Chassin, Brook (1984) admit that respondent fatigue can set in after two or three rounds. Sahal (1975) cites his references Gettys, Kelly and Peterson (1973), Peterson (1973), and Martino (1972), as stating that rounds beyond two may not result in any advantage, a position echoed by Linstone and Turoff (1975), and Brockhoff (1975). 

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8 Milholland et al (1973) found that while uncertainties remained, there was a marked increase in the consistency of answers from the first to the second round.
Fink, Kosecoff, Chassin, Brook (1984) assert that Delphi reliability increases with the size of the group, but that too large a group becomes difficult to manage. Millholland et al (1973) state that the quality of a response improves with increasing group size up to about 13.

Fink, Kosecoff, Chassin, Brook (1984, 982) recommend that desired consensus must be defined in advance of a study. Consensus in Delphi is very often measured through comparison of measures of central tendency such as a median (Rowe, Wright and Bolger 1991). Millholland, Wheeler, Stanley, and Heieck (1973) consider the median of responses to be the best single number for describing group consensus. Kendall (1977), like Milholland (1973) used changes in interquartile ranges as indicators for convergence from one round to the next. Differences between rounds also can be assessed using Spearman Rho rank correlation coefficients (Sweigert and Schabacker 1974). In contrast, Dajani (1979) advocates that a Chi-squared test should be used to determine the stability of responses between rounds. When population criteria are met, regression analysis may be used (Salancik 1973).

Helfer (1971) and Salancik, Wenger, Helfer (1971) consider that information return is maximized when Delphi statements are neither overly specified nor vague, i.e. the correct degree of complexity—about 20-25 words for events of average familiarity. In contrast, Laurent (1972, in Sahal 1975) suggests that long statements may actually enhance reporting performance because the respondents take cues from the information complexity in the item, so additional, and more accurate, information may be elicited.
Curley, Young and Yates (1989, 116) regard ambiguity of opinion, whether due to "lack of evidence, the presence of conflicting evidence, unreliable evidence, or some other source of inherent uncertainty in the clinical case" as important because "it reflects the inadequacy of a point probability judgment." They found that a confidence rating for a respondent's evaluation of a survey item appeared to best reflect the construct of ambiguity as they defined it, and suggested that interview subjects should be asked "not only for their evaluation of an answer to a question but their certainty regarding it." Thus, confidence ratings should be included in survey responses, and in surveys that duplicate the findings of Curley, Young and Yates (1989), would be very important.

Methods other than Likert scale and confidence scale ratings may be used to provide probabilistic judgments (Poses, Cebul and Centor 1988). Sahal (1975) quotes his reference Martino (1970) as stating that assessors tend to prefer to evaluate probabilities in terms of ratios and that a diversity of probability responses expressed as ratios may tend to follow a log-normal distribution. Data transformations for medians of year estimates and probabilities also may be considered (Kendall 1977).

Variants of Delphi are described in Kendall (1977), Rauch (1979) and Webler et al (1991). In the group Delphi variant Webler et al (1991), a two-part questionnaire using open questions and Likert scales was iterated among rotating sub-groups to build consensus and to define disagreement. Kendall (1977) suggested other modifications of the Delphi Technique with the objective of making forecasts more precise.
Bias may be present in improperly conducted Delphi technique studies. Decisions derived through Delphi can be influenced by the circumstances of the study, such as each participant's awareness of other individuals' knowledge and talents (Christensen 1993). Information shared before, as well as during a Delphi study, would tend to invalidate it.

One early assumption was that group consensus would tend to be more conservative than individual opinion. In contrast, however, subsequent observations have tended to promote a perception that groups tend to be upwardly biased, or more optimistic than individuals — a phenomenon termed "risky shift". However, the data for this hypothesized group dynamic of "risky shift" may be controversial (Sahal 1975, esp. footnotes 166-67).

Delphi technique, when abused through fraudulent manipulation of statistical feedback from one iteration to the next, will influence responses in the direction of the bias introduced (Nelson 1978). This finding underlines the need for careful survey design to minimize known sources of bias, and serves as a reminder that properly conducted consensus experiments may retain unrecognized sources of bias. The potential biases in surveys of any type are well discussed in Woodward, Chambers, and Smith (1991). Forms of bias mentioned in the Discussion also could apply.

Cognitive biases in interpretation also exist. Shafer (1986) implies that an assumption that a respondent used Bayesian logic could lead to interpretation bias, and also that the dynamics of the formation of opinions by groups cannot be confused with the formation of opinions by individuals. Genest and Zideck (1986, "Rejoinder", 147-48) suggest that the challenge of the theory of combining [subjective opinion data]
distributions is that it is not always clear when a "given situation calls for compromise, summarization, or consensualization." He suggests that combination of opinion should be guided by the decision context.

Opinion data, e.g. in Delphi surveys, are subject to many forms of bias. Potential errors in probability assessment include three principles that are utilized to generate subjective probability estimates: representativeness, availability and anchoring (Taversky and Kahnemann\textsuperscript{10}). Under conditions of uncertainty each of these may lead to biased judgments about probability assessments. The principle of "representativeness" is illustrated when an estimate of a certain datum is referred to, or derived from, a larger class of data in which the assessment is better known. "Availability"\textsuperscript{11} is employed by accessing memories that are the most prominent—e.g. due to a series of different reasons including unusualness, meaningfulness, recent events vs. those long past, or consequences (i.e. consequences of a particularly serious condition). "Anchoring" is a tendency of survey or interview respondents to choose particular probabilities. In many cases, these would tend to be midrange probabilities. For others, or in other circumstances, people may falsely anchor rare probabilities as extremely rare (approaching zero), or probable events as closer to a probability of one, than reality would dictate. Waltert (1989) cites his reference Winterfeldt and Edwards (1986) as stating that extreme probabilities are best identified in a logarithmic fashion for survey respondents and also states that estimates of extreme probabilities are especially prone to effects of availability bias.

\textsuperscript{10} Reference 260 of Weinstein and Fineberg (1980, Chapter 6, 176-77)
\textsuperscript{11} References 31-35 of Woltert (1989)
Kahneman and Tversky (1996) believe that frequency judgments as well as probability judgments can be susceptible to large and systematic biases.

Redelmeier (1991) commented that physicians may be swayed in evaluations of diagnostic judgments not only by availability bias, but by wishful thinking. Another cognitive bias that may influence physicians' medical decision making when facing complex situations has been described by Redelmeier and Sharir (1993). They found that increasing the number of options paradoxically can increase the "probability of maintaining the status quo, selecting a default option, or delaying the decision".

Along with the anchoring and availability biases already mentioned, Shafer (1986) mentions framing, conjunctive bias, and disjunctive bias as cognitive illusions that lead respondents to make biased or inconsistent probability estimates. Framing bias can arise from inadequate ordering and phrasing of items designed to elicit responses, leading, for instance, experimental subjects to over-estimate probabilities of moderately likely events. "The effect of this bias would depend on whether one inquires about the probability of the event 'or that of its complement (). It is usually advisable to ask about both" (Woltert 1989). Hill and Fowles (1975) suggest that the Delphi Panel should contribute the phrasing for many event statements if the experimenter is going to avoid potential phrasing bias in his survey and eventual findings. Conjunctive and disjunctive bias is explained by Woltert (1989) as follows: "Subjects tend to overestimate the joint probability of independent events (e.g. winning three times successively in the game of craps) and to underestimate the probability of the union of disjunctive events (e.g., losing on the first, second or third try)."
Experts apparently are less influenced by these cognitive biases when dealing within their specialty (Winkler 1986; Woltert 1989 reference 42).

Physician determinants of opinion, especially two main categories of care giver characteristics classified as institutional and person dependent, must be taken into account during consensus studies (Liberati, 1986). Variations in clinician opinion not only influence clinical treatment planning, but proven variations in treatment planning\(^{12}\) could influence a clinician's range of clinical experiences, which in turn might bias his/her opinions. Liberati cites Palmer and Reilly (1979) as stating that although predictors of therapeutic behavior are not fully supported in the literature, the ones most frequently considered are characteristics that may be classified as "institutional"-- e.g. the size of the hospital, volume of patients, and availability of ad-hoc programs or facilities-- and personal-- e.g. the amount of training after medical school, specialization, age and graduation time. Other factors as-yet-unquantified may apply (Liberati 1986).

\(^{12}\) The survey-based restorative decision making analysis by El-Mowafy and Lewis found variations in restorative dentistry treatment planning that could be associated with age of practitioner, sex, university of training, amount of continuing education, and type of practice (El-Mowafy and Lewis 1994). Grembowski, Melgrom, and Fisset (1989) stated that reasons for variations in treatment patterns include different sources of education in practitioners of various ages. Dolan et al (1992) concluded that a patient's age influences general dentists treatment planning decisions, "perhaps limiting the treatment options offered to older adults", and Johnson (1993) concluded that non-dental factors can influence dentists' decisions to extract teeth in older adults. Of the latter, the most influential and pertinent non-dental factors, relevant in 13-17% of cases, were patient/family requests, financial limitations, and inability to care for one's teeth. Dental factors cited for the extraction of teeth in older adults were, in decreasing frequency of citation:

1. non-restorability of the tooth (54%),
2. caries (46%)
3. prosthetic considerations (45%), and
4. periodontal disease (40%).

The economic structure of the delivery of services also may influence choice of treatment (Liberati et al 1986), citing Hornbrook and Berk (1985)
2. UTILITIES AND POTENTIAL OUTCOME VARIABLES

The concept of utility determination and application is explored in Lane (1987). Utilities are founded on modern utility theory, a "normative, rational model of decision making under uncertainty" (Torrance 1987). Utilities can be evaluated and compared for validity and acceptability to subjects, reliability precision and ease of use (Torrance 1987). The relatively better validated methods of determining utility assessment are discussed in the article Stiggelbout et al (1994). Techniques used for determining utilities include standard gamble, time trade off, and rating scales.

Quality of life assessments are an ultimate goal for utilities and for validation of outcomes in a decision analysis. It is interesting to note parenthetically that quality of life has been correlated with prognosis for survival duration (Coates 1993).

Health-care providers often prefer not to evaluate quality of life in its entirety, but to focus with greater sensitivity and practicality on health-related quality of life. Generic instruments for assessing general health status can, in turn, be supplemented with disease-specific supplements or batteries, which by themselves are specific and sensitive to the effects of a particular disease. "The preferred strategy depends on project aims, methodological concerns and practical constraints. Generic measures are necessary to compare outcomes across different populations and interventions, particularly for cost-effectiveness studies. Disease-specific measures assess the special states and concerns of diagnostic groups. Specific measures may be more sensitive for the detection and quantification of small changes that are important to clinicians or patients" (Patrick and Gale 1989).
Although the measurement of outcomes as qualities of life is not practical in this research, some relevant literature should be mentioned. Concepts of quality of life in oncology are reviewed in the references (Osoba 1992; Osoba 1991a; Osaba 1991b; Morris 1994; Lindley 1992; Aaronson 1988) and books listed on page 270S of "Controlled Clinical Trials" Volume 12.

Liberati et al (1986) suggest a growing role in oncology for clinical decision analysis utilizing patient-derived outcome measures:

"...In assessing the efficacy of anti-cancer measures, clinicians and public policy makers have traditionally given overriding consideration to the effect of therapeutic procedures on survival. However, and this is particularly true for solid tumors, almost all standard and experimental treatments have now reached a plateau of success, mortality becoming an insensitive end point for the definition of risk-benefit profiles."¹³ "As a partial byproduct of this situation, patient-oriented end-points (i.e. quality of life assessments) are now being considered among the variables essential to the therapeutic decision making process"¹⁴ Similarly, Castillo (1994) stated, "Flexibility is needed in selection of therapy to allow effective treatment of the tumor, sparing anatomy when demanded, maintaining respect of the patient's own definition of quality of life".¹⁵

¹⁵ Degner and Sloan (1992) found that in the case of cancer, 64% of the public thought that they would want to be highly involved in treatment decision making.
Reviews of quality of life assessment in head and neck cancer include Gotay and Moore (1992), and Hassan and Weymuller (1993). Head-and-neck-cancer-specific quality of life measures include the efficient and validated Browman et al (1993) "Head And Neck Radiotherapy Questionnaire", a morbidity/quality of life instrument\textsuperscript{16} for clinical trials of radiation therapy in locally advanced head and neck cancer. The Cella (1993a) scale version of the efficient, validated, and very general Cella et al (1993b) "Functional Assessment of Cancer Therapy Scale" includes a sub-scale adapted for head and neck cancer. It consists of 28 general items, 11 specific items and 6 experimental items. A now-validated thirty-item "EORTC Core Quality of Life Questionnaire" and a "Diagnosis-Specific Module for Head and Neck Cancer Patients" also exists (Bjordal and Kaasa 1992).

Validated quality of life assessments for oral complications of head and neck cancer therapy are essentially lacking (Browman 1993; Epstein 1997). Lacking validated scales for quality of life in these patients, clinimetric scales\textsuperscript{17} for dimensions associated with quality of life are alternatives, at least as surrogates.

Oncology outcomes assessed for measurability, relevance and applicability by Pater (1994) include survival, response, symptoms, toxicity, quality of life and cost. Osaba (1993) stated that there has been in oncology an overwhelming emphasis on collection and collation of quantitative biological data such as "survival, disease-free intervals, time to progression, and response rates", with a relative lack of emphasis on

\textsuperscript{16} (Dimensions: oral stomatitis, throat, digestive, skin, energy, and psycho-social)
\textsuperscript{17} (Feinstein 1987)
collection of symptom rating data, because these "soft" data were not considered
amenable to quantitative evaluation. He further suggests that "our capability to evaluate
fully the perceived benefits accruing from cancer therapy" would be enhanced if
quantitative evaluation of symptom control was incorporated routinely into evaluations of
health outcomes, even if these are not directly relatable to quality of life in the simplified
format of data gathering employed as a step towards validated patient-derived quality of
life estimates." Osaba's symptom check list for patients with recurrent head and neck
cancer undergoing dose-intensive chemotherapy includes items related to the presence of
the following symptoms in a four unit rating scale ranging from 1 = not at all, to 4 = very
much. The symptoms rated by patients include nausea, vomiting, anorexia, tiredness,
difficulty swallowing solid and liquid food, shortness of breath, difficulty opening the
mouth, pain, medication for pain, and residual pain following medication.

Other surrogate scales exist for dimensions related to quality of life in head and
neck cancer patients, and following therapy for head and neck cancer, or complications of
same. These include the List, Ritter-Sterr and Lansky (1990) performance status scales
for head and neck cancer patients, the stomatitis-measuring tools described by Hyland
(1986), and measures for pain (Epstein and Stewart 1993). List, Ritter-Sterr and Lansky
(1990) provide a clinician-rated assessment tool containing three sub-scales: normalcy of
diet, understandability of speech, and the ability to eat in public. "Results indicate that the
scale is reliable across cross-raters and sensitive to functional differences across a broad
spectrum of head and neck cancer".
Prosthodontic status also influences quality of life (as measured by a "feeling thermometer" approach) (Jacobson et al 1990). Characteristics of the prostheses found to be most important to quality of life were, in descending order of importance, comfort, function, and appearance.

Murry et al (1994) relate the ability to swallow as a key issue in the quality of life. (The bedside swallow assessment was used in combination with the Browman et al (1993) "Head And Neck Radiotherapy Questionnaire").

Oral status also is associated with systemic health quality of life and economic productivity (Hollister and Weintraub 1993). Further, "Both systemic health and quality of life are compromised when edentulousness, xerostomia, soft tissue lesions, or poorly fitting dentures affect eating and food choices. Conditions such as oral clefts, missing teeth, severe malocclusion, or severe caries are associated with feelings of embarrassment, withdrawal and anxiety. Oral and facial pain from dentures, temperomandibular joint disorders, and oral infections affect social interaction and daily behaviors. Dental disease accounts for many loss of work and school days. Lower wage earners and minorities are disproportionately affected" (Hollister and Weintraub 1993).

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18 Objective assessment of swallowing function in head and neck cancer patients can be provided by scintigraphy (Muz 1991).
Laurin (1994) found that the nutritional status of elderly individuals with poor masticatory performance is impaired. The Hollister and Weintraub (1993) review article found poor mastication especially associated with reduced Vitamin C intake, and further consider the literature to indicate that xerostomia is associated with a lower total dietary intake of calories, particularly for institutionalized patients, and also with impaired intake of protein, vitamins A and C, thiamin and riboflavin. They cite Rhodus and Brown (1990) as stating the xerostomia is so highly associated with nutritional deficiency that it should be considered a clinical indicator for nutritional deficiency. The xerostomic individual tends to have a very sore mouth with difficulty swallowing and potential changes in taste perception which in turn can decrease the desire to eat.

Coulter, Marcus and Atchison (1994) disagree with arbitrary separations sometimes made between general health and oral health, to the diminishment of the latter, explaining impacts of poor oral health on general physical and psychological well-being, and associations with stress and economic and social dysfunction. Hollister and Weintraub (1993) cite literature which suggests the possibility of an association in the debilitated patient between teeth (most likely teeth of poor periodontal health) and aspiration pneumonia. They then conclude that the effects of oral disorders on quality of life include "pain, poor oral and facial aesthetics, impairments to eating, chewing and speaking, a decreased desire to interact socially, and/or a poor sense of well-being."19

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19 Truyn et al (1986, in Hollister and Weintraub 1993)) found that aesthetics and food intake impairments may cause withdrawal from society, and feelings of anxiety, depression, low self-esteem and sorrow. Employment, social and sexual relationships were all made less comfortable. Impairments of masticatory function were associated with missing anterior teeth, less than 24 teeth, and needs for extractions.
Dental and facial pain affects quality of life, and effects may depend on the duration and severity of the pain (Hollister and Weintraub 1994). Others conclude that patient subjective utilities, at least those involving pain, appear to bear more strongly on final, rather than intermediate, subjective intensities, with duration less important (Redelmeier and Kahneman 1996; Frederickson and Kahneman 1993; Varey and Kahneman 1992).\footnote{Varey and Kahneman (1992) proposed in their study that utility integration over time could be considered a normative rule for the evaluation of extended episodes. To investigate this, they asked subjects to assign global utilities to different symptomology histories. One goal was to test whether the integration of disutilities over time would be associated with an integration of symptomology, such as pain, over time. They did not find this to be the case. The subjects showed extreme sensitivity to symptomology trends at the end of the sequence of symptomology and a disregard for the length of time of discomfort, etc. Thus, subjective utilities, at least those involving pain, would appear to bear more strongly on final outcome than intermediate subjective states. Redelmeier and Kahneman (1996) found similar results in association with two short term medical procedures.} Confirmation of the applicability of these findings to in vivo chronic conditions (e.g. ORN, or more typical radiotherapy experiences) seems lacking at the present time, but Epstein and Stewart (1993) found that pain often increases throughout the course of radiation and persists following treatment, in some cases for six to twelve months.\footnote{Epstein and Stewart (1993), in their article "Radiation Therapy and Pain in Patients with Head and Neck Cancer," employed a portion of the McGill pain questionnaire along with visual analogue scales (VAS) for pain, recording of medications employed, their effect, and the location of the pain. Though the pain frequently required systemic analgesics in addition to oral rinses, patients reported generally mild pain over typical durations of one to three months or three to six months, rising as described above. Two asides worth noting are: 1. Oral pain could not be considered an indicator for oral disease because many types of oral disease do not cause pain in the early stages (Hollister and Weintraub 1993). 2. Future research into pain outcomes could incorporate the work of Moore (1996, "Combining Qualitative and Quantitative Research Approaches in Understanding Pain.".)}
3. CLINICAL PROBLEM

A. ORAL CANCER EPIDEMIOLOGY AND PREDISPOSING FACTORS

"[Osteoradionecroses] ... result from the aggressive treatment of cancer, many would not occur if cancers could be detected and treated at an early phase. The emphasis of [the NIH Consensus Development Conference on osteoradionecrosis] on the prevention and treatment of complications should not detract from the basic goal of prevention and early detection of cancer"(NIH 1990).

The oral cavity may be defined as the anterior two thirds of the tongue, the floor of the mouth, the buccal mucosa, gingiva, retro-molar trigone, and hard palate (Crooke and Esche 1993). Yasumoto et al (1995) defines four anatomical regions of the oropharynx:

1. anterior: base of the tongue and vallecula
2. lateral: tonsilar and faucial pillars
3. superior: soft palate and uvula
4. posterior: posterior pharyngeal walls.

Baden (1987) uses the term "oro-pharyngeal cancer" to mean "oral cancer plus pharyngeal cancer". Other authors appear to use the term "oro-pharyngeal cancer" to refer to "oral pharynx cancer". Thus, the term "cancer of the oral cavity/pharynx" will be substituted below when Baden (1987) uses the term "oro-pharyngeal cancer". Cancers of the lip are excluded from most discussions below because their epidemiological characteristics, and the potential of treatment to produce osteoradionecrosis, tend to be different from other cancers of the oral cavity.

A multi-factorial pathogenic mechanism is suggested for cancer of the oral cavity/pharynx (Baden 1987), and squamous cell carcinoma of the oral cavity may be
associated with an increased risk for cancers of the upper digestive and respiratory tracts (Shibuya 1987). 95% of oral cancer cases are found in people over 40 years of age (Nikiforuk 1991). 4% of all cancers in males and 2% in females in 1987\textsuperscript{22} were cancers of the oral cavity and pharynx, accounting for approximately 2% of all male cancer deaths and 1% of all female cancer deaths. A worldwide male to female prevalence ratio has changed from 6:1 in 1950 to 2:1 in 1987\textsuperscript{23} (Baden 1987). Oro-pharyngeal cancer incidence rates exhibit great geographical variation, and in 1971 accounted for 47% of all admissions to the Cancer Hospital of Bombay (Baden 1987, citation). The sex ratio for mouth cancer mostly ranges between 4:1 and 1.5:1 male:female, being highest in southwestern, southeastern, and central Europe. Contributing factors for geographic variation in incidence and death rates may include ethnicity and exposure variability (Smith, Pindborg and Binnie 1990, 10). For instance, the chewing of betel nut confers additional risk in India (Baden 1987).

American age-adjusted oral-and-pharyngeal mortality rates between 1973 and 1987

- ranged from $\sim$8 to $\sim$10 / 100,000 for American Black males, without clear secular trend,

- declined from $\sim$6 to $\sim$4.5 / 100,000 for American white males,

- held stable at $\sim$2 / 100,00 for black females, and

- very slowly declined from $\sim$2 for white females ((White et al 1994), cited in (I.O.M. 1995, 66))

\textsuperscript{22} apparently worldwide

\textsuperscript{23} possibly in association with changed female and male exposures to tobacco.
Also, National Cancer Institute age-adjusted death rates for oral and pharyngeal cancer would appear to have declined by 14% among persons over age 65, and by 21% for persons under age 65, between 1973 and 1990 (Beardsley 1994). However, assessment of incidence and prevalence rates of oral or oro-pharyngeal cancers reflect diagnostic capabilities, and any diagnostic bias present in secular trends over time may distort the apparent rates of oral (or oro-pharyngeal) cancer even if these rates are adjusted for the increasing age of the population.

Sex- and age-specific incidence rates for cancers of the tongue and mouth in B.C. in 1993 are listed in Table 1.

<table>
<thead>
<tr>
<th>AGE CATEGORY: (YEARS)</th>
<th>INCIDENCE RATES (New Cases per 100,000 Persons per Year):</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>CANCER of the MOUTH MALES</td>
</tr>
<tr>
<td>0-34</td>
<td>0.3</td>
</tr>
<tr>
<td>35-44</td>
<td>0.7</td>
</tr>
<tr>
<td>45-54</td>
<td>4.7</td>
</tr>
<tr>
<td>55-64</td>
<td>7.1</td>
</tr>
<tr>
<td>65-74</td>
<td>22.0</td>
</tr>
<tr>
<td>75-84</td>
<td>15.0</td>
</tr>
<tr>
<td>85-124</td>
<td>35.7</td>
</tr>
<tr>
<td>0-124</td>
<td>3.8</td>
</tr>
</tbody>
</table>

White, Caplan, and Weintraub (1995) use American Cancer Society 1993 data to illustrate survival for head and neck cancers, relative to other types, in their Figure 15, "Estimated Relative Five-year Percentage Survival for Selected Types of Cancer By Race, United States, 1988", p.54, reproduced as Figure 4.
FIGURE 4. "ESTIMATED RELATIVE FIVE-YEAR PERCENTAGE SURVIVAL FOR SELECTED TYPES OF CANCER BY RACE, UNITED STATES, 1988" after Figure 15, (White, Caplan, and Weintraub 1995, 54)

CANCERS: EST. 5 YR. % SURVIVALS

<table>
<thead>
<tr>
<th>TYPE OF CANCER</th>
<th>KEY:</th>
<th>SERIES:</th>
<th>American</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pancreas</td>
<td></td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Lung</td>
<td></td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>Leukemia</td>
<td></td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>Non-Hodgkin's Lymphoma</td>
<td></td>
<td>4</td>
<td></td>
</tr>
<tr>
<td>ALL SITES = 5</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ORAL CAVITY AND PHARYNX = 6</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Colon</td>
<td></td>
<td>7</td>
<td></td>
</tr>
<tr>
<td>Cervix</td>
<td></td>
<td>8</td>
<td></td>
</tr>
<tr>
<td>Prostate</td>
<td></td>
<td>9</td>
<td></td>
</tr>
<tr>
<td>Bladder</td>
<td></td>
<td>10</td>
<td></td>
</tr>
<tr>
<td>Breast</td>
<td></td>
<td>11</td>
<td></td>
</tr>
<tr>
<td>Hodgkin's Lymphoma</td>
<td></td>
<td>12</td>
<td></td>
</tr>
<tr>
<td>Melanoma of the Skin</td>
<td></td>
<td>13</td>
<td></td>
</tr>
</tbody>
</table>

Tobacco use, nutritional status, alcohol intake, the presence or absence of neck dissection, irradiation dose, use of hyperbaric oxygen, cancer stage, and other variables have been examined for relevance to the risk, prognosis, and/or outcomes of head and
Tobacco use, nutritional status, alcohol intake, the presence or absence of neck dissection, irradiation dose, use of hyperbaric oxygen, cancer stage, and other variables have been examined for relevance to the risk, prognosis, and/or outcomes of head and neck cancer and/or osteoradionecrosis. Beumer et al (1979a) considers the prognoses for tumor and patient to be important in dental treatment planning for head and neck cancer patients at risk for osteoradionecrosis. These observations justify a brief review of cancer prognosis.

Oral and/or pharyngeal cancer incidence rates rise in association with exposures to tobacco smoking, snuff dipping, reverse smoking, tobacco and betel nut quid chewing, and excessive alcohol consumption. Increased incidence of squamous cell salivary carcinomas and other cancers of the lip are associated with ionizing radiation, and solar actinic radiation (e.g., wavelengths of 320 to 400 nanometers)(multiple references, cited by Baden (1987, 50-55). Individual factors such as genetic makeup, biochemical status, and immune deficiency may be some of the factors contributing to a possible hypothetical individual susceptibility to oral or pharyngeal cancer (Baden 1987).

Evidence is scanty and/or contradictory regarding whether nutritional deficiencies, occupational risks, biological risks such as dental trauma or oral sepsis, or micro-organisms cause oral or pharyngeal cancer (Baden 1987, 54-56, and references.).

In the absence of exposure to betel nut, Roush, Holford, Schymura, and White (1987, 47) associate relative risk factors of 2-10 with tobacco use, 2-6 with alcohol use, and about 20 in comparison with use of neither alcohol nor tobacco. Table 2 reproduces a table, "Major Risk Factors Associated with Oral Cancer" from (Anon./Douglass, 1996).
TABLE 2. MAJOR RISK FACTORS ASSOCIATED WITH ORAL CANCER
(after table of same name in (Anon./Douglass 1996, 3)

<table>
<thead>
<tr>
<th>RISK FACTORS:</th>
<th>MALES</th>
<th>FEMALES</th>
<th>COMBINED SEXES</th>
</tr>
</thead>
<tbody>
<tr>
<td>Smoking and Alcohol ✶</td>
<td>1.5-37.7</td>
<td>5.1 - 107.9</td>
<td></td>
</tr>
<tr>
<td>Alcohol (between 5 &amp; 30 drinks/wk) ✶</td>
<td>1.7 - 8.8</td>
<td>1.3 - 9.1</td>
<td></td>
</tr>
<tr>
<td>Smoking ✶</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(20 to &gt; 40 years of age) ✶</td>
<td>1.9 - 3.6</td>
<td>2.9 - 5.0</td>
<td></td>
</tr>
<tr>
<td>(&lt; 20 to &gt; 40 cigarettes/ day ) ✶</td>
<td>1.2 - 2.8</td>
<td>1.8 - 6.2</td>
<td></td>
</tr>
<tr>
<td>Leukoplakia ✶</td>
<td>12.7</td>
<td>4.3</td>
<td></td>
</tr>
<tr>
<td>Genetic Factors-- brother with oral cancer ✦</td>
<td></td>
<td>7.4</td>
<td></td>
</tr>
<tr>
<td>Human Papillomavirus ✶</td>
<td></td>
<td>6.2</td>
<td></td>
</tr>
<tr>
<td>Types 16 and 18 ✶</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Types 6 and 11 ✶</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mouthwash ✶</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(High Alcohol Content) ✶</td>
<td>1.6</td>
<td>1.9</td>
<td></td>
</tr>
<tr>
<td>(Low Alcohol Content) ✶</td>
<td>0.7</td>
<td>0.8</td>
<td></td>
</tr>
<tr>
<td>Edentulousness ✦</td>
<td></td>
<td></td>
<td>1.7</td>
</tr>
<tr>
<td>PROTECTIVE FACTORS:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cessation of Smoking ✶</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(&lt;10 yrs) ✶</td>
<td>1.1</td>
<td>1.8</td>
<td></td>
</tr>
<tr>
<td>(&gt;20 years ✶)</td>
<td>0.7</td>
<td>0.4</td>
<td></td>
</tr>
<tr>
<td>Fruit ✶ containing vitamins A, C, and E ✶</td>
<td>0.2 - 0.7</td>
<td>0.5 - 0.8</td>
<td></td>
</tr>
</tbody>
</table>

✶ (Blot, McLaughlin, Winn, et al. 1988)
✶ (Winn, Blot, McLaughlin, et al. 1991)
✦ (Day, Blot, Austin et al. 1993)
◆ (International Agency for Research in Cancer Monographs. 1995)
◇ (Winn 1995)
Consider also: (Spitz 1994) and (Blot, Devesa, McLaughlin, and Fraument 1994)

Prevention of osteoradionecrosis ultimately would be assisted by prevention of the same cancers that contribute to osteoradionecrosis as a side effect of treatment. One may suggest that cessation or reduction of tobacco and alcohol use (and, in alcoholics, supplementation of diet with proteins, vitamins and trace metals to decrease the promoter

---

24 Exposure to betel nut is not reflected in this table.
25 "An odds ratio expresses the risk of developing oral cancer associated with any specific factor. Values larger than 1.0 indicate increased risk; values less than 1.0 represent a decreased risk or protective effect. Values are usually statistically adjusted to reduce the influence of other risk variables associated with the disease."
effect of alcohol) should tend to reduce the incidence and prevalence of cancer of the oral cavity or pharynx (Baden 1987), and thus its complications.26

Stell (1991) found that the primary predictor of survival, both from initial presentation and from the date of recurrence, was the site, irrespective of other host factors. Roland, Caslin, Nash and Stell (1992) found through retrospective analysis of a series of 3,294 patients that site was closely associated with grading (poorly differentiated tumors being more common in the pharynx, and well-differentiated tumors being more common in the mouth and larynx.) Rates of metastasis were 46% (near metastases) and 3.4% (distant metastases) in patients with poorly differentiated tumors, and 28% and 1.8% in patients with well-differentiated tumors. Survival rates were 27% and 33%, respectively, for poorly and well differentiated tumors, and recurrence rates 27% and 25% respectively, for poorly and well differentiated tumors at the primary site, and 30% and 26% respectively, in the lymph nodes (Roland, Caslin, Nash and Stell 1992). Umeda (1992) also observed a correlation between histologic grade of malignancy and the prevalence of neck metastasis, and Cusumano and Mark Persky (1988) that survival correlated best with the TNM stage of disease at initial presentation, although Zatterstrom et al (1991) criticized TNM classification and histopathologic grading systems as only semi-quantitative and subjective, then went on to find that histologic grade, clinical stage, tumor size, and patient age did not correlate with prognosis. Other proposed prognostic variables for oral squamous cell carcinoma include DNA ploidy (Tytor 1989), and for squamous cell carcinoma of the mobile tongue, tumor thickness (Nathanson 1989).

26 Barker et al (1992) lists resources for promotion of tobacco cessation and nutritional enhancement.
B. ORAL SQUAMOUS CELL CARCINOMA LESIONS AND TREATMENT STRATEGIES

90% of all carcinomas of the oral cavity are squamous. A number of variants of squamous cell carcinoma of the oral cavity exist. These include verrucous, adenoid squamous, spindle cell, and basaloid (Cadier et al 1992). Common locations for oral squamous carcinoma are the oral portion of the tongue, the mandibular gingiva, and the floor of the mouth. Floor-of-the-mouth lesions are characteristic of alcoholics.

Many squamous cell carcinomas arise from malignant transformation of premalignant lesions, as described in Silverman (1987). Thus, excisional biopsy is indicated in many cases to prevent malignant transformation (Silverman 1987). Squamous cell carcinomas of the oral cavity themselves are infiltrative, aggressive, and generally require aggressive therapy including irradiation (McGaw and Pan 1996). Therapeutic irradiation can cause residual as well as transient pathology in the tissues irradiated to high dose. Surgery to remove affected tissue and potential spread is usually involved.

Mortality from oral cancer is high. (Less than one half are cured.) Of the 10,000 deaths per year in the U.S. (2.5% of all cancer related deaths), the survival rate increases dramatically when the cancer is detected early (i.e., when the lesion is less than 3 cm in diameter and there is no regional cervical lymph node involvement (Silverman 1987).

\[27\] in overview. The relative merits of different techniques (types of irradiation, chemotherapy subtypes, etc.) as squamous cell carcinoma tumor control measures will not be detailed, since the treating dentist would accept these for a particular case or a particular decision analysis as assumptions given to him/her by others. Since osteoradionecrosis arises from radiation therapy (usually treating squamous cell carcinoma), this treatment modality will be emphasized.
Neck dissection often is undertaken to remove metastases. Concern has been expressed, however, that this when elective ("just in case the lymph nodes are involved"), might needlessly compromise the tissues or blood supply. Mendenhall (1988) found no difference whether radiotherapy alone was administered, or an elective neck dissection also took place, with regard to rates of disease control at the primary site or ability to surgically manage patients who developed primary site recurrences of head and neck squamous cell carcinoma.

Lampe (1971) considers squamous cell carcinoma to be a radioresponsive and radiocurable neoplasm. Super-voltage radiation may be used in-and-around bone to minimize acute and chronic cutaneous radiation reactions and spare bone tissues, but low voltage irradiation may be used for superficial lip carcinomas and orthovoltage radiation for larger or older lip lesions or broader involvements. These extra-oral approaches may be combined with brachytherapy (e.g. low intensity radium needles) to provide additional impact on the neoplasm. Cure often occurs but some tumors may not be eradicable because of metastasis or tumor radio-resistance to dose ranges that are tolerable by normal structures. (The tongue is well vascularized and tolerates high radiation doses.)

Radiotherapeutic doses necessary for tumor control are "almost inevitably" followed by osteoradionecrosis in cases where the squamous cell carcinoma has invaded the mandible28 (Henk 1985; Henk and Langdon 1995) McGregor and MacDonald (1988) found that invasion of the non-irradiated edentulous mandible most frequently is through the residual alveolar occlusal ridge, but found that the irradiated mandible

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28 Radiation doses associated with the "almost inevitable" ORN arising in this circumstance were undefined. They might be implied, from the Henk and Langdon (1995) discussion of Bedwinek (1976), to be ≥7000 cGy. {A cited reference, (Carter 1980), does not define the relevant doses.}
tended to be prone to much more variable routes of tumor entry. McGregor and MacDonald (1989) reported that two modes of spread of squamous cell carcinoma in the mandible are observed, "spread in relation to the inferior alveolar nerve, and spread in the spaces between cancellous bony trabeculi".

Hyperbaric oxygenation is frequently employed to treat, and less commonly to prevent, osteoradionecrosis. An in-vitro experiment by Sklizovic (1993) suggests that squamous cell carcinoma should not grow at a higher rate in the presence of hyperbaric oxygenation. Bradfield, Kinsella, Mader, Bridges, and Calhoun (1996) conclude that this finding is typical of results reported for transplanted tumor cells. However, Bradfield, Kinsella, Mader, Bridges, and Calhoun (1996) provide a few anecdotes associating "rapid progression of head and neck squamous carcinoma after hyperbaric oxygenation", and suggest that some evidence reported in the literature would appear to support "a role for hyperbaric oxygen in enhancing growth of persisting tumors."

Bernstein et al (1993) describes carcinogenesis as a potential late complication of cancer therapy. He states that intermediate doses of radiation, for instance 200 to 1000 cGys, appear to be more tumorigenic than larger doses, "perhaps because larger doses of radiation result in cell death, whereas intermediate doses are more likely to result in mutations capable of producing tumors". However, Bernstein et al (1993) cite their

---

29 McGregor and MacDonald (1989) reported that the pattern of spread in cancellous bone in irradiated mandibles and the incidence of nerve-related spread was not significantly different in irradiated or non-irradiated mandibles. In contrast to the alternative of spread through the spaces between cancellous bony trabeculi, a tendency for nerve-related spread was identified as more frequent in the edentulous mandible than in the partially dentate non-irradiated mandible. Totsuka et al (1991) reported that most squamous cell lesions with erosive bone defects showed an "expansive" pattern histologically. They found that the extent of the radiologically detected bone defect approximated the size of the histologic involvement.

30 a comprehensive review of the biology of chronic radiation effect on tissues and wound healing.
reference (Hellman 1985) as stating that it is very difficult to demonstrate increases in the incidence of cancers after therapeutic irradiation except in children, and (Friedman et al 1988) states that irradiation to high dose would appear "neither to protect against, nor induce multiple primaries, within head and neck radiation portals".

Guillamondegui (1993) states "It has been clearly established that adequate, individualized selection of treatment is the most significant factor in the treatment of oral cavity cancer. Surgical and functional rehabilitation of the patient represents a further step in the decision making sequence. Every patient and his tumor should be considered as components of a unique equation. The most suitable form of therapy should be selected in each individual case."

The Summary of (Harrison and Fass 1990) reflects the philosophical approach of one institution:

"Radiation therapy using both external beam and brachytherapy is one of the mainstays of treatment for oral cavity cancer. For early lip, tongue, and floor of mouth lesions, radiation alone is highly effective and produces an excellent functional result. More advanced lesions are frequently treated with combined therapy or radiation alone with surgical salvage."

"Buccal mucosa and gingiva lesions are generally treated with surgery but can be managed by radiation therapy if they are early. More advanced lesions are treated by surgery plus post operative radiation."

"Retromolar trigone lesions can be managed by radiation alone if they are small, but larger lesions are generally treated by combined therapy."

"Clearly, the goal of treatment of squamous cell cancer of the oral cavity is cure of a disease with optimum function results. These goals could be achieved only by cooperative interdisciplinary evaluation and management by the surgeons, radiation oncologists, and dentists involved in the care of these patients" (Harrison and Fass 1990).

(However, Bernstein et al (1993) references Shore (1984), Shore (1990) found that infants given irradiation averaging 2,250 cGy to treat presumed thymic enlargement demonstrated a significantly higher incidence rate for skin cancer than their control siblings. Bernstein et al (1993) also cite references for "numerous cases of basal cell carcinoma arising within radiodermatitis...".  

an excellent review of intra-oral procedure for radiation therapy for oral cavity cancer
A comprehensive overview of current techniques and indications for radiotherapy of head and neck cancer patients is provided in Ang, Anders and Peters (1994).

EXTERNAL IRRADIATION

X and gamma rays are high energy photons of very short wave length produced in an electrical device such as a linear accelerator that accelerates electrons to a high energy then stops them on a target of tungsten, gold, etc., thus producing the x-rays. On the other hand, gamma rays are emitted from natural sources as unstable radioactive nuclei prone to achieve lower energy states (Bernstein, et al 1993). Bernstein et al (1993) state that until 1950 most external beam radiotherapy involved kilovoltage (orthovoltage) machines generating x-rays at voltages up to about 300 kilovolts peak (KVP). Gehrig (1969) observed one mild case of osteoradionecrosis in a patient who received only 2500 cGy of orthovoltage, but cited another author (Meyer) as indicating that in general a minimum of 4000 cGy was required. Unless otherwise specified, future discussions in this thesis should be assumed to refer to the newer super-voltage x-radiation which, relative to orthovoltage, is bone-sparing and is associated with higher dose thresholds for onset of osteoradionecrosis.

Criteria for selection of type of irradiation therapy includes the origin of the irradiation voltages used in external irradiation may include

1. ortho-voltage (150-250 KVP) (Rubin and Doku 1976) (150-400 KVP) (Behesti and Javid 1978);
2. super voltage (500 KeV to 8 MeV) (Buschke and Parker 1972) in (Rubin and Doku 1976)
   a) x-rays produced by an x-ray therapy machine, or
   b) 60CoBalt, which emits high energy photon gamma rays with an average energy of 1.2 MeV (Rubin and Doku 1976, who stress this is not megavoltage.)
3. mega-voltage x-rays (20-MeV, capable of greater penetration), (Behesti and Javid 1978) and
4. electron beam (electrons in range of 8 to 50 MeV) (Behesti and Javid 1978), produced by linear accelerators, that are less penetrating than megavoltage x-rays [as illustrated in Figures 1, 2 and 3 of Bernstein et al (1993), which illustrate the effect of increasing beam energy on the penetration of a beam of photons (X or gamma rays in tissue), the penetration of a spectrum of electron beam energies in tissue, and the skin-sparing dose build-up effects seen with MV irradiation.], and thus are appropriate for treating superficial lesions. (Bernstein et al 1993)
tumor, the size and location of the tumor, and the sensitivity to irradiation.

X-rays are composed of photons which interact with living tissue through a combination of photoelectric and Compton effects. The amount of energy absorbed by tissues through photo-electric effect is approximately dependent on the cube of the tissue's atomic number: 5.9 for adipose tissue, 7.4 for muscle, and 13.8 for bone. Therefore, since the ratio of the atomic numbers of bone in relation to soft tissue is about 2, the amount of energy absorbed by bone through photoelectric effect would be approximately $2^3$, or eight fold, that of soft tissue. A second way in which radiation is absorbed is the Compton Effect, which is proportional to the electron density of the living tissues. At the energy range of 250 KVP, more Compton effect is present, so the ratio of energy absorbed through all methods in bone is 2:1 overall, rather than the 8:1 ratio that would exist if only the photoelectric effect was present. Radiation in the 1 to 10 MeV range (e.g. $^{60}$Cobalt, 1.2 MeV) tends to have radiobiologic effects dominated by the

Betatron irradiation consists of two types: beta rays (negatively charged particles) and photons (x-rays). Electrons of energies from 3 to 45 MeV, and x-rays of over 30 MeV may be delivered (Rubin and Doku 1976).

Linear accelerators are capable of emitting x-rays and electrons in the range of 4 to 40 MeV. Neutrons may be produced in a cyclotron. These large particles are effective against hypoxic cells in the center of a tumor mass equally as they are to more superficial and oxygenated tissues. Mesons have the unique advantage of becoming radiobiologically active only after penetrating tissues to a designed depth. This spares tissues superficial and deep to the lesion while being equally active at different levels of tissue oxygenation (Rubin and Doku 1976).

External radiation builds up to maximum intensity not at the skin surface but below. Ortho-voltage (200 KVP) builds up to 100% effect 1 mm below the skin surface, Cobalt 60 (1.2 MeV) is 100% active at 4 mm depth, Betatron irradiation (3 to 45 MeV range) electrons are 100% active in the depth range 2 mm to 2 cm, while x-rays in the 33 to 45 MeV are 100% active at a depth of 5 cm. Effects of low entrance doses of x-radiation may be avoided in superficial tissues if the beam first hits a "bolus" or sheet of material placed over the tissue intended to provide dose buildup prior to the beam passing through the most superficial layers of tissues (Bernstein, et al 1993).

"Neutron therapy differs from standard photon or electron radiation therapy because of the biologic differences in the mechanisms of absorption of energy; this translates into a greater radiobiologic effectiveness and a lesser dependence on oxygen status, cell cycle status, and type of fractionation. In the mouth and throat area, this biologic advantage could lead to better management of the non-epidermoid cancers... The risks of normal tissue injury with neutrons compared to photon radiation are somewhat less for bone injury..." (Hendrickson, Saroja and Mansell 1987).

Meridith (1972) cited by Rubin and Doku (1976)
Compton Effect, so the range of energy absorbed by bone and soft tissues is approximately equal (a "bone sparing phenomenon") (Rubin and Doku 1976). At higher MeV produced by Betatron irradiation the Compton effect becomes less important relative to a new, previously unmentioned effect called pair production. With pair production the relative amount of radiation absorbed by tissues is linearly proportional to the atomic weight.

Radiation quality, a factor which takes into account the relative biologic effectiveness produced by different types of radiation, is often expressed in the unit termed the Linear Energy Transfer, LET. High LET radiation such as alpha particles and heavily charged ionic particles produce a relatively great biologic effect, transferring large amounts of radiation per unit track length through tissue. Examples of low LET radiation include x and gamma rays. These are less densely ionizing and thus exert relatively less biologic effect (Bernstein et al 1993).

BRACHYTHERAPY.

An alternative or complement to external irradiation could involve the intra-oral/nasal placement of radioactive devices (brachytherapy). Brachytherapy may achieve its effects, both good and bad, due to higher tumor dose, reduced treatment time, or other radiobiologic factors (Crook and Esche 1993). Crook and Esche (1993) consider brachytherapy an essential part of radiotherapy for early cancers (T₁ and T₂) of the oral tongue and the floor of the mouth, and cite their reference Wallner (1986) as stating that it has been found to be an independent prognostic factor. Pernot et al (1995)³⁵ consider

³⁵ not necessarily stating the majority opinion

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that "exclusive brachytherapy is preferable to the combination of external beam irradiation plus brachytherapy for $T_1$, and $T_2N_0$ tumors."

A number of materials and techniques may be used in brachytherapy. Mandibular doses of greater than 7000 cGy appear to put the mandible at risk for osteoradionecrosis, but the dose may be reduced by lead sheets incorporated into acrylic appliances shaped as dentures or mouth guards with apical extensions along either side of the teeth and marginal gingiva as far as the reflection of the vestibular mucosa (Levendag, Visch, and Driver 1990). Spacers to reduce the radiation dose to surrounding normal tissues and to help prevent osteoradionecrosis also may be used (Fujita et al 1994). To spare the tongue, tongue repositioning devices may be used (Poole and Flaxman 1986).

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*Radium* ($^{226}$Ra) needles of 2 to 4.2 cm in length may be held in splints against lesions of the lips, maxillary sinus, floor of mouth, buccal mucosa, or the anterior two-thirds of the tongue. Radium has an extremely long half-life, the needles, which may deliver potentially high doses of 100 to 1,200 roentgens per day, must be retrieved. Capsules approximately 4 by 1.5 mm containing radioactive radon ($^{222}$Rn) gas with a short half-life {active life span of one month (Behesti and Javid 1978)} may be left permanently in place, and used where radium needles would be too large, for instance, at the base of the tongue, the tonsillar pillar, etc. (Rubin and Doku 1976).  

$Iridium$ is now used sometimes as a substitute for radium. $^{125}$Iodine and $^{241}$Americium sometimes are employed to deliver beta irradiation (electrons, which may be effectively shielded from medical personnel. $^{125}$Iodine may be used as a permanent implant for tumor locations such as the deep base of the tongue where after-loading techniques are impractical {Meigooni and Nath 1992} and (Lee, Liberman, and Park 1991) in (Thornton, Gall and Rosenthal 1993). Yasumoto et al (1995) state that among tumors of the oro-pharynx, only the anterior (i.e. base of tongue and vallecula) lesions have been widely recognized as suitable for interstitial implantations using $^{192}$Iridium. Yasumoto et al (1995) explain that $^{198}$Gold grains are implanted permanently and are more easily administered without general anesthesia in comparison to $^{192}$Iridium implants, which also have a potential for severe bleeding as a major complication (Foot, Parsons et al 1990 in Yasumoto et al 1995). Thus, brachytherapy may be provided using $^{198}$Gold grains for high risk patients including the elderly over 80 years old, and those in which general anesthesia is contraindicated. (However (Yasumoto et al 1995) consider patients who are bedridden inadequate even for this procedure.)  

$^{182}$Tantilum emits gamma rays of 1.2 MeV and is supplied in the form of wire that may be placed inside a pre-positioned container. Iridium emits gamma rays of a 300 to 600 KeV energy. It has a half-life of 74.4 days and, like Tantalum, may be loaded into plastic ribbon positioners. $^{137}$Cesium has a long half-life -- 30 years -- and yields gamma rays of 660 KeV. $^{198}$Gold has a half-life of 2.7 days and may be used as a permanent implant yielding gamma rays of 412 KeV (Rubin and Doku 1976). (These acrylic appliances may also incorporate radiation sources such as radium needles.)
New approaches in radiotherapy include three-dimensional conformal radiotherapy in which target volumes are more precisely defined using high quality tumor imaging and localization techniques and dynamic beam shaping and orientation (Peters 1993; Thornton, Gall and Rosenthal 1993). This is useful, for instance, in minimizing damage to salivary glands. It has been observed by Keus, Noach, de Boer and Lebesqu (1991) that the homolateral mandible shows a mean decrease of 21% of integral dose when blocks customized blocks for sparing of normal tissue were employed.\textsuperscript{38}

Crook and Esche (1993) conclude that success will be maximized and complication rates of interstitial brachytherapy minimized with careful attention to "dental preparation, implant geometry, proximity of sources to the mandible and the use of intra-oral spacers or shielding..."

Yasumoto et al (1995) concluded that the incidence of bone and/or soft tissue complications was evenly distributed in their three treatment modality groups (implant alone, implant plus external radiation, and external radiation alone). Unfortunately, with regard to ORN, the small numbers compared may prevent this being a definitive conclusion. Shibuya et al (1993) seemed to find significantly different incidence rates for severe complications (in hard and soft tissue, \textit{combined}) following brachytherapy alone or with external irradiation.

\textsuperscript{38} They state, with reference to radiation therapy of parotid gland tumors, that "for a [parotid] tumor dose of 7000 cGys the average bone necrosis probability was reduced from 8.4% (no block) to 4.1% (blocks). For other normal tissue such as nervous tissue, other soft tissues and bones, a substantial reduction of integral dose was found for all patients when individual blocks were used."
C. PATHOLOGY OF RADIATION INJURY

"...In addition to the desired antitumor effects, head and neck radiation therapy induces damage in normal tissues that may result in oral sequelae such as mucositis, hyposalivation, radiation caries, taste loss, trismus, soft-tissue necrosis, and osteoradionecrosis. These sequelae may be dose limiting and have a tremendous effect on the patient's quality of life" (Jansma, Vissink et al 1992).

Most oral carcinomas require a dose of five to seven thousand cGy\textsuperscript{39} for curative treatment, usually given over a 4 to 6 week period of about one thousand cGy each week, or two hundred cGy each visit. This fractionation of absorbed dose delivery allows normal tissue to repair itself, and tumors to shrink slowly in such a way that oxygenation is maintained (Rubin and Doku 1976).

Side-effects of radiation therapy include mucositis, usually beginning at the end of the first week at 1000 to 1500 cGy. This includes reddening and an inflammatory response which can cause pain and interfere with mastication. At higher dosages, white patches may appear on the mucous membranes of the lips, cheek and tongue. The mucosa appears dry and glossy, the skin within the portal of radiation may be erythematous, edematous, tender, or temporarily pigmented.

Xerostomia (dry mouth) becomes evident from 1000-1500 cGy upwards, in many patients receiving $\geq$5000 cGys, and in at least 50% of patients receiving 7000 cGys per 7 x 7 cm field (Rubin, Cooper, and Philips 1975).\textsuperscript{40} This can contribute to difficulties in swallowing and decreased remineralization of the teeth by saliva, often promoting high rates of caries ("radiation caries"). Taste alterations are probable (Rubin and Doku

\textsuperscript{39} centiGray, or 0.01 Gray. One cGy is essentially equal to one "rad", an older measure.

\textsuperscript{40} cited in Rothwell (1987).
Maxymiw, Rothney and Sutcliffe (1994) cite Eine (1975) as documenting changes in the interprismatic enamel in teeth at doses in the range of 2000 cGys.

Beumer, Curtis and Harrison (1979a) document the shift in oral micro flora following therapeutic irradiation. Noteworthy among these is the striking increase in Streptococcus mutans portion of the total Streptococcus population in the plaque of such patients after radiation xerostomia has taken effect. This, plus the decreased remineralization potential under such circumstances and decreased buffering capacity of lower salivary pH increases the risk of caries dramatically.

Rubin and Doku (1976) cite the rat study of Meyer, Shklar, and Turner (1962) as suggesting a possibility of dental pulp damage during ortho-voltage (not 60 Cobalt) treatment. Trismus may accompany fibrosis and scarring of tissues in or around the temporo-mandibular joint, or muscles of mastication, when these receive therapeutic irradiation. Rubin and Doku (1976) consider the most important and irreversible damaging potential changes induced by therapeutic radiation to be the progression of initial periarteritis and endarteritis, to intimal thickening with fibrosis and near or total obliteration of the lumen of arteries of the mandible. This would contribute to reduction of oxygenation of tissues involved and contribute to osteoradionecrosis especially in the mandible, which lacks the diffuse blood supply of the maxilla. The radiation also decreases the number of osteocytes and osteoblasts, which in children stunts bone growth.

41 Optional illustrations of oropharynx radiotherapy local sequelae would be provided by Lockhart (1986) Figures 22-6 "Sequelae of Radiotherapy to the Oropharynx" and 22-8 "Dental Sequelae of Radiotherapy". Its Figure 22-14 "Preradiotherapy Treatment Planning" and Table 22-1 "Management of Oral Sequelae of Head and Neck Radiotherapy" also could amplify later thesis descriptions of these.

42 Although fungi do not usually cause dental disease, severe oral infections of Candida albicans can result in discomfort and illness in a patient following an up to 100 fold increase in oral fungal populations following therapeutic irradiation.
and can produce a developmental maxillo-facial deformity (Barker, Barker and Gier 1992). The capacity and speed of repair are usually reduced in all tissues.

Dental pulp exposed to some radiotherapeutic regimes may undergo fibrosis, atrophy and decreased vascularity, resulting in compromise of clinical pulpal response to infection, trauma and various dental procedures. Although pulpal pain associated with pulpal exposures is diminished, root sensitivity may become prominent in some patients. Cementum cellularity and capacity for repair undergoes changes analogous to those of bone. Therapeutic irradiation also causes periodontal ligament changes including disorientation of the network of fibres, thickening, and decreased vascularity and cellularity (Beumer, Curtis and Harrison 1979a).

Oral complications of radiotherapy may be separated into the acute and chronic, transient or permanent. Acute complications include treatment-related mucositis, dysgeusea, infectious stomatitis, and dermatitis, while chronic include dry mouth, caries, trismus, fibrosis, sensitivity to light (photosensitivity) and osteoradionecrosis (Toth, Chambers, Fleming, Lemmon, and Martin 1995). Although the relationship between overall time and radiotherapeutic effect is difficult to elucidate, prolonged treatment times tend to spare the severity of acute reactions, but not later reactions (Bernstein et al 1993). Prolonged treatment times also can be associated with decreased cure rates, given the same dose (Withers et al 1995b).

Fajardo (1982) describes "approximate limits of radiation tolerance of different human tissues as defined clinically.". "Tolerance doses" associated with a) 5%
complications within 5 years of treatment, and b) 50% complications within 5 years of treatment, for uninterrupted schedules of 5 fractions per week (200 cGy each), illustrate the relative radiosensitivities of these tissues. For bone, the doses are a) 6000 cGy, and 10,000 cGy; for mouth, pharx, and esophageal tissues [soft tissue, presumably], a) 6000 cGy and b) 7500 cGy; and for bone marrow acute injury, a) 50, and b) 500 cGy. For bone marrow acute injury, the doses are a) 50, and b) 500 cGy; for mouth, pharx, and esophageal tissues [soft tissue, presumably], a) 6000 cGy and b) 7500 cGy; and for bone, a) 6000 cGy, and 10,000 cGy. The severity of the morbidity experienced by a therapeutic irradiation patient may be exaggerated with age (Toth, Martin and Fleming 1991).

Toth, Chambers, Fleming, Lemmon and Martin (1995) distinguish between mucositis, the result of chemotherapy, and stomatitis, defined as "when mucosal integrity has been lost due to local trauma, i.e. biting denture irritation or even infection".

Crook and Esche (1993) cite three articles to suggest that necrosis in general is more common with combined external radiation therapy and interstitial irradiation than with interstitial alone. Although the studies cited by Crook and Esche (1993) suggest

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44 The articles (Toth, Martin and Fleming 1990, and to some extent, 1995) offer clinimetric grading criteria for mucositis and for oral toxicity (dryness, burning, irritation, soreness, erythema) associated with therapeutic radiation. Sonis (1995) states in fact that at least 15 different schemes currently are being used to assess mucositis: some being subjective, others functionally based, and the remainder focusing on objective clinical findings.

Zlotolow, in his review of (Toth et al 1995) comments that studies about radiation-induced mucositis are subject to questionings on a number of clinical epidemiologic grounds including

1) lack of homogenous study populations,
2) lack of placebo controls or double-blindedness, and
3) a lack of examination or adequate consideration of potential confounding factors such as histopathology, staging, age, sex, and treatment modalities, which perhaps should be addressed with subset analyses (Zlotolow 1995).

Sonis (1996) also states that the lack of standardized mucositis scoring systems hinder standardized experiments. Cautionary comments analogous to those in this paragraph also would apply to future osteoradionecrosis grading systems studies.
that the presence of intersitial radiation can adversely impact osteoradionecrosis rates, their small numbers in combination with the multiple anatomical and case variables present would tend to limit the significance of their incidence data. Further, Withers et al (1995a) did not appear to consider the presence or absence of interstitial radiation as a significant variable affecting complication rates in their large multi-center study, and Yasumoto et al (1995) concluded that "among our patients with their primary lesion under control, the incidence of bone and or soft tissue complications was evenly distributed in the three treatment modality groups (implant alone, implant plus external radiation and external radiation alone)."  

Bernstein et al (1993) consider that there are four treatment factors of particular significance to therapeutic irradiation, the inter-related factors of: a) total dose; b) total tissue volume treated; c) length of irradiation; and d) fractionation (dose fraction size). Fractionation is a method of dividing of the total dose of external beam radiotherapy into a number of smaller doses in order to increase the differential effect of radiation of a tumor as compared with normal tissues (Henk 1985). Normal tissue tolerance in the head and neck is thought to decrease when larger volumes are irradiated with megavoltage irradiation. Withers et al (1995a) found a

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45 Crook and Esche (1993) cite Lefebre, Coche-dequeant, and Castelan (1990) as associating a 4% incidence of osteonecrosis with interstitial radiotherapy of oral tongue cancer. Eschwege (1985) is cited by Crook and Esche (1993) as observing 7 and 19% rates for osteoradionecrosis with implant alone, and combined implant and external radiation. Finally, Pierquin (1987) is cited as reporting that necroses were not found where only one source of interstitial radiation was close to the mandible, but 17% (6 of 35) treated with two sources became associated with necrosis, while 3 sources close to the mandible were associated with a rate of 27% necrosis (6 of 22).

46 Yasumoto et al (1995) also concluded, "Therefore these complications may not be the key factor when selecting an appropriate treatment modality to suit each patient's condition."

positive relationship between field size and mandibular necrosis and fracture, but not for complications in muscle or mucosa. Dose per fraction was also significant (Withers et al 1995a).

A first rationale for fractionation of delivery of absorbed dose delivery was to allow normal tissue to repair itself (Rubin and Doku 1976). A second rationale is to ensure interaction with cells while they are in radiosensitive stages of cell division (Bernstein et al 1993, Figure 4). Hyperfractionation {e.g. twice-daily doses of only 115 cGys (Peters 1993)} is an approach hoped by some to minimize tissue complications, but some hyperfractionated regimes have been discontinued due to associations with excessive osteoradionecrosis rates 48 (Niewald et al 1996). A recent comprehensive study of tonsil radiotherapy, fractionation and complication rates, Withers et al (1995a), was not able to reach definitive conclusions on many fractionation issues.

In summary, the oral complications of radiotherapy may include injuries to the salivary glands, oral mucosa, oral musculature, alveolar bone, periodontium, and to a lesser extent, teeth. Side-effects may include xerostomia, rampant dental caries, mucositis, taste loss, osteoradionecrosis, infection, dermatitis and trismus (NIH 1990, 3).

48 e.g., Niewald (1996) found a 22.9 % ORN rate in 52 patients treated with two daily fractions of 1200 cGy, 4 hours minimum apart, total 8280 cGy, vs. 8.6% ORN rate in 116 patients treated with conventional single doses of 2000 cGy, total 6000 to 7000 cGy. (p = 0.029 but dose could be a potential confounder.) The experience of Legros et al (1994) was different: an ORN rate of 23% in hyperfractionated treatment, and 44% in normal, among 39 patients. Withers et al (1995a), a 9 center study that evaluated 676 patients retrospectively, concluded that if there was any effect of twice daily treatment (as opposed to daily), the effect was slightly negative.
D. OSTEORADIONECROSIS PATHOGENESIS, DEFINITION, DIAGNOSIS, CLINICAL PRESENTATION, AND TREATMENT

In their widely recognized study of 536 cases of osteoradionecrosis, Marx and Johnson (1987) propose three pathophysiological origins for ORN, supporting this with a Figure 2 illustrating the incidence of ORN ascribed to these different etiologies:

a) "early (Type I) trauma-induced ORN related to concomitant surgical and radiation wounding"

(the curve appears to decline exponentially from an almost immediate peak of \( \geq 105 \) cases, terminating at 1.4 years),

b) "spontaneous necrosis related to higher levels of radiation tissue injury"

(the curve appears normal, rising from 0 cases at 0 years to a sharp peak of \( \geq 100 \) cases at 1 year, skewed with a short "tail" down to \( \geq 15 \) ORN at 2 years, and no cases at 3.1 years) and

c) "Late (Type II trauma-induced ORN related to trauma within hypovascular-hypocellular hypoxic tissue")\(^{50} \) \(^{51}\).

(an apparent broad peak rising sigmoidally from 0 cases at 1.4 years to \( \geq 28 \) cases at 5 - 5.5 years, then declining in a fashion that could be described either as linear, step-wise, or exponential, to \( \geq 10 \) cases per year incidence at 8 - 8.5 years, when illustrated follow-up stops.)

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\(^{49}\) The discussion of Marx and Johnson (1987, 384) confirms that their Figure 2 reports incidence, not prevalence.

\(^{50}\) Underlining mine. The hypovascularity and hypocellularity primarily results from the high dose irradiation.

\(^{51}\) Daum and Negus (1988) explain that a tooth extraction is an example of a traumatic incident that produces a requirement for protein synthesis dependent on both cellular elements (such as fibroblasts) and an intact vascular network capable of nutrient delivery and perfusion with oxygen (Maxymiw, Wood and Liu 1991). Thus, extraction could produce in hypoxic and hypocellular tissue, metabolic demands in excess of the physiological capacity.
Marx and Johnson (1987) found that 39% of their 209 cases of osteoradionecrosis were "spontaneous", while 61% were related to trauma. 84% of the trauma-induced cases were induced by the removal of a tooth. They also found that osteoradio-necrosis could be avoided if teeth were extracted 21 days prior to therapeutic irradiation. (Unfortunately, this is not practical in many cases due to tumor control considerations.)

Semba, Nealey and Hallmon (1994) cite Marx, Johnson and Kline (1985) as finding that 35% of osteoradionecrosis occurs "spontaneously in association with the high radiation dose rather than after secondary trauma", but cite Marunick and Leveque (1989) as suggesting that some of these "spontaneous cases" may be traceable to overlooked etiologies such as occlusal trauma associated with function or parafunction. (However, most authors do not mention occlusal trauma as a highly important ORN risk factor.)

Semba, Nealey and Hallmon (1994) also cite Marunick and Levesque (1989) as suggesting that these latter poorly recognized causes of trauma merit consideration, especially when radiation dosages exceed 6500 cGys.

Marx and Johnson (1987) found that severity correlated mainly with the "type of radiation delivered, the total dose, the dose fraction, and concomitant therapy..." "In general, severity increased with total dose (particularly doses greater than or equal to 7000 cGy), increased dose rates (fractions greater than or equal to 200 cGy per day), implant sources, neutron beam, concomitant surgery, concomitant chemotherapy, or hyperthermy". Many articles cited later support the concept of a dosage threshold for sharply increased ORN risk. Epstein et al (1987a) found a significant difference between the mean tumor dose of osteoradionecrosis patients and those who did not develop necrosis (5,906 cGys versus 5,397).
Marx and Johnson (1987) did not attempt to correlate tumor location with incidence or severity of osteoradionecrosis, but suggested that the location of osteoradionecrosis within the mandible is influenced by anatomic considerations. The mandible is considered particularly susceptible to ORN because its blood supply is relatively restricted (NIH 1990, 13).\footnote{Discussion of anatomical ORN predisposition will occur later.} Consistent with this, Legros et al (1984, transl.) suggest that irradiation of the carotid glomus could induce distal osteoradionecroses.

Marx and Johnson (1987) found a linear relationship over time with the ratio of tissue oxygenation outside the radiation port and inside the radiation port. This is noteworthy: if the ratio of tissue oxygenation of non-irradiated tissues, over the oxygenation level of irradiated tissues, increases with time, at some point so should the risk for necrosis of the irradiated tissues. (This point in time would depend on individual susceptibility to a particular radiation dose. Individual tissue characteristics, anatomical characteristics of the blood supply, condition of arteries, metabolic state, etc., may be relevant.)

Opinions vary about the risk of osteoradionecrosis over time (Semba, Nealey and Hallmon 1994). Epstein et al (1987a) reported onset of osteoradionecrosis from 2 days to 13 years after radiotherapy, with the greatest risk during the first 6 months. In contrast, Beumer, Harrison, Sanders and Kurrasch (1984) found the peak occurring during the first 12 months and then falling off gradually, and Marx and Johnson (1987) provided data supporting complex incidence relationships\footnote{described on page 62 of this thesis} in which notable ORN incidence persisted at 8.5 years post-radiotherapy. (This was consistent with their histologic evidence.)
suggesting that the microperfusion of the bone decreases over the years, and thus could predispose increasing risk for osteoradionecrosis.)

The latent period between radiation treatment and development of ORN is considered by Dambrain (1993)\textsuperscript{54} to be dependent on whether or not surgical interventions are performed before or after radiation, the radiation mode, and the dose prescribed.

It is interesting to note that Beumer, Curtis, and Harrison (1979a) and Legros et al (1984, \textit{transl.}) presaged in a number of respects the description of the pathophysiology of osteoradionecrosis of Marx and Johnson (1987). Legros et al (1984, \textit{transl.}) suggested that the destruction of osteoblasts and osteoclasts by irradiation and formation of an obliterative/destructive arteritis and decrease in a periosteal vascular contribution can contribute to the genesis of osteoradionecrosis. They also suggested that irradiation impairment of the salivary glands can cause xerostomia, a change in the intra oral pH towards the acidic, and a consequent modification of oral bacterial flora. Kluth, Jain, Stuchell and Frich (1988)\textsuperscript{55} suggest that changes in the pH and quantity of saliva following therapeutic irradiation may predispose exposure and infection of the irradiated bone.

Perrier and Moeller (1994, \textit{transl.}) describe their citation (Dambrain 1993) as characterizing post-radiation-osteitis (his term for osteoradionecrosis) by infection as well as ischemia, but others would term this state "infected osteoradionecrosis", "radio-osteomyelitis", "Septic Osteoradionecrosis Of The Mandible"\textsuperscript{56}, or "osteomyelitis of the

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\textsuperscript{54} citation in (Perrier and Moeller 1994)
\textsuperscript{55} citing three references, including Baker (1982)
\textsuperscript{56} "S.O.R.M." (Millett, Chapple, Hirschmann and Corrigan 1990)
irradiated mandible".

Millett, Chappie, Hirschmann and Corrigan (1990) present in

their Table 1, "Possible Schemes in the Development of S O R M " ,

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two pathways for its

pathogenesis:
1. Irradiation -> Decreased Salivation -> Increased Plaque Retention -> Gingival
Inflammation -> Periodontal Pocket Formation -> Suppuration -> S O R M .
2. Irradiation -> Atrophic Mucosa, which in the presence of trauma of potential
surgical or denture irritation cause, etc., -> Ulceration, -> Mandibular
Exposure, -> Introduction of Microorganisms [into bone] -> SORM.
Perrier and Moeller (1994, transl.) cite Gutenberg (1974) as characterizing osteomyelitis
of the irradiated mandible as having a variable rate of progression and ultimately being
capable of producing severe functional and cosmetic deformities, which, as previously
mentioned, can severely impact the patient's quality of life (NIH 1990).
Morton (1986) states that Regaud described osteoradionecrosis of the jaws in
1922, while Ewing termed this pathology "radiation osteitis" in 1926. Epstein et al
(1987a, 48) describes osteoradionecrosis as "necrosis of bone that occurs in association
with radiotherapy for cancer in the absence of recurrent or metatstatic disease. The
diagnosis of osteoradionecrosis is primarily based on clinical signs and symptoms of
ulceration or necrosis of the mucous membrane, with exposure of necrotic bone for more
than 3 months." This definition is typical of many in the literature, and the duration of 3
months is in agreement with the criterion described by Beumer, et al (1984), although
other durations occur in the literature. Carlson (1994) proposed as a "general working,

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Parulekar and Paonessa (1990), cited in Perrier and Moeller (1994, transl.).

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(Septic OsteoradionecRosis Of The Mandible)

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clinical definition of osteoradionecrosis...any exposed bone in a field of irradiation which has failed to yield for at least 6 months." Maxymiw, Wood and Liu (1991) cite (Marx 1984) as defining osteoradionecrosis as the presence of exposed bone for a minimum of 6 months. Semba, Nealey and Hallmon (1994) contrast the Epstein et al (1987a) recognition of osteoradionecrosis based primarily on three months or more of soft tissue ulceration or necrosis overlying the exposed necrotic bone with the Marx (1983) description of the clinical manifestation of osteoradionecrosis as "a persistent, chronically non-healing bone that neither produces extensive suppuration nor consistently breaking down in a septic course." Semba, Nealey, and Hallmon (1994) cite Balogh and Sutherland (1989) as stating that soft tissue ulceration exposing underlying bone is found in more than 90% of the cases of osteoradionecrosis.

Osteoradionecrotic lesions of the pelvis, the sternum, the clavicle and the head of the femur have been described (Perrier and Moeller 1994). Ecahvez, Tami, Kelly, and Swift (1992) describe cases of osteoradionecrosis of the hyoid bone as well as the clavicle. Sikand and Longridge (1991) state that osteoradionecrosis of the temporal bone may predispose the patient to an aggressive or chronic infectious process or cause direct tissue destruction and necrosis, either of which may damage nearby structures and even result in death.

Henk (1985) states that mandibular osteonecrosis normally starts on the alveolar margin and is accompanied by ulceration of the alveolar mucosa. "This gives a characteristic appearance of a flat ulcer with the brownish looking dead bone at its base. Pain is not normally a feature of osteoradionecrosis per se, and even a pathological fracture due to this cause may be completely painless. However the necrosis is often
complicated by secondary infection in which case there may be severe pain with trismus, fetor, and general ill health...[and]in the case of soft tissue necrosis, bone necrosis must be distinguished from tumor recurrence." However, these distinctions may not have great clinical relevance, and the NIH (1990) consensus statement simply reports the clinical association of pain with osteoradionecrosis. Herzog, Sader, Deppe and Zeilhofer (1995, transl.) also report in association with osteoradionecrosis general characterizations of intense pain, diminished appetite, fistula formation, sequestration, and pathological fractures in exceptional cases. Perrier and Moeller (1994, transl.) state that infection, trismus, spontaneous fractures, acute pain, paresthesia or anesthesia may accompany osseous tissue changes associated with osteoradionecrosis.

Henk (1985) cites Bragg (1970) as stating that osteoradionecrosis of the mandible was associated with open mucosal wounds in most cases. Henk (1985) further states that sometimes mucosal necrosis can precipitate bone necrosis, whereas the reverse may be true in other cases. Perrier and Moeller (1994, transl.)\textsuperscript{59} suggest that 90% of ORN cases present with necrosis of the soft tissues that expose the underlying affected bone, but that a small proportion of patients may have affected bone under a healthy mucous membrane. Morton (1986) cites Gowgiel (1960) as finding osteoradionecrosis occurring under intact gingivae. It was Gowgiel's contention that such osteoradionecrosis would require disruption of the gingival surface to become clinically evident -- perhaps occurring as a result of trauma related to teeth or dentures. Morton (1986) concludes, "it appears therefore, that whereas trauma is not directly responsible for ORN, it is in many cases

\textsuperscript{59} citing their reference (Balogh and Sutherland 1989)
responsible for making it clinically evident". This last point is important because many clinical definitions of osteoradionecrosis depend on exposure of bone, and the transient or long-term potential for bone necrosis hidden under intact mucosa may confound accurate diagnosis, and thus estimation of incidence or prevalence, at a particular point in time.

Semba, Nealey and Hallmon (1994) state "radiographic changes are generally delayed and do not reflect the total area involved because considerable changes in bone mineral content are required before radiographic detection." Epstein, Wong, et al (1992) found that radiography was demonstrably abnormal at the time of osteoradionecrosis diagnosis but remained abnormal even following positive improvements in that health state. This article, like Henk (1985), states that the diagnosis of osteoradionecrosis is based primarily upon clinical observation of soft tissue ulceration exposing underlined necrotic bone, possibly accompanied by pain, dysesthesia (altered, abnormal, possibly prolonged sensation to touch), fetor oris, dysgeusia (altered taste), and food impaction.

In contrast, Legros et al (1984, transl.) used as criteria for osteoradionecrosis the definition of Cachin and Vandenbrouck (their reference): "an osteolysis detectable by a radiographic examination and surfacing in the period following irradiation treatment for cervical facial carcinoma, without any evolution of a tumor in the bone for neighboring areas". They note however that the radiological signs which may relate to osteolysis (and rarely, sequestrae), may underestimate the extent of osteolysis found clinically.

60 Radiographs do not generally change until 30 to 60 % of calcium salts are lost in a sufficient volume to be visualized (Murray, Daly, and Zimmerman 1980)(Alexander 1976).
61 A sequestrum (plural, sequestrae) is a piece of necrotic bone separate from a larger mass of bone.
Radiological signs of ORN can include bony islands, a thickening of the periosteum, radiolucency, or sequestration (Perrier and Moeller 1994). The radiographic diagnostic criteria used in the 1988 Makonnen thesis, derived from Makonnen's reference Cupps (1975), were "increased radiographical thickness, mottled areas of osteolysis, sequestra, osteoporosis, or fracture. However, Makkonen also cites his reference (Dolezal et al 1982) as stating that in all cases after therapeutic irradiation the mandible undergoes an asymptomatonic osteoatrophy characterized by disruption of normal bony trabeculation and a slight cortical thickening and demineralization, and therefore suggests that slight cortical thickening of the bone alone is not a sufficient diagnostic criterion for osteoradionecrosis.

More modern technical aids now can assist ORN diagnosis. Herzog, Sader, Deppe and Zeilhofer (1995) state that the diagnosis of osteoradionecrosis is mainly through clinical findings, conventional radiography, computerized tomography, nuclear spin tomography, and S.P.E.C.T. (single-photon-emissions computer tomography).\(^{62}\)

Hermans (1996) observed in his computerized tomography cortical interruptions and loss of spongoasa trabeculation on the sides of the mandible where osteoradionecrosis was proven pathologically or by clinical follow-up.\(^{63}\) The authors conclude that bony abnormalities distant from the position of original tumor, for instance

\(^{62}\) No published magnetic resonance imaging diagnostic studies of oral osteoradionecrosis appear to exist.

\(^{63}\) These affected areas were mostly seen in the pre-molar and molar region of the body of the mandible (8 of 10 patients, including 2 patients with extension into the retromolar triangle, and 2 with extension into the mandibular angle). The remaining two of ten patients demonstrated osseous abnormalities consistent with osteoradionecrosis in the ramus of the mandible and its angle. Cortical destruction localized to the lingual side was observed in the two patients treated with iridium implantation. Three others demonstrated pathological fractures. Buccal cortical destruction was observed in two of the patients, and both buccal and lingual in three of the other five patients. Four actually showed abnormalities on the contralateral mandible.
the buccal surface or opposite side of the mandible, and possibly within an associated soft tissue thickening, should suggest the possibility of diagnosis of mandibular osteoradionecrosis.

Hutchison, Cullum, Langford, Jarritt and Harris (1990) found that osteoradionecrosis may be associated in experimental situations utilizing $^{99}\text{mTc}$-methylene diphosphamate radioactive tracings with paradoxically increased uptake of this substance. Hutchison, Cope, L. T. Richardson, and Harris (1990) found that osteoradionecrosis may be marked by decreased amounts of deoxygenated hemoglobin, as identified through near infrared spectroscopy.

Epstein et al (1992) indicate that Technetium ($^{99}\text{Tc}$-m-labelled diasphosphamate) can identify osseous pathology earlier than conventional radiographs because these scintillation scans reflect osteoblastic activity. Gallium citrate uptake is apparently more correlated with bone inflammation than osteoradionecrosis, and osteonecrosis is not necessarily associated with inflammation. Therefore, gallium scans are not good diagnostic indicators for osteoradionecrosis, although they may be good indicators of healing of Stage I osteoradionecroses following hyperbaric oxygen therapy (Epstein et al 1992).

**HYPERBARIC OXYGENATION; ORN TREATMENT/ DENTAL CARE OF EXISTING LESIONS**

This review is not exhaustive. The use of hyperbaric oxygen as a therapeutic or prophylactic measure is widely advocated (e.g. Friedman (1990, 147) and Myers and Marx (1990, 151-157), in NIH (1990)), but remains a matter of some controversy, as explained below. Note also should be made of concerns that hyperbaric oxygenation may
enhance the growth of existing tumors (e.g. Bradfield, Kinsella, Mader, Bridges, and Calhoun (1996) and other references in the section "2. ORAL SQUAMOUS CELL CARCINOMA LESIONS AND TREATMENT STRATEGIES", above.)

Brunton (1994) suggested that "prophylactic HBO [hyperbaric oxygen treatment] does not reverse the deleterious effects of radiation therapy, but rather alters the hypoxic, vascular, and cellular components to an environment more conducive to healing." The article most frequently cited to indicate the efficacy of hyperbaric oxygen in minimizing osteoradionecrosis is Marx, Johnson, and Kline (1985, "Prevention of Osteoradionecrosis: A Randomized Prospective Clinical Trial of Hyperbaric Oxygen versus Penicillin". Its abstract reads, "The results indicated, in a high risk population who required tooth removal in irradiated mandibles, that up-front HBO produced an incidence [in number of patients "osteoradionecrotized"] of ORN of 5.4% as compared with the antibiotic group of 29.9% (p = 0.005). Hyperbaric oxygen should be considered a prophylactic measure when post-irradiation dental care involving trauma to tissue is necessary." A prophylactic regime was proposed in which 20 preoperative hyperbaric oxygen sessions were employed prior to extractions during or after radiotherapy; 10 more would follow it in the cases selected. Costantino, Friedman and Steinberg (1995) stated that the "Marx protocol" effectively deals with ORN, while Hartmann, Almeling and Carl

in the two series of 37 patients undergoing the extraction of 135 or 156 teeth in mandibles irradiated above 6000 cGys. The "osteoradionecrotized" tooth extraction socket incidence dropped from 22.9% to 2.6%.

If this apparent strong efficacy is generalizable, then epidemiological data associated with papers such as Morton (1986) that were published without reference to hyperbaric oxygen could not be compared directly with those that do employ prophylactic HBO.

However, Marx, Johnson, and Kline (1985) has been criticized on methodological grounds including the fact that "This study was both prospective and randomized, but neither palcebo nor double-blind design was incorporated for several reasons... "(Marx, Johnson, and Kline 1985).
(1996) concluded that the "prophylactic use of hyperbaric oxygen has been shown to prevent the development of ORN after tooth removal", and that "Clinicians can be encouraged to use hyperbaric oxygenation for the treatment of osteoradionecrosis of the mandible."

Both Costantino, Friedman and Steinberg (1995) and Hartmann, Almeling and Carl (1996), however, are review articles rather than original research; Marx, Johnson and Kline (1985) remains the only "Randomized Prospective Clinical Trial". Sheps (1992, a formal technology assessment) and Zlotolow (1995) expressed reservations about the latter study's design, and thus its conclusions. Mounsey, et al (1993) admitted this doubt at the beginning of their paper, stating, "[HBO] has not been conclusively proven to be of benefit" but then concluded from their retrospective review that "HBO is of benefit in the management of ORN." The very recent pair of articles (Lambert, Intriere, and Eichstaedt 1997; Clayman 1997) are relevant; they share a common lead title, "Clinical Controversies In Oral And Maxillofacial Surgery", but represent protocols for tooth extractions in irradiated jaws with, and without, hyperbaric oxygen therapy. Lambert, Intriere, and Eichstaedt (1997) conducted a retrospective review of 256 men, of which 75 received HBO therapy. None of the HBO group followed up demonstrated ORN. Based on this, they concluded that even the selective approach to the use of hyperbaric oxygen advocated in Stevenson-Moore and Epstein (1993) may be less cost-effective and appropriate than the universal use of hyperbaric oxygen. In contrast, the companion article Clayman (1997, 278-279) provided a critique of some traditionally cited evidence for the efficacy of HBO therapy for treating existing ORN, then, using maintenance of
continuity of the mandible as an outcome of primary importance, questioned assumptions made when the universal use of HBO as ORN prophylaxis is advocated for patients at risk for ORN. The conclusion of Clayman (1997) was, "Thus, these data do not support the mandatory use of HBO before removing teeth in irradiated mandibles, particularly when one considers that in the most recent reports of ORN after dental extractions (refs.) the rate was only 2.1%.

This and subsequent sections of the thesis emphasize ORN prevention, rather than treatment of existing lesions, but a brief outline of treatment is appropriate.

"Management of osteoradionecrosis should be conservative when possible and radical when necessary" (Patel, Raybould, and Maruyama 1989). Conservative approaches include monitoring the lesion, removing loose bone sequestra, and hyperbaric oxygen, theoretically to shift the oxygenation balance back to viability or to assist coping with transient sources of irritation or repair. Radical measures include resection of part or all of the mandible, with potential loss of mandibular continuity and consequences on function.)

Galler, Epstein, Guze, Buckles and Stevenson-Moore (1992) advocate the potential use of hyperbaric oxygen to treat sites developing osteoradionecrosis subsequent to periodontal disease. Hyperbaric oxygen treatment could be considered cost-effective when compared to the effects and outcomes of radical debridement and reconstruction (Toth, Chambers, Fleming, Lemmon, and Martin 1995), but others express reservations.65

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65 e.g., previously stated concerns about the efficacy of hyperbaric oxygen therapy (Sheps 1992) and its (possibly theoretical) potential for enhancement of growth of persisting tumors (Bradfield, Kinsella et al 1996).
Regarding dental evaluation and care of existing osteoradionecrotic lesions, Beumer, Harrison, Sanders and Kurrasch (1984) state that "the most useful clinical predictor of the future clinical course of radiation bone necrosis was the [periodontal] nature of bone exposure at the time of initial evaluation".66 "...Equal to or possibly greater in importance as a predictor of clinical outcome is the oral home care compliance of the patient". Beumer, Harrison, Sanders and Kurrasch (1984) suggest that only a few of the 23 patients requiring mandibular resection varied from their non-resecting counterparts and to physical factors related to dosage or other therapeutic variables; most had poor oral hygiene and poor compliance with required cleansing procedures required to maintain the osteoradionecrosis bone exposure in a hygienic state and promote success of conservative therapeutic approaches. They further state that unless professional irrigation on a daily basis is available to substitute for inadequate patient home care, patient counseling and social support groups encouraging proper home care may be appropriate.

Herzog, Sader, Deppe and Zeilhofer (1995, transl.) advocate chronic

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66 Analyzing 53 ORN cases within the zone of attached gingiva and 30 extending beyond, they found that osteoradionecroses within the zone of attached gingiva were amenable to conservative treatment in 66% of cases; those outside in only 37% of the cases. Only 18.8% of bone necroses within the zone of attached gingiva progressed to require radical resection of the locally involved mandibular bone, while 43% involving an extension beyond the attached mucosa required mandibular resection (Beumer, Harrison, Sanders and Kurrasch 1984).

This article also provides anecdotal evidence that hyperbaric oxygen therapy is particularly useful in treating osteoradionecroses that initially extended beyond the muco—gingival junction. Hyperbaric oxygen therapy would seem to lessen tendencies towards infection and progression of necrosis in these patients and promote healing.

Beumer, Harrison, Sanders and Kurrasch (1984) provide the opinion that regardless of other factors, the greater the volume that is exposed to high dose irradiation, the less effective is conservative treatment of mandibular osteoradionecroses, possibly due to obliteration of the inferior alveolar artery. (their citation (Rohrer, Young and Fayos 1979)).
conservative treatment with irrigation, systemic antibiotics, local application of antiseptics, while the removal of free bone sequestra often can be supplemented by careful radical resection of the involved area, or and/or supplemented by hyperbaric oxygen therapy or ozone. Novel ORN treatments examined have included electrical charges (Mustoe and Porras-Reyes 1993), electromagnetic stimulation (Barak et al 1988) ultrasound (Harris 1992), and periosteal tibial transplants (Aitasalo et al 1995).

In summary, mandibular osteoradionecrosis follows partial vascular/microvascular obliteration, relative hypoxia, and cellular death. Although radiography may assist its diagnosis, most authors consider the diagnosis of ORN to be based primarily on clinical signs and symptoms of ulceration or necrosis of the mucous membrane, with exposure of necrotic bone for more than 3 months (Epstein et al 1987a, 48). Since ORN lesions can have severe consequences on quality of life and can be extremely refractory to treatment, the preferred health strategy is prevention rather than cure (NIH 1990). Prophylactic hyperbaric oxygenation is good in theory but some question its universal effectiveness. Conservative therapy usually has far fewer negative consequences than radical, but radical surgery sometimes is necessary.

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67 Ozone has a strong antibacterial and antifungal activity through the creation of free radicals: peroxide forms on tissue surfaces as the result of ozone and oxygen tends to diffuse into the tissues. This was first used for the treatment of a diabetic ulcer (Wolff 1982), cited in (Herzog, Sader, Deppe and Zeilhofer 1995).

Therapy for the osteoradionecrosis in (Herzog, Sader, Deppe and Zeilhofer 1995, transl.) was primarily surgery with simultaneous antibiotic therapy. However, treatment modalities such as hyperbaric oxygen therapy were applied in 7 patients, and ozone therapy in a further 9. The surgical interventions themselves were as follows, assuming accurate translation from the German: radical "box" resection, often of a quadrant, but always maintaining continuity around the lower border of the mandible, 31 instances; a lesser, partial resection in 29 cases; surgical curettage, 17 cases; ozone and curettage 9 cases; and hyperbaric oxygen therapy 7 cases. Herzog, Sader, Deppe and Zeilhofer (1995, transl.) state that if later surgical procedures are necessary, there should be systemic antibiotic coverage, if possible in conjunction with hyperbaric oxygen therapy.
E. ORN-PROPHYLACTIC DENTAL SCREENING STRATEGIES (STRESS: PERIODONTAL, ENDODONTIC, AND INFECTION STATUS)

Risk for osteoradionecrosis can be reduced by effective pre-irradiation-treatment oral assessment and interventions affecting ORN prognostic variables (NIH 1990).

This section will initiate discussion of the first three potential ORN prognostic variables: periodontal and endodontic pathology, and infection.

"Individuals undergoing cancer therapy may be at risk for a wide variety of oral problems that can significantly affect morbidity and mortality... As the aggressiveness of cancer therapy increases, comprehensive oral evaluation with clinical, radiographic, and adjunctive components before treatment is warranted" (Sonis, Woods, and White 1990).

"Potentially complicating oral disease should be identified and corrected as early as possible before commencement of anti-cancer therapy. Significant problems include poor oral hygiene, third-molar pathology, periapical pathology, periodontal disease, dental caries, defective restorations, ill fitting prostheses, orthodontic appliances, and any other potential sources of irritation."... "Dental foci may be potential sources of systemic infection and should be eliminated or ameliorated... "Sources of infection and irritation are important targets for early intervention. At the initial dental evaluation, all cancer patients should undergo thorough oral hygiene procedures including root planing, scaling, and curettage. These procedures are beneficial in reducing the incidence of complications by removing bacteria that can result in local and systemic infection"(NIH 1990, 4+).

The periodontal status of the dentition may be considered the most important dental consideration aside from acute infections during pre-radiotherapeutic assessment for extractions (Beumer, Curtis and Harrison 1979a). Cementum and periodontal ligament health and repair abilities are reduced, so even otherwise minor interventions such as curettage must be carefully undertaken. Periodontal infections in such sites seem associated with the development of osteoradionecrosis (Beumer, Curtis and Harrison

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68 Prevention-oriented protocols include those advocated in NIH (1990, multiple chapters), and Jansma, Vissink et al (1992). Lockhart (1986) and Barker, Barker and Gier (1994) are also highly relevant.
1979a) although proper oral hygiene may prevent the shift in microbiological homeostatic balance\(^69\) associated with the periodontal destruction and eventual osteoradionecrosis (Galler, Epstein, Guze, Buckles, and Stevenson-Moore 1992; Fattore and Bruno 1987).

Periodontal disease sites irradiated to a time dose factor > 10\(^9\) are at risk for osteoradionecrosis development (Epstein, Wong, and Stevenson-Moore 1987; Epstein, Rea, Wong, Spinelli, and Stevenson-Moore 1987). Galler, Epstein, Guze, Buckles, and Stevenson-Moore (1992), reporting on three cases osteoradionecrosis of the mandible that apparently arose from sites of periodontal disease activity, suggest that periodontal attachment loss or pocket formation, particularly on the buccal, may predispose the development of complications (including osteoradionecrosis), and further that one should recognize the possibility of special prognostic indicators (e.g. buccal pocketing?) for extraction/maintenance of the tooth in patients irradiated to high dose.

Beumer, Harrison, Sanders and Kurrasch (1984) make an observation that would tend to substantiate the stress that (Galler et al 1992) placed on the importance of buccal periodontal defects:

"[Osteoradionecrotic] bone exposures extending into the buccal vestibule, beyond the muco-gingival junction, had a very poor prognosis in our experience. Almost all such exposures progressed to intractable pain, widespread involvement of the mandibular body, and to eventual pathologic fracture and fistula formation. Conversely, many exposures extending lingually beyond the zone of attached gingiva healed or remained stable. This difference is probably due to the differences in the nature of the vasculature and the barriers to progression of the infection between the two sides of the mandible. At any rate, buccal extension of [osteoradionecrotic] bone exposure virtually indicated radical resection of the mandible, particularly as the exposure extended posteriorly into the region of the retromolar pad."\(^70\)

\(^69\) (a relative increase in Gram negative anaerobic bacteria, e.g. spirochetes)
\(^70\) Other potential prognostic variables reported by (Beumer et al 1984), including compliance with recommended home care, is reported in subsequent sections of the literature review.
Bras, DeJonge and Merkestyen (1990) also stated that they found that mandibular osteoradionecrosis arose from ischemia due to radiation-induced obliteration of the inferior alveolar artery, and suggested that potential revascularization of the area by branches of the facial artery is impaired because the irradiation produced vascular disease and periosteal damage, leading to a particular susceptibility of the buccal cortex of the premolar, molar and retromolar regions.

Horiot, Schraub, Bone, et al (1983) ascribed as the etiology of osteoradionecrosis, periodontal pathology in 4 cases, and diffuse dental caries in another 4 cases.\(^{71}\)

Beumer, Harrison, Sanders and Kurrasch (1984) comment that bone necroses occurring as a result of periodontal disease more often require radical measures for control of infection (36.8% and 45.4%, respectively). Increased severity and incidence of ORN seems associated with periodontal disease/infection and post-radiation extractions in the mandible (Murray et al 1980a;b;c; Beumer, Harrison, et al 1983).

Woods and Sonis (1989) cite Peterson (1986) as stating that "the degree of periodontal disease present prior to admission [of myelosuppressed bone marrow transplant patients] does not appear to correlate with the frequency of acute periodontal infection". Because of this weak correlation of periodontal infection with the presence of periodontal disease, Woods and Sonis (1989) suggested that screening for periodontal disease in these patients was of less proven cost-benefit worth than the elimination of sources of mechanical and other proven irritations. In contrast, Galler, Epstein, Guze, Buckles and Stevenson-Moore (1992) strongly advocate screening for periodontal disease in head and neck cancer patients; Toth, Martin and Fleming (1990) state that periodontally involved teeth with pockets deeper than 7 mm are at a significant risk for infection and thus should be extracted prior to radio- or chemo-therapy; and NIH (1990, 4)\(^{72}\) confirms the importance of periodontal disease.

\(^{71}\) 935 cancer cases were examined. Data from this article has limitations.
Sonis, Wood and White (1990) cite Greenberg et al (1982) as suggesting that infection around third molars, or pericoronitis) was a significant source of sepsis in patients undergoing treatment for acute leukemia, and advocate pre-radiotherapeutic extraction of diseased third molars. It is worth noting that the decision analysis of (Brickley et al 1995) finds that extraction (removal) of third molars in otherwise healthy patients is appropriate when there is a greater than 50% chance of recurrent pericoronitis. (Pericoronitis may be defined as infection around the crown of a third molar with partial soft tissue coverage.) Presumably this 50%-infection-risk decision threshold for tooth extraction would be reduced in the case of a debilitated radiotherapy patient who could suffer greater morbidity as a consequence of equivalent "insult" from infection.

Infection of endodontic origin of course would be an irritant predisposing osteoradionecrosis. Thus, teeth so involved must either be extracted prior to radiotherapy or endodontically treated with care recognizing the requirement to maintain an intact peri-apical periodontium (Cox 1976; Montgomery 1977; Beumer et al 1979b).

Seto et al (1985) found that 46 of 54 roots endodontically treated in 16 patients irradiated for head and neck cancer and followed up for a period ranging from 6 months to 54 months were maintained. Furthermore, no osteoradionecroses were seen in association with the endodontically treated teeth. They conclude that "endodontic therapy is a viable method of treating diseased teeth in patients irradiated for oral neoplasms".

Unlike Beumer et al (1979b) and Seto et al (1985), Toth, Martin and Fleming (1990) suggest that in the compromised host periapical infection can persist beyond root

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canal therapy and cause complications in the bone. Rather than endodontic treatment of posterior teeth, they advocate simple extraction. For anterior teeth they advocate consideration of conservative endodontology accompanied by a surgical apicoectomy and local debridement of the apically infected area. They suggest that delay of patient treatment is not a factor since primary closure, that should minimize complications, can be achieved.

Citing data from their earlier paper (Woods and Sonis 1989), and incorporating it into an idealized decision tree with simplified assumptions as to the effectiveness of dental interventions, Sonis, Woods, and White (1990) found that screening 100 patients and pre-treating and avoiding potential third molar complications that could follow cancer chemotherapy for acute leukemia, would result in potential savings of $245,000.73

Such pre-irradiation-treatment oral assessment is not fully evidence-based. "While preliminary studies strongly support the efficacy of pretreatment oral screening programs, a number of issues have yet to be addressed relative to patient-related and cost-related outcomes. Such studies should provide specific data regarding the focus of oral screening for specific malignancies, forms of cancer therapy and oral pathology..." (Sonis, Woods, and White 1990). Sonis, Woods, and White (1990) conclude that data should be collected on the effectiveness of intervention for periodontal disease, asymptomatic periapical disease, and defective restorations for patients about to undergo chemotherapy. They suggest linkage of this analysis with other patient variables such as age, diagnosis, and the projected cancer treatment plan.

73 [Peterson (1994) emphasized the need for cost-benefit analysis further to the study of Sonis, Woods and White (1990).]
F. OSTEORADIONECROSIS EPIDEMIOLOGY

"Much controversy regarding the incidence, cause, and management of this problem exists..."

"The considerable variance in reported results is the consequence of the author's interpretation of the clinical findings, the methods of treatment, and the period of time the patients are seen following treatment" (Fleming 1980, 161).

"The incidence of osteoradionecrosis varies from center to center where irradiation for oral cancer has been studied, the range quoted being from 5% to 22% in the literature published since 1974..." (Berger and Symington 1990).

This review of osteoradionecrosis epidemiology concentrates on ORN risk data appropriate for decision analysis probability nodes. Among other epidemiological data in the literature, probabilities for various severities of outcomes, e.g. categories of ORN, are reported occasionally. These are helpful in assisting the range of clinical experiences associated with ORN, and complement expert subjective assessments of the same in the Survey.

The International Classification Of Diseases Number Nine lists osteoradionecrosis as one of "Other Diseases Of The Jaw, Number 526.8" which also includes variations of anatomy acquired congenitally or during later growth and development ---cherubism, exostoses, fibrous dysplasia, latent bone cyst, tori, unilateral condylar hyperplasia or hypoplasia of the mandible. ICD-10, to be implemented in Canada in 1999, is almost equally vague, considering ORN under K10.2, "Inflammatory Diseases of the Jaws" (Rappaport 1996, 1997). Thus, separate aggregation of osteoradionecrosis statistics from hospital-, nationally-centered-, and world-wide- data bases utilizing the International

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Additional potentially relevant codes in ICD-9 include "990", 'Effects of Radiation, Unspecified", and the "E" adverse event code "E879.2", 'Radiological Procedure'" and possibly for ICD10, "Y78", 'Radiological devices associated with adverse incidents'.

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Classification Of Diseases system will be impractical until the classification system changes. Instead, the ORN statistics in this literature review will be gathered from the published literature.

Rates of ORN vary highly from center to center (Jansma et al 1992; Epstein, 1987), possibly reflecting differing medical/dental management strategies (Peri 1986). Management strategies for ORN can reflect not only variations in problem solving but factors such as the presence or absence of dental programs or hyperbaric oxygen facilities (Stevenson-Moore and Epstein 1993), other treatment variables (e.g. dose, fractionation, etc.), different case distributions, practitioner characteristics, and other sources of bias mentioned in the Discussion and Methodology sections of this thesis. Pooling of data from different centers must take into account and try to minimize inherent sources of bias or non-comparability of data.

Data reported in this sub-section include statistics on "Causes" of osteoradionecrosis. The term "Causes" is sometimes employed in the literature rather loosely, and in some cases the term "associations" would be more accurate.

Rankow and Weissman (1971) described a 10-30% risk for osteoradionecrosis of the mandible in patients irradiated to high dose, and a 10-20% possibility of death from osteoradionecrosis when it occurred. These numbers now would be considered high.

Daley, Drane and MacComb (1972) described "causes" of necrosis (listed in Table 3) for 71 incidents of osteoradionecrosis among 66 affected patients in a group of 304. Since it is entirely possible that Daley, Drane and MacComb (1972) used the term

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75 Among the conclusions of this thesis, such changes will be advocated for I.C.D. 11.
"spontaneous" in a different sense than used by Marx and Johnson (1987), and different technical and case characteristics are assumed to have existed in the 1966 through 1972 case era, these tabulations of "causes" of osteoradionecrosis should be considered with caution, as they should be during statistical interpretations of presumed causes of osteoradionecrosis. (To some extent, these comments apply to all studies.)

### TABLE 3. "CAUSES" OF OSTEORADIONECROSIS [AMONG 71 CASES]
(from Daley, Drane and MacComb (1972))

<table>
<thead>
<tr>
<th>CAUSES</th>
<th>NUMBER</th>
<th>RELATIVE %</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Spontaneous and/or Idiopathic</td>
<td>29</td>
<td>41%</td>
</tr>
<tr>
<td>2. Trauma other than Extractions</td>
<td>2</td>
<td>3%</td>
</tr>
<tr>
<td>3. Extractions before Irradiation</td>
<td>20</td>
<td>28%</td>
</tr>
<tr>
<td>4. Extractions after Irradiation</td>
<td>3</td>
<td>4%</td>
</tr>
<tr>
<td>5. Prosthesis Post Irradiation</td>
<td>5</td>
<td>7%</td>
</tr>
<tr>
<td>6. Jaw Surgery for Disease In Irradiated Area</td>
<td>12</td>
<td>17%</td>
</tr>
<tr>
<td></td>
<td>71</td>
<td>100%</td>
</tr>
</tbody>
</table>

Daley, Drane and MacComb (1972) further stated that surgery prior to or after radiation therapy was often a predisposing factor in the creation of bone necrosis.

Marx and Johnson (1987) found that 39% of their 209 cases of osteoradionecrosis were "spontaneous", while 61% were related to trauma. 84% of the trauma-induced cases were induced by the removal of a tooth, but Marx and Johnson found that

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76 To repeat some data previously reported in this thesis in association with the passage on ORN pathogenesis, Marx, Johnson and Kline (1985) consider that 35% of osteoradionecrosis occurs "spontaneously in association with the high radiation dose rather than after secondary trauma (although Marunick and Leveque (1989) suggested that some "spontaneous cases" may be traceable to "overlooked etiologies"). Marx and Johnson (1987) found that ORN severity correlated mainly with the "type of radiation delivered, the total dose, the dose fraction, and concomitant therapy..." In general, severity increased with total dose (particularly doses greater than or equal to 7000 rads), increased dose rates (fractions greater than or equal to 200 rads per day), implant sources, neutron beam, concomitant surgery, concomitant chemotherapy, or hyperthermy". Marx and Johnson (1987) did not attempt to correlate tumor location with incidence or severity of osteoradionecrosis, but suggested that the location of osteoradionecrosis within the mandible is influenced by anatomic considerations.
osteoradionecrosis could be avoided if teeth were extracted 21 days prior to therapeutic irradiation. (Unfortunately, this was, and is, not practical in many cases due to tumor control considerations.)

Fujita, et al (1996), a retrospective study of 148 patients with T1 and T2 carcinoma of the oral tongue treated between 1978 and 1989 with radiotherapy (mostly interstitial brachytherapy) alone, found that 11 of the 148 patients developed osteoradionecrosis. Of these patients, 2 (one T1, one T2) were treated with interstitial brachytherapy alone, while 9 (two T1 and seven T2) were treated with the combination of both external and internal radiation. "A significant increase in the incidence of bone complication was found at the total dose of 9000 cGys or more, and at the dose rate of 55 cGy per hour or higher. In combined treatment with external radiation and interstitial brachytherapy, the interstitial brachytherapy dose of 6000 cGy appears to be the threshold at which mandibular bone complication is induced when the external irradiation dose is 3000 cGys.) Significance levels were all $p \leq 0.04$ (Fujita 1996).

Another retrospective study, of 448 carcinomas of the oral tongue treated from 1972-1986 with brachytherapy, alone or in combination with neck dissection or in combination with external beam irradiation, and grading of tumors in proportions of 125 T1, 186 T2, 128 T3 and 9 T4, 78% N0, and 22% N+, found that the complications were most influenced by a total dose greater than 8000 cGy and a treated surface of greater than 12 cm squared (Pernot 1994).

Morton (1986) performed a retrospective survey of 200 patients treated with radiotherapy for squamous cell carcinoma of the oral cavity between 1973 and 1978. Half received prophylactic node neck node irradiation, 137 received megavoltage therapy
from a linear accelerator giving a tumor dose of 5500 cGy (rads) over a 21 day period, 62 patients received radium needle implants (mainly for tongue tumors) and a tumor dose of 5 to 7 thousand cGy over 7 days. Prophylactic neck irradiation, when present was 5000 cGy.

Morton (1986) found a male to female sex ratio in the tumors of 2.2:1 and in osteoradionecrosis, a 1.8:1. The average age of the patients with cancer receiving radiotherapy was 59.8 years, the average age of those developing osteoradionecrosis 59.3 years, and the average interval between radiotherapy and the development of osteoradionecrosis was an average (presumably, mean) of 19.4 months. (Range: 2 months to 5 years).

Morton (1986) proposes a classification scheme for osteoradionecrosis ("ORN") in which "minor" and "moderate" ORN heals spontaneously: the former over a period of "months", the latter over a range of 6 months to 12 months, without major pathology beyond the exposed bone and small or very small spontaneously shed sequestra. Thus, Morton's classifications "minor" and "moderate" correspond to Stage 1a in the Epstein (1987) scheme used in the survey for this thesis. In any case, Morton considers practically all other more serious types of osteoradionecrosis "major", whether simply involving large areas of exposed bone, large sequestra, fracture, or sinus formation, or potentially rapidly progressive. It is interesting to note that the subdivisions indistinctly drawn in the Morton scheme apparently are lost for small ORN lesions in the Epstein scheme, while the Epstein clinimetric scale is more accurate for "serious" ORN.

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77 largely on the basis of duration, which is not considered by respondents in the survey item 1040 to be very important as a criterion for evaluating ORN severity.
78 Another classification scheme (Stages "I", "II", "III", and "IIIr" ORN) is provided by Myers and Marx (1990) in association with a hyperbaric oxygen management protocol.
Of the 36 patients identified by Morton (1986) in the retrospective chart survey component of his article, 10.5% had Stage 1a ORN (about half "minor" and half "moderate"). 7.5% showed major ORN "i.e. other stages", including 3% who underwent hemimandibulectomy and thus presumably equivalent to an (Epstein 1987) Stage 3. This presumably left 4.5% as equivalent to Epstein Stage 2.

Epstein et al (1987a) observed that all 8 cases of osteoradionecrosis that he observed involved exposure of bone lasting longer than three months. 4 of 8 (50%) of Epstein's osteoradionecrosis cases were his Stage 1a, while Morton found $11 + 10 = 21$ of 36 patients (58%) in his initial retrospective analysis were minor and moderate ORN, equivalent to Epstein's Stage 1a.

The second component of the Morton (1986) article involved locating 72 patients 5 to 10 years after therapy and asking them to be examined or asking them to fill in a questionnaire returned via the mail. 14 of these 72 (19.4%) were charted previously as having osteoradionecrosis. An additional three were identified upon this follow-up examination or survey. (In total, 23.6% of all patients in the group followed up experienced ORN at one time or another.)

Of the 72 patients located for the second analysis, Morton found that 6 of the 20 patients dentate at radiation developed osteoradionecrosis, whereas 11 of the 52 edentulous patients at radiation developed ORN. This difference in ORN rates (30% versus 21%) for dentulous:edentulous was not found by Morton to be significant. He did however find a highly significant association of site of tumor and incidence of ORN: floor of mouth and alveolar tumors had a significantly higher incidence of ORN than
tumors in other locations. Among these, there was increased incidence of ORN with T-stage tumor size. Among osteoradionecroses associated with treatments of floor of mouth tumors, Morton thought that denture wearing in this group may have contributed to osteoradionecroses in 5 cases. Morton found that 70% of the osteoradionecroses persisting 5 to 10 years were associated with floor of the mouth tumors, and of these 8 representing the 70%, six, i.e. \( p \) of the 70%, = 53%, appeared to be caused by dental extractions; two, i.e. \( q \) of the 70% = 18%, appeared to be caused by dental sepsis.

Epstein et al (1987b) found that ORN caused pathologic fracture of the mandible in 23% of cases, progressive necrosis in 19%, and resolution only in 15% of cases.79

Tables 4., 5., 6., and 7. below are modified after Tables I., III., IV., and V. of Morton (1986): "I. Results of Published ORN Incidence Studies; III. Tumor Sites and Incidence [Rate] of ORN; IV. Tumor Stage And Incidence Of ORN; V. Treatment And Incidence of ORN."80

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1. Nodal involvement:
   Morton (1986), none;
   Epstein et al (1987a) perhaps approaching 50%:
   The Epstein (1987a) study included 28% WHO Stage IV (which may contain a few cases without nodal involvement, i.e. \( T_4N_0 \) or metastatic carcinomas without apparent nodal involvement; however a substantial portion of these Stage IV carcinomas would be presumed to involve nodes, as might be 0.7% involved with metastatic cancer and some of the 6.85% cases incapable of exact description may involve nodes. Epstein et al (1987a) also includes Hodgkin's Disease 13%, which is characterized by nodal involvement. In conclusion, it may be presumed that as many as 48% of the cases analyzed in Epstein et al's study involves nodes, so perhaps were at a more advanced stage than in Morton (1986).

2. Irradiation Type:
   Morton (1986): Approximately one third of the Morton patients received interstitial radiotherapy with a radium needle implant, in addition to megavoltage therapy from a linear accelerator.
   Epstein et al (1987a): In contrast only about 9% of the patients in the Epstein study received implants and external irradiation. The Epstein study does not characterize doses for the external radiotherapy directly, rather, it utilizes a product of time, dose and fractionation, so dose comparisons are hard to make. However, no patients in the Epstein study apparently received the 5000 rad prophylactic neck irradiation dose delivered to 50% in the Morton study. This may account for the higher overall rate of ORN of 18.1% found in the Morton study after slightly longer average follow-up than Epstein.

80 Another table that could be developed would be one on Gross Dose And Incidence Of ORN.
### TABLE 4. RESULTS OF PUBLISHED ORN INCIDENCE STUDIES

Table Format and First 11 Rows after Morton (1986) Table I "The Results of Published ORN Incidence Studies"

<table>
<thead>
<tr>
<th>YEAR</th>
<th>AUTHORS</th>
<th>SITE*</th>
<th>DOSE (cGy)</th>
<th># PATIENTS</th>
<th>ORN</th>
<th>%</th>
<th>YEARS</th>
</tr>
</thead>
<tbody>
<tr>
<td>1938</td>
<td>Watson &amp; Scarborough</td>
<td>1,2,4</td>
<td>1,2,4</td>
<td>1819</td>
<td>235</td>
<td>12.9</td>
<td>1930-1937</td>
</tr>
<tr>
<td>1958</td>
<td>Meyer</td>
<td>1,4</td>
<td>4,000 - 18,000</td>
<td>491</td>
<td>26</td>
<td>5.3</td>
<td>1940-</td>
</tr>
<tr>
<td>1962</td>
<td>MacComb</td>
<td>1</td>
<td>1</td>
<td>251</td>
<td>93</td>
<td>37.0</td>
<td>1952-1959</td>
</tr>
<tr>
<td>1966</td>
<td>Grant &amp; Fletcher</td>
<td>2</td>
<td>6,000 - 13,000</td>
<td>176</td>
<td>66</td>
<td>37.5</td>
<td>1954-1962</td>
</tr>
<tr>
<td>1971</td>
<td>Rankow &amp; Weissman</td>
<td>1,2</td>
<td>5,000+</td>
<td>176</td>
<td>12</td>
<td>6.8</td>
<td>1965-1968</td>
</tr>
<tr>
<td>1972</td>
<td>Beumer et al</td>
<td>1,2</td>
<td>5,000-7,000</td>
<td>278</td>
<td>10</td>
<td>3.6</td>
<td>1961-1969</td>
</tr>
<tr>
<td>1972</td>
<td>Daley et al</td>
<td>1,2</td>
<td>5,000-7,000</td>
<td>304</td>
<td>66</td>
<td>21.7</td>
<td>1966-1971</td>
</tr>
<tr>
<td>1976</td>
<td>Bedwinek et al</td>
<td>1,2</td>
<td>5,000-7,000</td>
<td>381</td>
<td>54</td>
<td>14.2</td>
<td>1966-1971</td>
</tr>
<tr>
<td>1980</td>
<td>Murray et al</td>
<td>1,2</td>
<td>2,000-8,000</td>
<td>404</td>
<td>77</td>
<td>19.0</td>
<td>1971-1975</td>
</tr>
<tr>
<td>1981</td>
<td>Morrish</td>
<td>1,2</td>
<td>5,000-7,500</td>
<td>100</td>
<td>22</td>
<td>22.0</td>
<td>1971-1977</td>
</tr>
<tr>
<td>1983</td>
<td>Coffin</td>
<td>1,2,3</td>
<td>2853</td>
<td>22</td>
<td></td>
<td></td>
<td>1970-1981</td>
</tr>
</tbody>
</table>

*Sites: 1 = Intra-oral 2 = Pharynx and Tonsil 3 = Salivary Gland 4 = Lip

### TABLE 5. TUMOR SITES AND INCIDENCE [RATE] OF ORN

Modification of Morton (1986) Table III "The Incidence of ORN at Different Tumor Sites"

<table>
<thead>
<tr>
<th>SITE</th>
<th>TOTAL</th>
<th>ORN INCIDENCE</th>
<th>ORN INC. RATE (%)</th>
<th>SITE RELATIVE PROPORTION (%)</th>
<th>SITE RELATIVE PROPORTION (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tongue</td>
<td>70</td>
<td>5</td>
<td>7.1</td>
<td>14</td>
<td>0</td>
</tr>
<tr>
<td>Floor of Mouth</td>
<td>56</td>
<td>17</td>
<td>30.3</td>
<td>47</td>
<td>37.5</td>
</tr>
<tr>
<td>Alveolus</td>
<td>32</td>
<td>8</td>
<td>25</td>
<td>22</td>
<td>37.5</td>
</tr>
<tr>
<td>Buccal Mucosa</td>
<td>30</td>
<td>5</td>
<td>16.7</td>
<td>14</td>
<td>0</td>
</tr>
<tr>
<td>Other</td>
<td>11</td>
<td>1</td>
<td>9.1</td>
<td>3</td>
<td>25</td>
</tr>
<tr>
<td>Total</td>
<td>199</td>
<td>36</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

81 The Coffin (1983) definition of osteoradionecrosis --so severe as to require surgical resection--invalidates comparisons between this paper and other papers. If Bedwineck (1976) had used this as his definition, his reported rate would have been 2.8%, about one fifth that reported.
TABLE 6. TUMOR STAGE AND INCIDENCE OF ORN
Modification of Morton (1986) Table IV "Tumor Stage and Incidence of ORN"

<table>
<thead>
<tr>
<th>STAGE</th>
<th>TOTAL (Morton 1986)</th>
<th>ORN (Morton 1986)</th>
<th>PERCENT (Morton 1986)</th>
</tr>
</thead>
<tbody>
<tr>
<td>T1</td>
<td>54</td>
<td>7</td>
<td>12.96</td>
</tr>
<tr>
<td>T2</td>
<td>121</td>
<td>25</td>
<td>20.66</td>
</tr>
<tr>
<td>T3</td>
<td>24</td>
<td>4</td>
<td>16.66</td>
</tr>
<tr>
<td>Total</td>
<td>199</td>
<td>36</td>
<td></td>
</tr>
</tbody>
</table>

TABLE 7. TREATMENT AND INCIDENCE OF ORN
Modification of Morton (1986) Table V "Treatment and Incidence of ORN"

<table>
<thead>
<tr>
<th>TREATMENT</th>
<th>TOTAL</th>
<th>ORN</th>
<th>PERCENT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Megavoltage</td>
<td>70</td>
<td>17</td>
<td>24.3</td>
</tr>
<tr>
<td>Megavoltage + Neck</td>
<td>67</td>
<td>18</td>
<td>26.9</td>
</tr>
<tr>
<td>XRT</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Implant</td>
<td>30</td>
<td>1</td>
<td>3.3</td>
</tr>
<tr>
<td>Implant + Neck XRT</td>
<td>32</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>TOTAL</td>
<td>199</td>
<td>36</td>
<td></td>
</tr>
</tbody>
</table>

Referring to Table 5, one can compare the percentage of ORN originating from different treatments of different tumor sites. The two Epstein et al (1987a) lower alveolus and one retromolar trigone cases have been combined in the assumption that they would have been both identified as of alveolus origin in the Morton classification.

Withers, et al (1995) is a potentially important paper that attempts to isolate statistically independent risk factors for osteoradionecrosis and estimate risk hazards. It analyzed "grades 3 and 4" late normal tissue complications of radiation therapy, for carcinoma of the tonsil only. As defined in Withers, et al (1995), bone morbidity scoring of Grade 3 reflected "bone severe pain or tenderness, self limited bone exposure", and Grade 4, "necrosis, spontaneous fracture". Thus, the Withers, et al (1995) criteria for
Grade 3 may approximate the Stage 1a of Epstein (1987b) and the combined minor and moderate ORN classifications of Morton (1986). Grade 4 criteria in Withers, et al (1995) may approximate the Morton (1986) "major" osteoradionecrosis classification, and the stage II and III of the Epstein (1987b) classification of osteoradionecrosis. For the sake of parallelism with Morton (1986) and standardization, the term "major" will be employed as a substitute for Withers et al (1995) Grades 3 and 4 complications, although Withers, et al prefer the descriptor "severe".

Stages 2 and 3 of Epstein (1987) would reflect chronic conditions whereas Stage 1 would reflect resolved conditions. In this sense, Epstein reflects the end-state of the pathology, as opposed to a cross-sectional analysis that may be referred to in the other two papers. This again makes assumptions of equivalence qualified, but this simplification could be accepted as a rule.

The rationale of Withers, et al (1995) for not documenting Grades 1 and 2 complications is worth noting. Recognizing a potential for reporting bias, he states "Grades 3 and 4 complications are unlikely to escape documentation, but accurate retrospective assessment of less severe complications from patient records is not feasible because such end points are subjective, and furthermore, may not be recorded routinely because they are sequelae that are routinely anticipated".

This retrospective analysis of 676 patients treated with a spectrum of fractionation regimens between 1976 and 1985 found that dose per fraction was a significant factor for both bone and muscle complications (estimated alpha/beta values of 85 cGy and 310 cGy, respectively). Total dose was also a factor for all three types of complications: mandible,
muscle, oral mucosa. Withers et al (1995) found that the field size was a significant factor for rates of bone complications, but not for soft tissue complications. Only 50% of the mandibular complications occurred within 4 years of treatment.

Withers, et al (1995a) states that the "actuarial incidence of major bone complications was 12.5% after 8 years, and refers to a table describing the "temporal (actuarial) incidence of complications in bone" as being at 4 years 0.055, and at 8 years 0.099. It further states that the absolute incidence of major bone complications was 32 in a population of 676 patients, an apparent incidence rate of 32/676 = 4.7%.

A comparison of the statistically complex analysis of Withers, et al (1995a, b) with Marx and Johnson (1987) is appropriate, since the general theory of pathophysiology of ORN brought to maturity in Marx and Johnson (1987) is generally accepted and their analysis of 536 ORN incidents highly regarded. Withers, et al (1995 a; 1995b) use Cox's Proportional Hazards multivariate regression analysis to determine factors contributing to complication rates. The Cox Proportional Hazards Model includes an assumption that the effect of the study factors on the hazard rate (e.g. for late bone complications such as osteoradionecrosis) does not change over time (Last, 1988). The use of the Cox Proportional Hazards Model, therefore, may not entirely be appropriate, given the Marx and Johnson (1987) data on osteoradionecrosis incidence.

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82 also discussed in the section of the literature search section on ORN pathogenesis and in footnotes early in this section
83 is multiplicative and
84 Consider the graphed curve that would result from summing the incidence curves illustrated in Marx and Johnson (1987) Figure 2, p. 381. Describing the resultant curve as an exponential decline, as one would assume would result if constant hazard applied, would be only a very crude approximation for the first three years and would ignore the apparent broad peak in ORN incidence (= 25 - 28/yr.) at 4 - 6 years.

{BACKGROUND (repeated from ORN pathogenesis literature review section)}
Nevertheless, the results of model fitting of Withers, et al (1995a, 565) provides data of a form highly appropriate for a decision analysis on ORN following treatment of cancer of the tonsil. Their Table 3, "Risk Factors for Late Complications", reproduced as Table 8 in my thesis, provides introductory or better data for relative risk hazards for changes in the total dose, the fractionation, the T stage, the field size, the wedge, the delivery of radiotherapy twice or three times a day, and the ratio alpha/beta⁸⁵.

**TABLE 8. "RISK FACTORS FOR LATE COMPLICATIONS: RESULTS OF MODEL FITTING"**

{Reproduces Table 3 of same name, Withers, et al (1995a)}

<table>
<thead>
<tr>
<th>VARIABLES</th>
<th>MUCOSAL</th>
<th>MUSCLE</th>
<th>BONE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total dose = nd</td>
<td>RH = 4.07 (p=0.001)</td>
<td>RH = 1.77 (p=0.01)</td>
<td>RH = 1.26 (p=0.20)</td>
</tr>
<tr>
<td>(α) (per 1000 cGy)</td>
<td>RH = 0.94 (p = 0.34)</td>
<td>RH = 1.20 (p = 0.01)</td>
<td>RH = 1.32 (p = 0.001)</td>
</tr>
<tr>
<td>nd² (β) per 1000cGy²</td>
<td>RH = 0.35 (p = 0.001)</td>
<td>RH = 0.79 (p = 0.52)</td>
<td>RH = 0.85 (p = 0.60)</td>
</tr>
<tr>
<td>Time (per 10 days)</td>
<td>Weak trend (p = 0.78)</td>
<td>Weak trend (p = 0.33)</td>
<td>(p = 0.39)</td>
</tr>
<tr>
<td>T-stage*</td>
<td>T4 &gt; T3 &gt; T2 &gt; T1</td>
<td>T4 &gt; T3 &gt; T2 &gt; T1</td>
<td>T4 &gt; T1 &gt; T2 &gt; T3</td>
</tr>
<tr>
<td>Field Size (per 10 cm²)</td>
<td>RH = 2.13, 1.87, 1.37, 1.00</td>
<td>RH = 3.30, 2.84, 1.41, 1.00</td>
<td>RH = 1.51, 0.51, 0.66, 1.00</td>
</tr>
<tr>
<td>Wedge†</td>
<td>RH = 0.98 (p = 0.80)</td>
<td>RH = 0.93 (p = 0.46)</td>
<td>RH = 1.15 (p = 0.02)</td>
</tr>
<tr>
<td>BID/TID</td>
<td>RH = 1.51 (p = 0.56)</td>
<td>RH = 0.59 (p = 0.50)</td>
<td>RH = 1.31 (p = 0.61)</td>
</tr>
<tr>
<td>α/β‡</td>
<td>RH = 1.38 (p = 0.56)</td>
<td>RH = 1.56 (p = 0.48)</td>
<td>RH = 1.21 (p = 0.77)</td>
</tr>
<tr>
<td>95% CI for α/β</td>
<td>(-∞, - 5.2); (20.8, ∞)</td>
<td>(0.7, 16.9)</td>
<td>(-0.48, 2.40)</td>
</tr>
</tbody>
</table>

**KEY:** next page

Marx and Johnson (1987) Figure 2 illustrates 536 ORN incidents* over time. In it, three curves illustrate ORN incidence ascribed to different etiologies: a) "early (Type I) trauma-induced ORN related to concomitant surgical and radiation wounding" (the curve apparently declines exponentially from a peak of 105, terminating at 1.4 years), b) "spontaneous necrosis related to higher levels of radiation tissue injury" (an apparent normal distribution curve rising from 0 cases at 0 years to a sharp peak of 100 cases at 1 year, skewed with a short "tail" down to 15 ORN at 2 years and no cases at 3.1 years) and c) "Late (Type II trauma-induced ORN related to trauma within hypovascular-hypocellular hypoxic tissue" (an apparent broad peak rising sigmoidally from 0 cases at 1.4 years to 28 cases at 5 - 5.5 years, then declining in a fashion that could be described either as linear, stepwise, or exponential, to 10 cases incidence at 8 - 8.5 years, when follow-up stops.) *Marx and Johnston's p.384 discussion confirms that their Figure 2 reports incidence, not prevalence.

Withers et al (1995) suggests through its Figure 1 Part C on page 566 that the proportions of bone experiencing major complications may be fitted approximately by a linear relationship of the proportion equaling 0.013 times the number of years. This linear relationship between proportion of complications and time would seem to be at variance with the data supplied in Marx and Johnson (1987).

(Alpha and beta are discussed in the Radiation Therapy Subsection)

⁸⁵ For further information, please see table footnotes, Withers et al (1995a, 565, etc.) &Withers et al (1995b, 553, 556, etc.)
KEY:
* Include T4, T3, T2, T1.
† No wedge = 0; all wedge = 1.
‡ RH denotes relative hazard for a unit change in the factor: values greater than 1 indicate increased hazard of a complication for increase in the factor.
§ Only once-a-day = 0, some twice-or thrice-a-day = 1.
# Negative values for ot/p reflect a p value close to zero.

BID = twice per day; TID = thrice per day; CI = confidence interval.

(Note: These data follow the irradiation of a single site, the tonsil.)

Table 9 reproduces Withers, et al (1995b) Table 4, "Results of multivariate analysis (Cox model), as these apply to the linear quadratic equation provided.

\[
\alpha \sum_{i=1}^{M} n_{i} d_{i} + \beta \sum_{i=1}^{M} n_{i} d_{i}^{2} + \gamma T
\]

where
- \( n_{i} = \) number of fractions in the \( i \)th series,
- \( d_{i} = \) dose per fraction in the \( i \)th series,
- \( M = \) the number of series,
- \( T = \) overall treatment time in days, and
- \( \gamma = \) is a coefficient for tumor growth.

**TABLE 9: "RESULTS OF MULTIVARIATE ANALYSIS (COX MODEL)"
(Reproduction of part of Table 4 of same name, Withers, et al (1995b))**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Relative Hazard</th>
<th>95% CI</th>
<th>p-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>N-stage (+ or -)</td>
<td>1.43</td>
<td>(1.06, 1.91)</td>
<td>0.016</td>
</tr>
<tr>
<td>nd (total dose) (per 1000 cGy)</td>
<td>0.62</td>
<td>(0.50, 0.77)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Treatment Duration (per 10 days)</td>
<td>1.31</td>
<td>(1.14, 1.51)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Shibuya et al (1993) performed a retrospective analysis of 370 patients in Tokyo (231 males and 139 females, average age 55 years) with Stage I \((T_{1}N_{0}M_{0})\) or Stage II \((T_{2}N_{0}M_{0})\) squamous cell carcinoma of the tongue. These were treated between 1966 and 1988 with interstitial irradiation alone or in combination with external radiation\(^{88}\).

\(^{87}\) Further details provided on p. 556.
\(^{88}\) Doses prescribed were as follows: for many "linear" sources, 7000 cGy for the entire period, and the doses for \(^{222}\)Rn and \(^{198}\)Au\{gold\} were 9500 cGys and 8500 cGys, respectively. Dose rates for the
Follow-up ranged from 2 years to 24, and no cases were lost to follow up; rather all cases were followed to death or until December 1990. Major goals of the study were to compare outcomes of local control neck control complication rates and occurrence rates of second primary cancers, and to some extent the associated control measures. Survival analysis utilized the actuarial method and Chi square test, and in sub-group analysis, Fisher's exact test for evaluation of differences.

Mandibular complications were defined as follows: Grade 0, no change; Grade I, transient bone exposure which disappears spontaneously; Grade II, bone necrosis healed by conservative treatment; Grade III, severe bone necrosis necessitating operation. These Grades I, II and III generally correspond to the Morton (1986) classifications for minor, moderate and major osteoradionecroses, and Grades I and II can be combined into Epstein Grade 1a while Grade III can be equated to Epstein 1b, 2 and 3 (Morton, 1986 "major").

Although the authors state that they are reporting on 370 tongue cancer patients (90 Stage I cases, 196 Stage IIa cases, and 84 Stage IIb cases), they report only on 291 patients during tabulation of complication rates. Also, while important information sorted by soft tissue and mandibular grade of complication is reported in their "Table 4," the discussion in the text related to some other subgroups not described fully in tabular

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radium needle were 40-45cGys per hour; for iridium, 35-75 cGy per hour. They did not reduce the total brachytherapeutic dose even if there was simultaneous treatment by external irradiation [external 60Co or 4-MV x-ray via unilateral portals in doses from 2000 cGys to 4000 cGys (average: 2700 cGys) in fractions of 250 cGys, 4 fractions per week.] In addition, 21 patients were also treated by chemotherapy with bleomycin or 5-fluoro-uracil. Brachytherapy doses were calculated according to the "Patterson Parker Rule" and a computer system was used for dosimetry from 1980 onwards. Mandibular protective spacers/guards were utilized from 1987 onwards.
form, combining complication incidences/rates for both soft and hard tissue complications. These make elucidation of relationships for osteoradionecrosis among subgroups treated with brachytherapy alone or in combination with external irradiation, etc., quite problematic. Thus, even where Shibuya et al (1993) state a significant relationship for complication rates of soft and hard tissue combined, they will be reported for our purposes (of analysis of osteoradionecrosis prognosis) as merely suggestive.

Shibuya et al (1993) noted that the incidence rate of combined hard and soft tissue severe (Grade 2 and 3) complications between T1 and T2b lesions given brachytherapy alone was 9.2% and 24.4% respectively, a difference almost significant at p < 0.062. Patients externally irradiated had an incidence of severe Grade 2 and 3 complications of 17.4%, while the incidence in those given brachytherapy alone was 14.5% (a difference significant @ p< 0.011). Iridium irradiation approximately doubled the incidence rate of complications (to 52%, a difference significant @ p<0.004) in comparison with that produced by other sources (radon seed, gold, radium needle) (Shibuya, et al 1993).

The prophylactic cervical irradiation of the head and neck cancer patient sometimes employed following brachytherapy was discontinued in 1974. This, plus the introduction of strict dosimetry via computer in 1980, and the introduction of the spacer during brachytherapy in 1987, seemed to reduce overall incidence rates. In the 31 patients in which all three of these innovations were utilized, only one Grade 1 "bone exposures" (3%, 1/31) and five Grade 1 local soft tissue ulcers (16%, 5/31) occurred during the minimum follow-up period of 2 years. [The lone bone exposure was simultaneous with an apparently separate tissue ulcer.]
38% of the cases experienced complications, e.g. small erosive ulcerations, or minimal bone exposure. Among these 110 patients representing 38% (110/291), no significant differences in incidence rates were seen in soft tissue ulcers and bone exposures compared across stages of tumor (p = 0.5). Complications were observed to occur from 1 month to 9 years (116 months) following the start of treatment. 95% of mucosal complications and 49% of bone complications occurred within 18 months. Bone exposures occurred between 2 and 9 years after the start of treatment (average = 32 months). However, the 31 patients whose treatment included both the modern techniques of the use of a spacer and computer dosimetry experienced only 1 minor (Shibuya Grade 1) bone exposure, i.e. 1/31 = 3%, and 5 minor (Grade 1) local ulcers at a rate of 16%, during the first two years (Shibuya, et al 1993).

Further data, much taken from Table 4 of Shibuya et al (1993), is tabulated in "Table 10. Some Osteoradionecrosis Case Data, Shibuya et al (1993) Study ".

| Grade 0: 242 No mandibular complications (but 181 demonstrated soft tissue ulceration); |
| Grade 1: 20 mandibular complications (11 in combination with soft tissue ulceration); |
| Grade 2: 20 mandibular complications (8 in combination with soft tissue ulceration); |
| Grade 3: 9 mandibular complications (1 in combination with soft tissue ulceration). |

Most data derived from Table 4 of (Shibuya et al 1993) [Note: Soft tissue ulceration in the following is not the bone exposure included in the definition of "mandibular complications"]

| Grade 0: 242 No mandibular complications (but 181 demonstrated soft tissue ulceration); |
| Grade 1: 20 mandibular complications (11 in combination with soft tissue ulceration); |
| Grade 2: 20 mandibular complications (8 in combination with soft tissue ulceration); |
| Grade 3: 9 mandibular complications (1 in combination with soft tissue ulceration). |
Of the 10% of cases for which simultaneous osseous and soft tissue complications were reported, 55% were Grade I; 40% were Grade II; 5% were Grade III.

49% (24/49) of the osseous complications occurred within 18 months.

17% (49/291) of patients experienced osteoradionecrosis; in 41% (20/49) of these, that is 7% (20/291) of the total, soft tissue ulceration accompanied ORN.

Mucosal ulcerations were present in the majority of low grade 0 and 1 osteoradionecrosis, but a minority of the more severe osteoradionecroses.

Description of the Murray et al (1980a; 1980c) articles will be prefaced with some background. Murray et al (1980a) states that Nichols (1962) reported a 35% osteoradionecrosis rate in mandibles that had undergone total tooth extractions within the irradiated volume, in the understanding that such extractions were appropriate to reduce the rate of ORN. Murray further describes Daley and Drane as starting a 1966 study eventually finding that a 24.5% osteoradionecrosis rate could be the result of a different program in which only the poor dentitions were extracted, fair dentitions were extracted only in the high dose irradiation volume, and good dentitions were preserved in the irradiated field with a fluoride gel treatment regime. This led to the adoption of a formal dental service at the M.D. Anderson Hospital in 1969. Murray conducted two studies [reported together in Murray et al (1980a; 1980c)] comparing the M.D. Anderson (U. Texas) Cancer Center patient base experience between 1966 and 1969 with that between 1971 and 1975. The first analyzes the pre-dental program incidence of osteoradionecrosis, and the second refers to the ORN rates after two changes:
1. Institution of a dental program. The dental protocol adopted included routine restorative procedures, regular oral prophylaxis, and daily fluoride application.

2. A new policy of conserving all teeth except those that were considered unsalvageable. [Murray et al (1980a) states that the high incidence of bone necrosis associated with dental extractions in Study 1 resulted in the adoption of a different protocol in which a more conservative policy towards dental extractions has resulted in a decrease in incidence of necrosis that could be attributed to this trauma, but also has resulted in an increase in incidence of "spontaneous necrosis", possibly due to dental pathology among other factors. [N.B.: The (Murray 1980a) classification of "spontaneous" ORN does not necessarily equal that of Marx and Johnson (1987)]

Among the variables examined in Murray et al (1980a; 1980c) for significant impact on ORN risk were dose, other potential bioradiological variables, presence of teeth, spontaneous or unknown causes, trauma, dental prostheses, dental extractions before and following irradiation, jaw surgery, or disease. (Voltages used in radiotherapy were not, apparently, described in this article. It is assumed that the voltages employed in studies 1 and 2, 1966-69 and 1971-75 were equivalent.)

A highly significant (p=0.01) decrease in osteoradionecrosis from one study to the next was found among the dentate patients, while no evidence of a significant decline was noted in edentulous patients (Murray et al 1980a). Nevertheless, despite the fall from 35.7% ORN in Study 1 to 24.2% in Study 2 in patients who were dentate prior to assessment and pretreatment management, there was still a relatively smaller risk of ORN
in the edentulous patients (11.9%) The reduction in ORN associated with extractions of teeth declined from 32.4% in Study 1 to 5.2% in Study 2. This decline in overall incidence could account for the observed increase in the proportion attributed to spontaneous bone necrosis, which increased from 38.2% of the total in Study 1 to 74% in Study 2.

In summary, Murray et al (1980a) found that 19.1% of 404 patients irradiated for oral cancer treatment developed osteoradionecrosis of the mandible. Three effects, dental status, tumor dose, and anatomical tumor site were found to significantly affect the incidence of necrosis.

Murray (1980a) created a multiple logistic regression equation that relates tumor location, tumor dose and dental status to the necrosis risk for given patient. This equation, presented in Table 7 of Murray et al (1980a), is interpreted as follows:

\[
\ln \left\{ \frac{a}{1-a} \right\} = -1.70 - 0.63 \frac{(X_1 - 2.66)}{0.55} + 0.45 \frac{(X_2 - 8.81)}{0.17} - 0.57 \frac{(X_3 - 1.43)}{0.50}
\]

where
- \( a \) = the probability that the patient will have necrosis (a figure between 0 & 1)
- \( \ln \) = natural logarithm,
- \( X_1 \) = anatomic site 1 if the tumor is related to bone (i.e., high risk), 2 if the tumor is adjacent to bone and teeth, or 3 if other (i.e., low risk);
- \( X_2 \) = the natural log of the tumor dose
  High risk = 8000 cGy (rad)
  Low risk = 5000 cGy (rad)
- \( X_3 \) = dental status  1 if dentate, i.e. high risk; 2 if edentulous (low risk).

and 2.66, 8.81, and 1.43 are the mean of the associated variables \( X_1 \), \( X_2 \), and \( X_3 \); 0.55, 0.17, and 0.50 are the respective standard deviation of the respective variables \( X_1 \), \( X_2 \), and \( X_3 \).
Murray et al (1980c) found relative rates of osteoradionecrosis of 18.7% and 16% respectively for extractions before irradiation in Studies 1 and 2, and 100% and 83.3%, respectively for extractions after irradiation in Studies 1 and 2. However, the numbers involved for all but the first category, \((20/107 = 18.7\%)\) were too small for reliability and generalizability (i.e., \(4/25 = 16\%\), \(2/2 = 100\%\), and \(5/6 = 83.3\%\)), and the differences not significant (\(p = 0.51\) for extractions before irradiation, and \(p = 0.75\) for extractions after irradiation.)

Murray (1980a) found non-significant associations in which implant irradiation alone appeared to be associated with the highest ORN rate, combination external and implant irradiation with an intermediate ORN rate, and external irradiation alone with the lowest ORN rate. (This presumably was due to the use of implants in floor of the mouth carcinomas adjacent to the mandible, with high doses to the adjacent bone.)

---

89 Murray et al (1980c) made the following treatment recommendations. (Note however that some suggestions, especially those marked with an asterisk* may be superseded).

1. Diseased teeth should be removed prior to irradiation, and sufficient healing time allowed. Ten days* minimum healing was suggested, and clinical evaluation at ten days may suggest need for further healing time. Murray et al (1980c) cites Murray, Daley, and Zimmerman (1980b) as finding an association between osteonecrosis and dental disease with a probability of \(p = 0.09\). It cites Hayward et al (1968) as providing the criteria "extensive caries, moderate to advanced periodontal involvement, lack of opposing teeth and consequent loss of function and self-cleansing action, partial impaction with incomplete eruption, and extensive periapical lesions."

2. Murray et al (1980c) states that conservative treatment of osteoradionecrosis is successful in 50% of cases and is quite preferred in terminal patients who can be spared the trauma of surgery. Nevertheless they advocate that "intractable pain" or "recurrent severe infection or trismus" indicate need for mandibular resection, at which time all irradiated bone as well as presently involved bone should be removed.* They state "patients...should not have to suffer the incapacitating symptoms of bone necrosis for long periods prior to the inevitable definitive surgery."

3. Murray et al (1980c) further suggest that dentures may be worn by the edentulous patient who has undergone definitive therapeutic irradiation. They cite their reference Curtis et al (1976) as attributing only 3 cases of osteoradionecrosis to dental prostheses, though 300 were very carefully constructed. Murray et al (1980c) and Morton (1986) found the dentures more frequently to be the apparent cause of osteoradionecrosis. However, Murray observed that many of these latter were ill fitting.

4. Murray et al (1980c) also suggests that in then-contemporary maxillo-facial centers a standard interval between irradiation and the construction of dentures was one year, a duration that he considered somewhat arbitrary but which he considered appropriate.* More recent papers suggest that this waiting period may be inappropriate, citing diminished vitality of loss of the bone as time progresses.
Murray et al (1980b, "The Relationship between Dental Disease and Radiation Necrosis of the Mandible") is a highly worthwhile article but its data should be considered in context. In it 104 patients with malignancies of the floor of the mouth and retromolar trigone were analyzed for association between dental disease and osteoradionecrosis in this selected population of patients treated radiotherapeutically for tumors in close proximity to the bone and teeth. Thus, this patient population cannot be generalized to all oral cancers but reflects a population specifically designed to elucidate relationships between dental disease and osteoradionecroses in bone exposed to especially high radiation doses. Dental disease was diagnosed according to the criteria of Hayward et al (1968). Hayward et al (1968) suggested that the decision for preradiotherapeutic tooth extraction be based on tooth involvement with

"1. extensive caries
2. moderate to advanced periodontal involvement
3. lack of opposing teeth and consequent loss of function and self-cleansing action, and
4. partial impaction, or incomplete eruption, and
5. extensive periapical lesions" [Murray et al (1980b) explanation]

To this end, panoramic radiographs were reviewed for all of the patients. The authors admit that clinical assessment and more specific radiographs, for instance periapicals at initial examination would have improved the accuracy of diagnosis of dental disease and produced a higher level of association. Furthermore, one could question the diagnostic reliability of panoramic radiographs for diagnosis of osteoradionecrosis itself. Table 1 of Murray et al (1980b, 101), adapted as Table 11, tabulates the results.
TABLE 11. "ASSOCIATION BETWEEN DENTAL DISEASE AND RADIATION NECROSIS OF THE MANDIBLE IN 46 PATIENTS IRRADIATED FOR MALIG­NANT TUMORS OF FLOOR OF MOUTH AND RETROMOLAR TRIGONE"
[Title & raw data from Table 1, Murray et al (1980b) p. 101 ; algebraic equivalents added.]

<table>
<thead>
<tr>
<th>SIGNIFICANT DENTAL DISEASE</th>
<th>RADIATION NECROSIS</th>
<th>TOTAL</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td>+</td>
<td>10 &quot;a&quot;</td>
<td>&quot;b&quot; 11</td>
</tr>
<tr>
<td>-</td>
<td>6 &quot;c&quot;</td>
<td>&quot;d&quot; 19</td>
</tr>
<tr>
<td>TOTAL</td>
<td>16 &quot;Algebraic Equivalents&quot; 30</td>
<td>46</td>
</tr>
</tbody>
</table>

[Thus, e.g., radiation necrosis is present with in association with dental disease in 10 patients.]

Murray et al (1980b) interpreted their data to suggest an association between dental disease present before irradiation to high dose and subsequent necrosis

" p (10/16, 11/30)" , "p (dental disease / no dental disease) " at a probability p = 0.09.

They also calculated a sensitivity of ( 10 / 21) = 0.476 = 47.6% and a specificity of (19 / 25) = 0.76 = 76.0%.

However, these data may be interpreted differently: If one considers the presence of dental disease as diagnosed on panoramic radiographs as the test result, and radiation necrosis the disease that one is trying to assess, then the prevalence rate of radiation necrosis in a population of patients with and without dental disease irradiated close to the bone would be [ (a+c) / (a+b+c+d) ] = 16/46 = 0.348. The sensitivity would be [a / (a+c) ] = 10 / 16 = 0.625, and the specificity = [ d / (b+d) ]=19/30 = 0.63 or 63%. More to the point, the positive predictive value, that is the proportion of patients with positive x-ray test results who have the target disorder osteoradionecrosis, would produce a positive predictive value of [ a / (a+b)]= 10/21 = 0.476.  {Methodology reference: ( Sackett, Haynes, Guyatt and Tugwell 1991)
Pernot et al (1995) comment that Rodgers et al (1993) and some others, report studies which mix radiation therapeutic modalities, which makes it difficult to ascertain the separate effects of external radiation and interstitial irradiation or "radiosurgery". Therefore Pernot et al (1995) reviewed a series of 207 epidermal carcinomas of the floor of the mouth treated by exclusive irradiation (the modality of which changed slightly over the series). These cases did not form a fully inclusive population since the cases reviewed tended to be very large tumors refused by surgeons due to problems of age or health or tumor spread, making surgery "unreasonable or even impossible"; also, Pernot et al considered the extension of tumor to the mandibular gingiva or mandible itself a contraindication to exclusive irradiation.

Pernot et al (1995) report that their analysis of general factors revealed that patients with large (T3, T4) tumors unsuitable for surgery\(^{90}\) commonly had poor general health status, chronic infection and a long history of tobacco and alcohol abuse. One may infer that studies associating complication rates with tumor stage could be confounded if the concurrent factors were not adjusted for.

Bone complications were classified into four groups according to the degree of discomfort and the duration of the lesion:

1. Grade 1: minor duration and minor degree of discomfort

   [median duration/healing time of cases reported in this category = 5 months]

---

\(^{90}\) The very large tumors selected by Pernot et al (1995) were referred by surgeons for treatment by exclusive irradiation due to the surgical difficulties of treating such large tumors. However, Yasumoto et al (1995) cite Jesse and Sugarbaker (1976) to justify their preference for a combination of surgery and radiotherapy when treating large tumors. Yasumoto et al (1995) state that operations were usually not selected for treating most early stage lesions based on the understanding of their surgeons that "small oral pharyngeal carcinomas have a better chance of cure by radiotherapy without any loss of structures and function due to surgery".
2. Grade 2: moderate durations and degree of discomfort

3. Grade 3: severe osteoradionecrosis, often involving severe complications such as hemimandibulectomy

4. Grade 4: fatal complications.


<table>
<thead>
<tr>
<th>GRADE</th>
<th>SIMPLE</th>
<th>CUMULATIVE ACTUARIAL*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>@ ~ 2 YEARS</td>
</tr>
<tr>
<td>1</td>
<td>17</td>
<td>~2</td>
</tr>
<tr>
<td>2</td>
<td>12</td>
<td>~7</td>
</tr>
<tr>
<td>3</td>
<td>6</td>
<td>~4</td>
</tr>
<tr>
<td>4</td>
<td>0.5</td>
<td>0.5</td>
</tr>
</tbody>
</table>

* Cumulative actuarial percentage of complications according to the number of patients exposed to risk, alive, and with sufficient follow-up.

§ (15 / 7 ) = 2.143; (8.5 / 4) = 2.125, Mean = 2.134

Ω The 0.5 % corresponds to one case.

Yasumoto et al (1995) observe that "it may be inevitable for any retrospective study to have a bias in selecting a treatment modality no doubt based on the treatment policy of the institution of the authors." Yasumoto et al (1995) performed a retrospective analysis of the outcomes associated with 171 oropharyngeal squamous cell carcinoma patients (151 males and 20 female, mean age 61.7 years, range 24-87) between 1971 and 1990. Only 5 of the 171 patients received neck irradiation without radiotherapy for the primary lesion, while 1 who received preoperative irradiation did not undergo the planned surgery. All patients were followed up for 2 to 21 years. No cases were lost to follow up.
All 171 patients' charts were reviewed and the patients retrospectively restaged according to the UICC (Union Internationale Contre le Cancer 1987\textsuperscript{91}) TNM classifications.

140 cases were actually analyzed by Yasumoto et al (1995). [The 171 total was reduced by the 5 that received only elective neck irradiation and no radiotherapy for tumor control, one who did not undergo the planned surgical treatment for cancer, and 25 who were excluded from analysis because they died before the minimum 2 year follow-up.] Of the 140 patients, 8 received interstitial irradiation with $^{222}$Radon and 62 received it via $^{198}$Gold. Megavoltage external beam irradiation equipment included $^{60}$Cobalt and a 4 MV linear accelerator. No deliberate prophylactic lymph node irradiation was applied. Data on complications was analyzed using the Chi-square test.

Yasumoto et al (1995) found "bone complications" in 13 patients, and osteoradionecrosis among 7 of these, 3 of which required sequestrectomy. The crude incidence of osteoradionecrosis was therefore $7/140 = 5\%$. Yasumoto et al (1995) concluded that "among our patients with their primary lesion under control, the incidence of bone and or soft tissue complications was evenly distributed in the three treatment modality groups (implant alone, implant plus external radiation and external radiation alone). Therefore these complications may not be the key factor when selecting an appropriate treatment modality to suit each patient's condition." Unfortunately, with regard to the complication of osteoradionecrosis, the small number of ORN compared do not permit this statement to stand alone as a definitive conclusion. The same reservation can be expressed about the (Yasumoto et al 1995) indication without detailed

\textsuperscript{91} (Yasumoto et al (1995) reference 11).
justification or statistics that the incidence and severity of these complications is lowered when brachytherapy doses are below 8500 cGy for interstitial implants alone, or below 7200 cGy for combined external beam irradiation and implant treatment.

Yasumoto et al (1995) suggest that the selection of a treatment modality should include a consideration of functional complication rates (xerostomia, loss of taste and trismus). Most of their patients treated with brachytherapy, whether or not this involved external irradiation, seemed to preserve salivary gland function and the sense of taste, while patients treated with external irradiation alone tended to manifest xerostomia and reduction in taste sensation.

Herzog, Sader, Deppe and Zeilhofer (1995) report on 60 patients presenting at their clinic with osteoradionecrosis. Although the numbers of patients involved in the study subgroups could limit the external validity of their data, and confounding variables could limit the application of their data to other circumstances, interesting data are presented. Please see Table 13, "Osteoradionecrosis Case Data" (Herzog, Sader, Deppe And Zeilhofer (1995) Study)⁹², for a summary of some of these data.

Herzog, Sader, Deppe and Zeilhofer (1995) reported among their clinical findings one case of gangrene, a finding not duplicated in the other literature reviewed. Herzog, Sader, Deppe and Zeilhofer (1995) also report that [presumably these] osteoradionecroses may be characterized generally by intense pain, diminished appetite, fistula formation, sequestration, and pathological fractures in exceptional cases.

⁹² Every attempt has been made to ensure the accuracy of the translation.
TABLE 13. OSTEORADIONECROSIS CASE DATA
(SUMMARY OF HERZOG, SADER, DEPPE AND ZEILHOFER (1995) STUDY)

<table>
<thead>
<tr>
<th>CASES OF OSTEORADIONECROSIS:</th>
<th>60, INCLUDING 3 MAXILLARY AND 57 MANDIBULAR 13 BILATERAL 3 &quot;SUBTOTAL&quot;</th>
</tr>
</thead>
<tbody>
<tr>
<td>PATIENT SEXES</td>
<td>51 MALE, 9 FEMALE</td>
</tr>
<tr>
<td>PATIENT AGE RANGE:</td>
<td>14 TO 82 YEARS</td>
</tr>
<tr>
<td>PATIENT CANCERS</td>
<td>58 CARCINOMAS; 1 SARCOMA; 1 NON-HODGKIN’S LYMPHOMA</td>
</tr>
<tr>
<td>IRRADIATION DOSES:</td>
<td>RANGE IN NEARLY ALL CASES: 6000 CGYS TO 7000 CGY, BUT FOR 3 PATIENTS WITH NEED FOR RECURRENT IRRADIATION, DOSES &quot;SPIKED&quot; AT 10,000 CGY</td>
</tr>
<tr>
<td>TIME INTERVAL BETWEEN THE COMPLETION OF RADIOTHERAPY AND THE INITIATION OF THERAPY FOR OSTEORADIONECROSIS, AMONG THE 60 PATIENTS (RANGE: 3 MO.- 22 YR.)</td>
<td></td>
</tr>
<tr>
<td>19 MONTHS</td>
<td>MEDIAN 32 %</td>
</tr>
<tr>
<td>&lt;12 MONTHS</td>
<td>33 %</td>
</tr>
<tr>
<td>13 TO 24 MONTHS</td>
<td>22 %</td>
</tr>
<tr>
<td>25 TO 36 MONTHS</td>
<td>2 %</td>
</tr>
<tr>
<td>37 TO 48 MONTHS</td>
<td>7 %</td>
</tr>
<tr>
<td>49 TO 60 MONTHS</td>
<td>5 %</td>
</tr>
<tr>
<td>&gt; 60 MONTHS</td>
<td>5 %</td>
</tr>
</tbody>
</table>

PERCENTAGE OF OSTEORADIONECROSIS CASES, BY AGE OF PATIENTS AT START OF ORN TREATMENT

<table>
<thead>
<tr>
<th>AGE OF PATIENTS AT START OF ORN TREATMENT</th>
<th>1.5 %</th>
<th>7 %</th>
<th>30 %</th>
<th>40 %</th>
<th>15 %</th>
<th>5 %</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 20 YEARS</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>21-30 YEARS</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>31-40 YEARS</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>41-50 YEARS</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>51-60 YEARS</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>61-70 YEARS</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>&gt;70 YEARS</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

--- Table Continues---
### TABLE 13. OSTEO RADIONECROSIS CASE DATA, *continued.*
(SUMMARY OF HERZOG, SADER, DEPPE AND ZEILHOFER, 1995 STUDY)

**Clinical Findings**

**N.B.: One ORN may have more than one finding, and one patient may have a finding repeated.** (Thus, the total below is > 100%).

**N.B.: Please also see paragraph following table.**

<table>
<thead>
<tr>
<th>Finding</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Denuded Bone</td>
<td>126.7 %</td>
</tr>
<tr>
<td>Acute Pain</td>
<td>85 %</td>
</tr>
<tr>
<td>Soft tissue necrosis</td>
<td>61.7 %</td>
</tr>
<tr>
<td>Abscess formation</td>
<td>13.3 %</td>
</tr>
<tr>
<td>Gangrene</td>
<td>1.7 %</td>
</tr>
</tbody>
</table>

**Apparent Causes of 60 Osteoradionecroses**

**N.B.: One ORN may have more than one cause.** (Thus, the total below is > 100%).

**Odontogenic Infections and Post-Irradiation Tooth Extractions**

- Deep periodontal involvement: 61.7%
- Periapical involvement: 43.3%
- Superficial (presumably mild or moderate) periodontal involvement: 18.3%

**Prosthetic Pressure Area**

- 13.3%

**Previous Irradiation**

- 13.3%

**Surgery in the Area**

- 10 - 13.3%

**Incomplete Healing of Tooth Extraction Socket (presumably prior to radiotherapy)**

- 13.3%

**Other**

- 15%

Herzog and Samek (1986) reported on 103 patients treated for malignancies of the head and neck between 1981 and 1984. Of these, 5 patients developed an infected osteoradionecrosis causing the loss of the irradiated bone in 4 cases. It recommended an intensive dental program during high irradiation radiotherapy. Tentative translation of one sentence in this article suggests that 4 of the 5 cases of osteoradionecrosis occurred.
with irradiation between 6400 and 7000 cGy, and that one case of ORN occurred in a patient exposed only to only 5000 cGy.

Ohyama et al (1985) reported on the osteoradionecrosis produced by interstitial irradiation of 82 histologically proven squamous cell carcinomas of the tongue. The incidence of mandibular osteoradionecrosis was 18 (= 22%). As with Herzog (1986), Ohyama et al (1985) cannot be described further due to translation difficulties.

Schultheiss (1990) found that the head and neck was observed to be the site with the highest tolerance to high energy neutron beam therapy, as opposed to thorax, pancreas and pelvis. The only complications tallied for the head and neck were mandibular necrosis, soft tissue necrosis, chondronecrosis and severe fibrosis within a four and one half year follow-up. Mandibular neutron radiation osteomyelitis rates were also tabulated as a separate entity. A visually linear relationship between neutron dose between 2100 cGy and 2700 cGy and the percentage probability of complication is observed when the latter (probability) is plotted on a logistic scale. Between 2000 and 2199 cGy of neutron irradiation, the rate of mandibular osteonecrosis was 4.1%; between 2200 and 2399, 13.2%; between 2400 and 2599, the rate was 35.2%, and above 2600 cGy, the rate was 41.7%. These rates were calculated for situations without censoring. Censoring would lower the figure, and the observed complication rates would be higher than those clinically realized, because patients whose dose tolerance has been exceeded would not survive to express the complication. Thus, these complication rates are liberal overestimates of clinical expression.
Schultheiss, et al (1990) cite Morrish et al (1981) as indicating that radiation osteomyelitis is rare in patients with a properly supervised plan of oral hygiene below irradiation of 6600 cGy in two fractions of photons. He comments that the 5 to 10 percent complication rate not uncommonly observed is a crude rate uncorrected for censoring. Schultheiss comments that the true rate of osteomyelitis was about 8% in their studies at a neutron dose of 2200 cGy, after adjustment for censoring. This figure would be lower than either an uncensored figure or a figure that took into account follow-up longer than four and a half years. The authors conclude that a RBE (Relative Biological Effectiveness, a comparison of the relative effectiveness in this case of neutron irradiation to gamma/Roentgen irradiation) of about 3 is reasonable and that the lower limit on the 95% confidence interval of the 20% complication dose would be about 23,200 cGy neutron irradiation. The authors suggest that their estimates of median doses associated with particular rates of complications were substantially lower in all sites studied than previous estimates [their citation, (Cohen et al 1989)].

Herzog, and Samek (1986) retrospectively reviewed 103 patients with head and neck cancer treated with irradiation to high dose between 1981 and 1984. 5 of these 103 cases developed infected osteoradionecrosis (Herzog and Samek 1986).

Patel, Raybould, and Maruyama (1989) stated that the University of Kentucky Department of Radiation Medicine observed an osteoradionecrosis of the jaws rate of 10.9 % in 220 patients irradiated head and neck cancer patients before 1974. However, "After a program of oral care was instituted, the incidence declined to 2.7 %. Of 109 patients who received radiotherapy between 1976 and 1985, only 3 (2.7 %) developed
ORN of the mandible. There was also a reduction in the patients treated with interstitial therapy during this time. A review of the most recent experiences shows that, with present management methods at the University of Kentucky, ORN is not a significant problem. Of 30 patients treated in 1986, only 1 had ORN, and this was of the maxilla."
(Patel, Raybould, and Maruyama 1989)

The good success rates observed by Patel, Raybould, and Maruyama (1989) may be due to a number of factors. The authors commented that few patients received interstitial implant therapy (especially toward the end of the study), and this "undoubtedly contributed to the decline ... of ORN at this institution." It can also be observed that there was only one case of floor of the mouth cancer, two of the tongue, and two of the retromolar trigone in 1986; thus their experience of only one case of osteoradionecrosis may be associated with relatively low doses to the mandible (6438 ± 623 cGy with 32 ±5 fractions over 6.7 ± 0.9 weeks.) Nevertheless this incidence is consistent with the 3/109 observed between 1975, when the dental program was started⁹³, and 1985. Post-

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⁹³ Patel, Raybould, and Maruyama (1989) suggest that management of osteoradionecrosis should be conservative when possible and radical when necessary. Conservative measures would include conservative bone debridement and packing topical and systemic antibiotics, good oral hygiene and careful removal of debris from the area, and hyperbaric oxygen therapy. They conclude that their dental program (initial dental evaluation, prophylaxis, fluoride therapy, efforts to improve oral hygiene, and prompt treatment of oral infections) have controlled the problem of osteoradionecrosis. They classify patients by dental status into risk categories with which different pre-radiotherapeutic management strategies may be associated (their Table 5, page 330):

1. Edentulous (no teeth) patients indicate removal of soft and hard tissue pathology tori, exostoses, and sharp ridges, etc.
2. Poor risk patients (teeth beyond repair by ordinary dental procedures) indicate full mouth extraction and mandibular alveolectomy and primary closure.
3. Fair risk (some teeth restorable by ordinary dental means, periodontal pockets less than 3 millimeters) indicate extractions of indicated teeth, restorations, periodontal treatment, and fluoride.
4. Good risk (few carious lesions, good oral hygiene, and normal alveolar bone) indicate periodontal evaluation, prophylaxis, restorations, no pre- irradiation extractions and fluoride. These measures should be appropriate elsewhere.
irradiation extractions were not identified as a significant ORN risk. Hyperbaric oxygen was used for persistent ORN (Patel, Raybould, and Maruyama 1989).

Marciani and Plezia (1974) is cited by Patel, Raybould, and Maruyama (1989) as finding a 10.5% (23/220) ORN incidence among some patients treated before the University of Kentucky medical center dental program was instituted in 1975. Bedwinek (1976) statistics for 381 similar patients also are cited; these are illustrated in table form, and supplemented with CKC relative risk calculations:

<table>
<thead>
<tr>
<th>DOSE:</th>
<th>ASSOCIATION:</th>
<th>ORN RATE:</th>
<th>RELATIVE RISK:</th>
</tr>
</thead>
<tbody>
<tr>
<td>6000 cGy over 6 weeks</td>
<td>0 %</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;7000 cGy over 7 weeks</td>
<td>1.8 %</td>
<td>1</td>
<td>5.0</td>
</tr>
<tr>
<td>&gt; 7000 cGy over 7 weeks</td>
<td>9.0 %</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Tumor Near Bone</td>
<td>9.4 %</td>
<td>1</td>
<td>4.5</td>
</tr>
<tr>
<td>Tumor Not Next to Bone</td>
<td>2.1 %</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Patel, Raybould, and Maruyama (1989) also cites his reference Schweiger (1987) as finding in another population of 325 patients a 1.9% ORN rate.

To suggest better criteria for dental programs, Beumer, Harrison, Sanders and Kurrasche (1984) studied 70 patients for possible dental factors that could predispose the patients to osteoradionecrosis (as defined by bone exposure). 34 patients had received pre-therapeutic dental evaluations and then were followed after therapy, while 36 were evaluated dentally only following therapy.

An apparent intended lack of random sampling (re Male:Female ratio, Dentulous:Edentulous ratio) may influence the generalizability of this study's findings if unrecognized confounding factors are present in the selected populations. Categories of
findings paralleling those reported in the "Summary of Herzog et al 1995 study" table are tabulated in Table 14 ("Osteoradionecrosis Case Data, Beumer, Harrison, Sanders And Kurrasch 1984 Study")

### TABLE 14. OSTEORADIONECROSIS CASE DATA (BEUMER, HARRISON, SANDERS AND KURRASCH 1984 STUDY)

<table>
<thead>
<tr>
<th>CASES OF OSTEORADIONECROSIS: (DEFINITION: BONE IN HIGH DOSE VOLUME EXPOSED 3 MONTHS OR LONGER)</th>
<th>83 (5 MAXILLARY, 78 MANDIBULAR) INCLUDING 13 RECURRENT</th>
</tr>
</thead>
<tbody>
<tr>
<td>PATIENT NUMBERS /SEXES</td>
<td>70: 38 MALE, 32 FEMALE</td>
</tr>
<tr>
<td>STATE OF DENTITION:</td>
<td>69 DENTULOUS, 1 EDENTULOUS</td>
</tr>
<tr>
<td>PATIENT CANCERS</td>
<td>OF HEAD AND NECK; APPARENTLY NOT FURTHER SPECIFIED.</td>
</tr>
<tr>
<td>PATIENT AGE RANGE:</td>
<td>APPARENTLY NOT SPECIFIED.</td>
</tr>
<tr>
<td>IRRADIATION:</td>
<td>RAW DOSE DATA NOT SUPPLIED. PORTIONS OF THE JAWS WERE WITHIN THE HIGH DOSE VOLUME IN EVERY CASE.</td>
</tr>
<tr>
<td><strong>CKC OPINION:</strong> FIELD SIZES VARIED BUT ORN ASSOCIATIONS WERE NOT DRAMATICALLY DEMONSTRATED</td>
<td><strong>60 OF 83 CASES (72.3%) OF ORN OCCURRED AFTER EXTERNAL IRRADIATION ALONE;</strong></td>
</tr>
<tr>
<td></td>
<td><strong>22 (26.5%) ORN OCCURRED AFTER INTERNAL/EXTERNAL IRRADIATION,</strong></td>
</tr>
<tr>
<td></td>
<td><strong>1 CASE (1.2%) OCCURRED AFTER INTERNAL IRRADIATION ONLY.</strong></td>
</tr>
<tr>
<td>TIME INTERVAL BETWEEN THE COMPLETION OF RADIOTHERAPY AND THE RECOGNITION OF OSTEORADIONECROSIS, AMONG THE 83 CASES OF ORN (NOT THE 70 PATIENTS).</td>
<td>GIVEN FOLLOW-UP OF 1 YEAR OR LONGER, PROPORTION OF ORN CASES AT TIME INTERVAL:</td>
</tr>
<tr>
<td><strong>&lt; 12 MONTHS</strong></td>
<td><strong>46% (38)</strong></td>
</tr>
<tr>
<td>12 TO &lt; 24 MONTHS</td>
<td>18% (15)</td>
</tr>
<tr>
<td>24 TO &lt; 36 MONTHS</td>
<td>13.2% (11)</td>
</tr>
<tr>
<td>36 TO &lt; 48 MONTHS</td>
<td>5. % (4)</td>
</tr>
<tr>
<td>48+ MONTHS</td>
<td>18. % (15)</td>
</tr>
</tbody>
</table>

"Time of onset had no visible affect upon treatment outcomes"

Table continues »»
TABLE 14. OSTEO RADIONECROSIS CASE DATA, continued
(BEUMER, HARRISON, SANDERS AND KURRASCH 1984 STUDY)

<table>
<thead>
<tr>
<th>Clinical Findings</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Clinical Findings</strong></td>
<td></td>
</tr>
<tr>
<td>The most common dental factors associated with bone necrosis manifestation were:</td>
<td></td>
</tr>
<tr>
<td>&quot;Breakdown of post-extraction wounds&quot;:</td>
<td>26.5% (22/83)</td>
</tr>
<tr>
<td>&quot;Spontaneous bone exposures associated directly with dentition secondary to dental disease within the radiation volume&quot;:</td>
<td>22.8% (19/83)</td>
</tr>
<tr>
<td>&quot;Dehiscence associated with pre-irradiation extraction sites&quot;:</td>
<td>20.4% (17/83)</td>
</tr>
<tr>
<td>&quot;Resection for persistent disease&quot;:</td>
<td>6.0% (5/83)</td>
</tr>
<tr>
<td>&quot;Denture irritation&quot;:</td>
<td>9.6% (8/83)</td>
</tr>
<tr>
<td>&quot;Spontaneous episodes of unknown etiology&quot;:</td>
<td>11% (9/83)</td>
</tr>
<tr>
<td>Predisposing factors for 83 ORN episodes observed in 70 patients:</td>
<td></td>
</tr>
<tr>
<td>Pre-radiation extraction</td>
<td>20.4% (17/83)</td>
</tr>
<tr>
<td>Post-radiation extraction</td>
<td>26.5% (22/83)</td>
</tr>
<tr>
<td>&quot;Spontaneous&quot; in the terminology of these authors, in association with dentition</td>
<td>22.8% (19/83)</td>
</tr>
<tr>
<td>&quot;Spontaneous&quot; in the terminology of these authors, in presumable association with other unknown, unidentified factors</td>
<td>10.8% (9/83)</td>
</tr>
<tr>
<td>Denture irritation</td>
<td>9.6% (8/83)</td>
</tr>
<tr>
<td>Major surgical intervention (resections) for &quot;persistent disease&quot;:</td>
<td>6% (5/83)</td>
</tr>
<tr>
<td>Tumor progression</td>
<td>3.6% (3/83)</td>
</tr>
<tr>
<td>Total</td>
<td>100% (83/83)</td>
</tr>
</tbody>
</table>

Beumer, Harrison, Sanders, and Kurrasch (1983) found that bone exposure of three months or longer developed in 22% of the post-radiation extraction cases (29% rate in mandible, 11% case in maxilla.) The risk of osteoradionecrosis increased to 38% when the dose to the bone exceeded 6,500 cGys and 75% or more of the body of the mandible was within the irradiated volume.94

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94 As previously stated in the last subsection, Beumer, Harrison, Sanders and Kurrasch (1984, 825) also were of the opinions that dosages to bone in excess of 7,500 cGys predispose to high rates of osteoradionecrosis, while those between 6500 and 7500 cGys promote intermediate levels at risk for
Of the osteoradionecroses analyzed in Beumer, Harrison, Sanders and Kurrasch (1984), 37.3% (31/83) could be classified as healed and 18% (15/83) as stable or improving, thus approximating Epstein (1987a) Stage 1a and Morton (1986) minor and moderate ORN classifications, with the balance 37 (44.6%) progressively worse approximating the Morton (1986) "major" ORN classification. Of the latter 37, 13 were treated with radical resection of the affected portion of the mandible, while 24 were treated with hyperbaric oxygen therapy (and either conservative measures or surgical sequestrectomy). "Radical resection was reserved for those patients whose bone necrosis proceeded to intractable pain and/or pathologic fracture usually accompanied by orocutaneous fistula." ORN's tended to be mild and self-limiting with doses < 6,000 cGy. "In bone necroses where the external radiation dose to affected bone exceeded 7,000 cGy, the mandibular resection rate was high (44%)." "Bone exposures associated with post-radiation extractions or occurring spontaneously in direct association with the remaining dentition were the least likely to be controlled with conservative measures. The overall rate of mandibular resection of those episodes occurring in the mandible was 29.5% (23/78)."

"Conservative treatment measures generally suffice for bone necroses occurring after dosages less than 6,500 rads, especially in bone exposures remaining confined within the zone of attached gingiva." Beumer, Harrison, Sanders and Kurrasche (1984) state that 93.3% (14 of the 15) of the patients who developed necrosis following doses <6,500 cGy were controlled with conservative measures, while only one of these cases [which actually was associated with a higher 6,700 cGy bone dose] required mandibular resection. In contrast, 40% (18 of 45) cases receiving > 6,500 cGy required mandibular resection.

Beumer, Harrison, Sanders, and Kurrasch (1984) found that bone necrosis arising from pre-radiation extraction sites required radical resection of the mandible in only 11.7% of cases, while osteoradionecroses occurring resulting from the wear of intra-oral prostheses required resection of the mandible in only 12.5% of the cases (1/8). "In contrast, those bone necroses occurring as a result of dental disease (periodontal disease), either spontaneously or in association with post-radiation extractions, more often with require radical resection for the control of infection (36.8% and 45.4%, respectively)." These figures and the data of Murray et al (1980a; 1980b) lead Beumer, Harrison, Sanders and Kurrasch (1984) to recommend against the 1972 opinion of Daley and Drane that teeth only be extracted in relatively severe circumstances. They cite their reference Hayward (1969) as providing reasonable criteria for tooth removal prior to therapy. [To review, teeth with a questionable prognosis regarding advanced caries near the pulp and/or evidence of periapical infection, periodontal disease including furcation involvements or other deficiencies that make maintenance and cleaning difficult.]

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Legros et al (1984, *transl.*) reports on a series of 39 cases of osteoradionecrosis of the mandible observed in a series of 878 cervical facial carcinoma patients treated by irradiation, apparently between 1978 and 1983. The authors describe this rate (4.4%) as approximately similar to the percentage reported by other French authors such as their references Gaillard (3%), Billet (3.5%), or the Foundation Curie (3.5%). Legros et al (1984) define osteoradionecrosis using the definition of Cachin and Vandenbrouck (their reference): "an osteolysis detectable by a radiographic examination and surfacing in the period following irradiation treatment for cervical facial carcinoma, without any evolution of a tumor in the bone for neighboring areas". Please see Table 15 for a summary of some of their data.96

The delay between the end of irradiation and the appearance of the first signs of disease varied with extremes noted at 3 months and 6 years, with an average of 13.4 months, a figure they relate as analogous to their reference Cachin (15 months average). This paper does not find irradiation protocols influencing the frequency of osteoradionecrosis but does observe that Curie therapy (radiotherapy?) is associated with limited sequestrations of bone while cobalt therapy may be associated with all types of osteoradionecrosis. Legros et al (1984) cite their reference Bailler as finding two factors associated with osteoradionecroses (assuming correct translation): the volume of the tumor and the location of the lesion.

96 (Every attempt has been made to ensure the accuracy of the translation.)
TABLE 15. OSTEO RADIONECROSIS CASE DATA  
(SUMMARY OF LEGROS ET AL 1984 STUDY)

<table>
<thead>
<tr>
<th>CASES OF OSTEO RADIONECROSIS:</th>
<th>39</th>
</tr>
</thead>
<tbody>
<tr>
<td>POPULATION BASE:</td>
<td>878</td>
</tr>
<tr>
<td>ORN RATE:</td>
<td>4.4%</td>
</tr>
</tbody>
</table>

**Other ORN rates cited by article:**
- GAILLARD: 3%  
- BILLET: 3.5%  
- FOUNDATION CURIE: 3.5%

**Study Time Period:** 1978-1983

**Patient sexes**
- 38 Male, 1 Female

**Patient cancers**
- Unknown

**Irradiation doses:**
- Apparently not identified

**Irradiation types:**
- 67% Cobalt =
  - 44% Conventional
  - 23% Hyperfractionated
  - 10% Iridium implant exclusively
  - 13% Iridium " + External Irradiation
  - 5% Surgery (then?) Radiotherapy
  - 5% Radiotherapy (then?) Surgery

**Time interval between the completion of radiotherapy and the first appearance of osteoradionecrosis, among the 39 patients:**
- Range: 3 months to 6 years.  
- Mean: 13.4 months

**Patient ages:**
- Mean = 54.5 years

**Notable clinical outcomes:**
- 2 deaths associated with surgery for ORN among 19 ORN in the horizontal angle/body region of the mandible.  
- 2 / 19 = 10.5%

**Apparent causes of 39 osteoradionecroses**
(N.B.: Each 2 1/2% = 1 case.)

1. Uncertain: 27 cases = 70%  
2. Dental extractions in the months before radiotherapy: 7.5%  
3. Poorly adapted dental prostheses: 5.0%  
4. Excessive radiation dose: 2.5%  
5. Inappropriate surgical trauma: 5.0%  
6. Irradiation of tumors in close proximity of the bone: 7.5%  
7. Treatment "fluore non suivi" (assumed "interrupted fluoride therapy"): 2.5%
38 of the 39 cases of osteoradionecrosis found by Legros et al (1984) were initially localized in the following:

1. amygdala (presumed tonsillar) region: 11 cases. \( \frac{11}{38} = \) as % of total, 29 %
2. "pelvi-linguale" (assumed "lingual floor of mouth") region: 6 cases = 16 %
3. anterior floor (presumed facial vestibule, if "pelvi-linguale" identified correctly): 8 cases = 21 %
4. mobile tongue: 3 cases; = 8 %
5. base of the tongue: 3 cases = 8 %
6. surface of the palate: 2 cases = 5 %
7. menton: 1 case = 3 %
8. internal aspect of the cheek: 1 case = 3 %
9. lateral lining wall of the pharynx: 1 case = 3 %
10. intermaxillary commissure: 1 case = 3 %
11. "adenopathie primitive" (enlarged lymph nodes under jaw?): 1 case = 3 %

This (Legros et al 1984) tabulation is not inserted in the table because its classification scheme is not directly comparable with other literature. In more general terms, 8 of the 39 cases (20%) were in the symphysis and para-symphysis region (i.e. anterior mandible), and 19 cases (49%) were in the horizontal-angle "branche" of the mandible, i.e. body of the mandible near its angle.

Legros et al (1984) describe some of their treatments\(^{97}\) and consequences.

Osteoradionecroses usually were treated initially with conservative measures, e.g.

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\(^{97}\) Although Legros et al (1984) states that indications for surgery sometimes are unclear, there are "extremely classic" clinical signs indicating need for surgery: in various combinations, significant pain (18 cases), pathological fracture (5 cases), trismus "serre" (13 cases), and "orostomes" [joining intra-extra-oral fistulæ?].

Legros et al (1984) conclude [in translation] that "The ideal treatment of an osteoradionecrosis is, of course, prophylactic and not surgical". Indications for a conservative approach include adequate oral status or function, good oral hygiene status, and a good patient psychology [presumably motivation and dental attitude and aptitude]. They state that criteria for avoiding prophylactic
antibiotics and corticosteroids, and nutritional supplementation. In 16 of the 39, only minimal local surgical care, such as abrasion of involved surgical crest, was added. In 23 cases, however, surgery (with an intra-oral approach if possible) was indicated either by failure of the treatment, "orostomes", or pathological fracture. They note esthetic consequences in some surgical cases in the mandibular symphysis/para-symphysis region. 2 deaths among the 19 cases of the body-of-the-mandible region were due to extension of necrosis into major vessels, and uncontrollable hemorrhage: one after days, the other after months. A further two other patients with ORN in the body-of-the-mandible region died due to quick recurrence of the neoplasm following surgery for ORN. The authors note that it is probable in these cases that ORN was associated with recurrent neoplasm, which may not always be obvious.

Rahn and Drone (1967) provide a 1960's perspective on dental aspects of the problems care and treatment of the irradiated cancer patient. Their Tables 1 through 4 provide data about the characteristics and locations, time of onset, etc., of series of 120 and 53 patients with oral cancer at risk for osteoradionecrosis mostly between 1960 and 1962. Similarly to statistics associated with the series of 108 oral cancer patients reported by Dodson (1962), it is not felt that the Rahn and Drone (1967) data are current enough to merit inclusion with the data used for decision tree formulation. Interestingly, Rahn and Drone (1967) mention that "...It is the opinion of Rominger, Looby, and Duncan, however that teeth lying within a tumor region should be allowed to remain since there is

interventions include adequate periodontal and caries status, and if translation suffices, lack of infected intra oral fistulae. Pre- and post- surgical antibiotics and fluoride is appropriate. When necessary, avulsion of teeth in an affected area [translation is unclear: perhaps this should be avulsion of bone involved in ORN] should be accompanied by alveoplasty and hermetic closure of the gingival mucosa.
a possibility that their removal may result in the dissemination of tumor cells." This theory has not been repeated in other, more recent articles since reviewed, so it may be assumed to have fallen out of favor.

Rahn and Drone (1967) also considered that the three primary complications after radiotherapy that the dentist should be concerned with are

- head and neck trismus [usually occurring 3-6 mos. after therapy]\(^{98}\)
- radiation caries, and
- necrosis.

Peri, Baudet and Chamard (1986, *transl.*) performed a multi-center survey-based study on the preventative treatment of osteoradionecrosis. 350 questionnaires were distributed to chiefs of services of hospitals and radiotherapy, stomatology, maxillofacial surgery, pathology and dental therapy in mid 1980's France. The overall response rate was 48.6%, limiting the generalizability of the sample results. However, the authors note that some colleagues had little familiarity with some of the problems questioned and that some of their responses were not able to be categorized.

Three main areas were analyzed:

1. *The problem of tooth extractions prior to and following radiotherapy, and dental indications for extraction in the time prior to radiotherapy.*

Surprisingly, 2% of practitioners did not assess dental status prior to starting irradiation, or apparently consider it to be an important prognostic factor.

\(^{98}\) a result of fibrosis of the masticatory muscles. Appropriate treatment could include, say these authors, attachment of an appliance to the patient's dentures to increase the vertical dimension of dentures, having the patient place as many wooden tongue blades between his teeth as possible (and trying to increase the number each time) and finally by having the patient exercise with a surgical
The opinions tabulated are remarkably prone to surgical intervention: within the irradiated volume, 49% of the respondents would extract healthy teeth, 55% would extract living teeth with non-satisfactory but restorable metal fillings. 100% of the dentists would extract unrestorable teeth, 91% would extract dead or unsuccessfully endodontically treated teeth, and 94% teeth "unenclosed" ["desenclusion" = "unenclosed"; unopposed = a hypothetical translation]. 59% would remove bonily impacted teeth, and 61% would remove healthy teeth in malposition. 98% of the practitioners favored extractions when a periodontal problem was present.

The opinions expressed were more conservative for dental situations outside the irradiated volume. Outside the irradiated volume 62% still were in favor of extractions when a periodontal problem was present, 68% of respondents said that they would extract dead teeth or teeth unsuccessfully treated endodontically, 100% of the dentists would extract unrestorable teeth outside the irradiation volume and 72% would extract "unenclosed" teeth outside the irradiation volume.

One item on the survey enquired as to policy for extractions of crowns and bridges prior to irradiation, possibly with the consideration of secondary radiation or potential for endodontic complications as relevant prognostic variables. 64% of respondents would remove the crowns or bridges within the irradiated volume, 27% outside.

54% of the practitioners suggested extractions within 10 to 15 days of irradiation but 22% suggested waiting 21 days.

Were subsequent extractions necessary, 85% and 78% of practitioners would respectively inside and outside the irradiated volume recommend the use of concurrent systemic antibiotics. Combinations of antibiotics often were suggested by the respondents: penicillin and erythromycin succinate,
penicillin and gentamycin or cephalosporin and gentamycin, the use of flagyl at a dosage of 3 grams per day was recommended by some. Others advised concurrent use of vitamin C in a dosage of 1.5 to 4 grams per day. The suggested duration of antibiotic therapy was 8 days prior to extractions and until 21 days following extractions or until complete healing (Peri, Baudet and Chamard 1986, transl.).

2. *The problem of prevention of osteoradionecrosis through the use of fluoride.*

The major problems mentioned were poor patient compliance with recommended routines either because of past history (the comment being made that people with a faulty or oral hygiene will never change their ways) or that fluoride gel self-application is sometimes abandoned due to intra-oral sensitivity or patient fatigue. One quarter of the respondents mentioned the importance of professional follow-up in maximizing oral hygiene status while 14% stressed the importance of measures promoting moisture in the mouth, and suggest a low sugar diet (Peri, Baudet and Chamard 1986, transl.)

3. *Problems associated with the wearing of removable of dental prostheses.*

Practitioners estimated that there are risks associated with the wearing of prostheses at greater than 4000 cGy irradiation. Nevertheless they believe that prostheses have important psychological worth when a marked esthetic impairment would result if they were not worn. 22% of the respondents recommend the use of soft resin (soft liners?), and 18% advocate special techniques or precautions during fabrication of dentures or prostheses. A further 25% advocate follow-up procedures or rebasing in excess of the standard denture patient. 42% would not do anything in particular for post-radiation prosthesis production (Peri, Baudet and Chamard 1986, transl.)
Hyperfractionation (e.g. twice-daily doses of only 115 centiGrays (Peters 1993)) is an approach hoped by some to minimize tissue complications, but some hyperfractionated regimes have been discontinued due to associations with excessive osteoradionecrosis rates (Niewald et al 1996).

Roos, Dische, and Saunders (1996) reported on the results of their current dental programs at the Mount Vernon Hospital in Middlesex, England used in association with "CHART" (Continuous Hyperfractionated Accelerated Radio-Therapy) for 99 cases of mostly advanced (85% T3, T4, or N3), oral (33%), pharyngeal (48%), or laryngeal (18%) proven squamous cell carcinoma. [72M: 27F = 2.7 : 1, median age 66 years, mean 64, range 23-84]. "CHART" technique (3 treatments/day @ 1500 cGy / fraction on 12 consecutive days) was hypothesized to be sparing of late normal tissue effects compared with normal fractionation. (However, in this study a control group with normal fractionation was lacking.) Only one minor osteoradionecrosis of the mandible was observed within an overall follow-up of 1 month to 8.5 years (median 2.2 years, mean 3.0 years). It arose in the high dose volume four years after radiotherapy in association with a patient with

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99 e.g., Niewald (1996) found a 22.9% ORN rate in 52 patients treated with two daily fractions of 1200 cGy, 4 hours minimum apart, total 8280 cGy, vs. 8.6% ORN rate in 116 patients treated with conventional single doses of 2000 cGy, total 6000 to 7000 cGy. (p = 0.029 but dose could be a potential confounder.) The experience of Legros et al (1994) was different: an ORN rate of 23% in hyperfractionated treatment, and 44% in normal, among 39 patients. Withers et al (1995a), a 9 center study that evaluated 676 patients retrospectively, concluded that if there was any effect of twice daily treatment (as opposed to daily), the effect was slightly negative.

100 A supposition supported by the ORN rate findings of Legros et al (1994), but more strongly refuted by the ORN rate findings of Niewald et al (1996)
a floor-of-mouth/tonsillar carcinoma and ipsilateral molar extraction prior to radiotherapy, resolved with conservative treatment, recurred one year later, then resolved similarly again, apparently permanently.

Roos, Dische, and Saunders (1996) found that 60% of patients were dentate prior to treatment, and that 59% of this group (35.4%) preserved at least some teeth prior to radiotherapy [59% = 25% no extractions, 34% some extractions (15% of total have no extractions pre-RT; 20% of total have some extractions]. During the (limited) follow-up, 21% of the latter group subsequently lost all their teeth, leaving only 28% with any teeth at the conclusion of the study. Proportions of patients with upper full or partial dentures increased from 61 to 76% pre-to-post-treatment, and with lower dentures from 46% to 66%, but the usage rate declined. ("Never Use Dentures" as a category increased from 7.8% to 12.5% pre- and post-treatment for upper dentures, and from 12.5% to 22.9% for lower dentures. However, the lower denture utilization rate may be biased by patient lack of familiarity as well as oral health status).

The generalizability of Roos, Dische, and Saunders (1996) findings to local institutions may be questioned because of the CHART technique and potential cultural differences among both patients and care givers. The latter is highlighted by the apparently stable ~ 40% rates for denture usage 24 hours a day both before and after therapeutic irradiation.

Widmark, Sagne and Heikel (1989) extensively analyzed data in association with 21 cases of osteoradionecroses found among 19 patients out of 431 patients treated for malignant tumors of the head and neck. Student's t-tests were utilized to find supposedly
significant differences among various subgroups. However, the wide range of types of
tumors treated with their consequent varying dosages to the mandible within the
subgroupings of factors associated with the osteoradionecrosis cases, lack of reporting
associated chemotherapy that contributed to an analysis leading to a conclusion that the
combination of tumor, surgery and chemotherapy with traumatic tooth extraction
predisposes to osteoradionecrosis, the graphing of six female cases of osteoradionecrosis
where only five were indicated in the introduction (which also mentioned that only
among men were multiple radionecroses found), and the reporting of osteoradionecrosis
rates apparently paradoxically reversed in association with surgical techniques of varying
levels of apparent induced bone trauma (i.e. one might assume that extractions would be
less traumatic and ORN-predisposing than "surgical" extractions) lead to reservations
about the conclusions of this paper. Withers et al (1995) may provide superior
relationships between the rates of osteoradionecrosis and patterns of fractionation.

Regarding timing between extraction and irradiation, evidence reinforcing the
conclusion of Marx and Johnson that extractions 21 days prior to radiotherapy do not
pose much risk for ORN is provided by the reference Starcke and Shannon (1977), cited
in Beumer, Curtis and Harrison (1979b), in which no osteoradionecroses occurred in all
62 cases (healing time prior to irradiation: 5 to 72 days; mean = 25.3 days.) These
Starcke and Shannon (1977) results are also consistent with a supposition of a critical
threshold for radiation damage sufficient to predispose ORN: 36 out of 62 cases were
irradiated at less than 6000 cGy, and the balance had irradiation not exceeding 7000 cGy.
In contrast, Daley and Drane (1972), as cited in Beumer, Curtis and Harrison (1979b) found that 22 of the 74 cases of bone necrosis in their investigation occurred at sites of pre-radiation dental extraction given a mean of 11.1 days healing prior to radiotherapy. They concluded that pre-radiation extractions carries a high potential for causing or predisposing osteoradionecrosis, and recommended against it. Beumer, Curtis and Harrison (1979b) cite their own data and analysis of 94 patients with osteoradionecroses at extraction sites. It is interesting to note that they found a rate of 39.3% (11/28) for incidence of osteoradionecrosis in patients treated via opposed mandibular fields (mean 7,400 cGy), while they found a rate of only 7.9% (3/28) in patients treated via fields that terminated anteriorly at the first bicuspid region and received a mean of 6,824 cGys. Of the 94 osteoradionecroses at extraction sites, Beumer, Curtis and Harrison (1979b) explain 13% (12/94) as "spontaneous" in nature and 2% (2/94) as being due to "denture irritations".

As with in many other studies, Beumer, Curtis and Harrison (1979b) found a shorter time between extraction and administration of therapeutic irradiation (average 7.8 days) in comparison to the group without osteoradionecroses, which in this study averaged 9.3 days between extraction and therapeutic irradiation.

Data supplied by Makkonen, Kiminki, Makkonen and Nordman (1987) suggests the possibility of a threshold for appearance of osteoradionecrosis at a dose range above that which they employed in the treatment of squamous cell carcinoma, other solid tumors and lymphoma. They reviewed the case histories of 224 patients treated with radiation therapy for head and neck malignancies at the central hospital in Turku, Finland.
during the years 1974 - 1977. Doses for squamous cell carcinoma and other solid tumors ranged from 2400 to 6600 cGy (median, 6100 cGy in 6 to 8 weeks), and for patients with lymphoma, 3600 cGy to 6400 cGy (median, 4300 cGy in 5 weeks). Radiotherapeutic regimes with Cobalt 60 apparatus or linear accelerator (photon energy 6.7 MEV) ranged from doses 2400 to 8500 cGys over 3 to 11 weeks, 1000 cGys per week with a nominal single dose varying from 825 to 1910 rets. [rets: (Ellis (1969)\textsuperscript{101}), cited in Makkonen, Kiminki, Makkonen and Nordman (1987)]

Of the 224 charts reviewed by the primary author of Makkonen, Kiminki, Makkonen and Nordman (1987) [and in contrast to the 90 reexamined at 5 years], 82 patients had irradiation only and 49 were treated with both irradiation and cytotoxic agents. 93 patients underwent both irradiation and surgery and 32 of these were also treated with cytotoxic agents. The 5 year survival rate for the 224 patients as a whole was 47% [close to the 54% cited for white Americans in 1988 by White, Caplan, and Weintraub (1995) using American Cancer Society 1993 data.]

Panoramic radiographs of all patients were taken in order to provide partial diagnosis of the presence or absence of osteoradionecrosis. Presumably Makkonen, Kiminki, Makkonen and Nordman (1987) would have diagnosed osteoradionecrosis as explained in Makkonen (1988, thesis, "Studies On Oral Complications Of Head And Neck Cancer Radiotherapy"); in the latter ORN diagnosis was based on both clinical and radiological examination. The radiological diagnostic criteria cited in the thesis were

"increased radiographical thickness, mottled areas of osteolysis, sequestra, osteoporosis, or fracture"\textsuperscript{102} The clinical diagnostic criteria were "visible infection [!] of oral soft tissue (edema, redness, fistula) sequestrum, trismus, and/or pain."\textsuperscript{103}

Using these diagnostic criteria, Makkonen, Kiminki, Makkonen and Nordman (1987) found no cases of osteoradionecrosis among patients treated in a single radiotherapeutic regime even though 45 teeth had been extracted before irradiation and 94 after irradiation. The authors state that preradiotherapeutic preventative dentistry measures such as extractions of non-restorable teeth or teeth with noteworthy potential for future disease, coupled with preradiotherapeutic patient motivation to maintain good oral hygiene, and attending their own dentist on a regular basis following discharge, and decay prevention measures, would seem to be sufficient at these dose ranges to prevent the onset of osteoradionecrosis.

In order to attempt to elucidate relationships associated with lack of osteoradionecrosis in extractions prior to irradiation, one may observe that only three of the thirty teeth extracted from the mandible were molars; nevertheless these extractions were performed in nine cases by private dentists in their own surgery and in 6 out of the 10 cases antibiotics were not administered. Also, among post irradiation extractions, 14 of the 66 mandibular post irradiation extractions were molars, yet osteoradionecrosis did not occur. Perhaps half of these extractions were covered with antibiotics at the time of the surgery.

\textsuperscript{102} Cupps (1975) cited in Makkonen (1988 thesis)
\textsuperscript{103} Dodson (1962) cited in Makkonen (1988 thesis)
The one incident of osteoradionecrosis reported in the (Makkonen, Kiminki, Makkonen and Nordman 1987) study occurred in a 37 year old male patient who developed osteoradionecrosis at the angle of the mandible following retreatment (2000 cGy irradiation and a total of 127.5 mg of bleomycin over 13 courses of treatment) following apparent recurrence of the original tumor 3 years after original radiation treatment at 6200 cGy (NSD = 1.579 rets). Osteoradionecrosis was diagnosed 2 years after this second course of irradiation and the patient died 2 years after that.

Criteria used by Makonnen for extraction reflect the consensus of his references and those of this thesis (Daley and Drane 1972; Beumer et al 1979a; Beumer et al 1979b; Murray et al 1980a; Murray et al 1980c; Morrish 1981). They further follow the recommendation of an earlier reference (Hayward et al 1969) that, whenever possible, surface coverage of bone should be complete prior to irradiation.

Makkonen, Kiminki, Makkonen and Nordman (1987) concur with the general recommendation that teeth should be treated before commencing radiotherapy in order to avoid post- irradiation extractions, when possible.104

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104 Makkonen, Kiminki, Makkonen and Nordman (1987) cite Beumer, Silverman and Beanak (1972) as stating that the period required for healing of extraction wounds is dependent on several variables including planned irradiation dose, the irradiated volume, the age of the patient, and the degree of difficulty of the extraction. For instance, extractions in the elderly were surgical extractions would take longer to heal.

Makkonen, Kiminki, Makkonen and Nordman (1987) cite three articles [(including (Beumer and Seeto 1981)] as expressing the opinion that post-irradiation tooth extractions on an elective basis are to be avoided wherever possible, and that the preferential treatment at this time may be to grind down the crown of the teeth to the level of the gingiva, presumably with close monitoring.
Clinical studies previously cited have showed that post-irradiation tooth extractions tend to predispose to osteoradionecrosis more heavily than pre-irradiation extractions. In his 1988 thesis Makkonen does not advocate post-irradiation extractions over pre-irradiation extractions but does in part present data and perspectives that, taken alone, could advance this contrary view. Makkonen (1988, thesis) explains that some of his references Wildermuth and Cantril (1953), Sulliman et al (1968) and Carl et al (1973) have claimed the risk for ORN following post-irradiation extractions to be as low as 0%. [However, Beumer and Seto (1981) state that "the risk of bone necrosis after extraction of teeth within the radiation field has been reported to be as high as 100% and as low as 0% [3 references]; interpretation of the data provided in these studies is difficult, however because of imprecise definitions of osteoradionecrosis and poor documentation of radiation dosages and radiation fields." ] Makkonen also cites Hoffmeister et al (1969) as stating that vascular compromise in bones and soft tissue is greatest 3 to 9 months after radiotherapy and persists at a level of 75% of normal 12 months after therapy. (The more authoritative article Marx and Johnson (1987) disagrees with this, indicating the trend for perfusion anomalies to persist and increase with time.) Makkonen (1988, thesis) also cites Jacobsson (1985), an animal study, as finding that bone regeneration immediately following irradiation is slower than 12 months later. If true and generalizable to human populations at risk for ORN, this would suggest the possibility that post irradiation extractions might heal at the relatively best rate following resolution
of the acute phase of tissue reactions to irradiation. However, this hypothesis has not
been subjected to experimental analysis in a controlled fashion.\footnote{As far as a personal literature search can determine. As an aside, Carlson (1994) interprets Marx and Johnson (1987) as suggesting that the highest risk for osteoradionecrosis occurs when teeth are extracted during the therapeutic irradiation, rather than before or after.}

Regarding post-radiation extractions, Beumer, Curtis and Harrison (1979b) cite data indicating that patients with extractions following therapeutic irradiation developed "spontaneous" osteoradionecrosis in 7 of 57 cases (12.3%) and one further case (2%) due to denture irritation, for a total ORN rate of 14%. It should be noted, even with the low sample size, that 2 of these 8 cases of post-radiotherapeutic extraction-associated ORN proceeded to pathologic fracture and the formation of oral cutaneous fistulas that eventually required resection; Beumer, Curtis and Harrison (1979a), do not mention such dramatic consequences in association with the pre-irradiation extraction-associated osteoradionecroses.

Beumer, Curtis and Harrison (1979b) cite 4 papers as providing other data regarding the incidence of osteoradionecrosis when teeth are extracted following therapeutic irradiation to high dose. One 1972 paper described a 100% ORN rate, while among others (1973, 1968, 1953) the risk range ranged as low as 0%.

Maxymiw, Wood and Liu (1991) investigated the effect of a specific conservative surgical technique on the incidence of osteoradionecrosis following post-radiotherapy extractions. They covered all such patients with 2 grams of Penicillin-V-Potassium orally 1 hour prior to the surgical procedure and then 600 mg 4 times a day for the following
week. Prilocaine plain or Prilocaine forte was employed as a local anesthetic epinephrine in a ratio of \( \leq 1 : 200,000 \) and a non-lidocaine local anesthetic.) "Atraumatic" surgical technique that avoided periosteal elevation was employed and only one, or at the most two teeth per quadrant, were extracted at the same appointment. Further extractions were performed on alternating quadrants during subsequent appointments. Careful instructions regarding the use of irrigators to maintain socket hygiene, and careful monitoring of the patients, was employed.

Using this careful oral surgical technique, Maxymiw, Wood and Liu (1991) removed 449 teeth from 72 patients ranging in age from 22 to 80 years (a median of 57.4 years). "Analysis of radiotherapy check-films revealed that only 196 teeth (44%) were included within the treatment volume. The mean prescribed tumor dose was 5000 cGys (range 2500 to 8400 cGys) in 20 fractions (range 10 to 37), with a median dose per fraction of 250 cGys (range 188-314 cGys). Follow-up time ranged from 68 days to 19.3 years (median 4.8 years). No instances of osteoradionecrosis occurred as a result of dental extraction with this conservative method."

While the findings of the Maxymiw, Wood, and Liu (1991) study may be positive, the apparent population of teeth at risk is reduced by recognition that only 49% (123 of 252) teeth extracted were encompassed in the high dose volume, and the extractions were maxillary as well as mandibular. The median doses to the left and right mandible were 4958 cGys and 4965 cGys, respectively. In the left mandible, the dose range was 2548 cGys to only 6274; in the right 2548 cGys to 8476. Thus, it may be
inferred that relatively few mandibular teeth in this study received a dose exceeding 6300 cGys, while some consider dose "thresholds" for high ORN risk to be higher {7000 cGy (Marx and Johnson 1987) or 7500 cGy (Beumer, Harrison, Sanders and Kurrasch 1984).}

Although this surgical approach was reported in the context of post-radiation dental extractions, there is every reason to suspect that it may be applicable to pre-radiation dental extractions.

Makkonen (1988, thesis) cites several articles as indicating that the field size as it relates to involvement of the parotid gland is a very important predictor of persistent salivary function following radiation therapy. There may be recovery of parotid flow only in patients whose parotid glands were not completely irradiated (Al-Tikriti et al (1984) in Makkonen (1988, thesis)).

Makkonen {1988, thesis, but in reference to the same set of cases reported in his paper Makkonen, Kiminki, Makkonen and Nordman (1987)} stated "Although numerous extractions have been performed and some patients also have periodontal infections, no case of osteoradionecrosis related to dental factors was diagnosed in the present study."

Makkonen (1988, thesis) also suggests that because of the higher risk for osteoradionecrosis following irradiation found at many centers, these extractions should be planned only after consideration of the total radiation dose and field coverage and after consultations with the radiotherapist and oral surgeon.

Fein et al (1994) found that the rate of severe complications was significantly higher (p = 0.01) for T3 patients treated with surgery, especially those patients treated
with post-operative radiotherapy as well. Fein et al (1994) defined a severe complication as one that "resulted in hospitalization or necessitated surgical intervention." A large apparent difference in rates of severe complications was found among T\textsubscript{3} tumors treated by surgery alone or in combination with radiotherapy (29% vs. 3%, \(p = 0.01\)). This finding is not duplicated, however, for T\textsubscript{1}, T\textsubscript{2}, or T\textsubscript{4} tumors, where analogous rate differences are associated, respectively, with \(p\)-values of 0.74, 0.5, and 0.24, and with rates ranging between \(-40\%\) and \(-10\%\). An explanation for the T\textsubscript{3} finding is not immediately apparent.

Kluth, Jain, Stuchell and Frich (1988) conducted a retrospective study of the 135 of 276 radiation therapy patients that were followed up in the dental clinic for a minimum of 18 months. Among these 135 patients, 14 cases of osteoradionecrosis and/or radiation osteomyelitis developed. These 14 cases were retrospectively matched, using criteria of similarity of tumors and radiation treatment, with the most similar 28 cases among the remaining 121 without osteoradionecrosis.

The Kluth, Jain, Stuchell and Frich (1988) study is noteworthy in its consideration of the use of tobacco and alcohol as potential risk factors for osteoradionecrosis. It was observed that 6 of the 8 dentulous eventual osteoradionecrosis patients continued to have a poor oral hygiene status even after radiotherapy, in contrast with zero among the 19 "controls" associated with these 6 patients. 13 of the 14 patients with osteoradionecrosis had continued the use of tobacco products even after

\[106\] They generally recommend surgical treatment for T\textsubscript{1} and T\textsubscript{2} patients with twice-a-day post-operative radiotherapy in selected cases.
osteoradionecrosis arose. (10 smoked cigarettes, including one using greater than two packs per day, one patient chewed tobacco, one smoked cigarettes as well as chewing tobacco, and one patient used snuff. One of the tobacco chewers chewed tobacco very heavily. The tobacco usage status of one of the 14 of osteoradionecrosis patients was not recorded.

Among the "controls", 6 of the 26 for whom a tobacco history was recorded smoked after radiotherapy but in no cases more than 2 packs per day.

10 of 13 osteoradionecrosis patients with recorded alcohol histories drank heavily (6 or more beer daily, more on weekends), while 2 were social or occasional drinkers. In comparison, only 1 of the controls (among that 17 of the 19 controls who had recorded alcohol histories) was a heavy drinker, 4 were moderate drinkers, 8 drank slightly, and 4 drank not at all after radiotherapy.

10 osteoradionecrosis patients continued heavy use of both alcohol and tobacco after radiation therapy, while 2 continued moderate use. In comparison, only 2 patients continued the use of both alcohol and tobacco after radiation therapy among the controls, and this use was moderate or less, while 4 stopped the use of alcohol and tobacco entirely, even before radiotherapy.

Although small numbers are present, these findings highly suggest an association between a tendency to smoke and drink and a predisposition to osteoradionecrosis. Kluth, Jain, Stuchell, and Frich (1988) consider alcohol and tobacco irritants that significantly increase the risk of mucosal breakdown leading to osteoradionecrosis and is
also associated with poor oral hygiene and possibly other factors that may contribute to sepsis and tissue irritation.

The finding of Kluth, Jain, Stuchell and Frich (1988) of equal numbers of men and women (7:7) among the osteoradionecrosis patients is unusual. They suggest that the association of osteoporosis in women above age 40 may account for their findings of infection in 3 of the 7 osteoradionecrotic women while only 1 case of infection (radiation osteomyelitis) was found among the men with osteoradionecrosis. (The age range of men in the study was 48 to 63 years and for women was 41 to 73 years, so age probably was not a confounding variable, although the ratio 3:1 may not be significant considering the small numbers involved.)

Larson (1993, "Long Term Effects Of Radiation Therapy In The Head And Neck") utilized an adaptation of the "Late Radiation Morbidity Scoring System" of the Radiation Therapy Oncology Group of the EORTC (European Organization for Research and Treatment of Cancer) during retrospective analysis of 128 of 569 adults treated with radiation therapy for squamous cell carcinoma of the head and neck at the M.D. Anderson Cancer Center between 1964 and 1975. His data may not be generalizable to present populations if therapeutic regimes have changed but the study is notable for its relatively long follow-up. 441 of 569 patients were excluded from analysis due to subsequent metastasis, recurrence of cancer, death, or prior surgical treatment, leaving 128. Follow-up was a minimum of 5 years, ranging up to 15. Larson (1993) graded retrospectively through chart review bone/tissue ulceration, necrosis, bleeding, and spontaneous fracture in 126 M.D. Anderson Hospital head and neck cancer patients. Its overall conclusion,
incorporating some material from a citation (Larson, Lindberg, Lane and Goepfert (1983)), was that osteoradionecrosis of the mandible resulted in partial hemimandibulectomy in almost all patients between 1964 and 1975 with the necrosis at the site of a tooth extraction, and overall, the osteoradionecrosis of the mandible required hemimandibulectomy in 41% of the patients who suffered from osteoradionecrosis. The osteoradionecrosis incidence rate varied according to primary site of tumor:

- oral tongue, 26.8%;
- floor of mouth, 41.9%;
- retromolar trigone, 30%;
- tonsillar fossa, 42.3%.

Cumulative incidence was

- 42% within 2 years after radiotherapy,
- 56% within 3 years, and
- 82% with 5 years.

Mandibulotomy involves sectioning of the mandible in order to provide greater access to tumors during surgical procedures. Even following reduction, mandibulotomies may be associated with permanent loss of function, for instance of the inferior alveolar nerve. When a mandibulotomy has been performed for access in primary surgery, union of the mandible and soft tissue healing should be deemed to be complete prior to starting radiotherapy unless early recurrence has occurred, or a greater risk for complications may be presumed (Shah, J. T. et al 1993). Carlson (1994) describes the mandibulotomy at the angle of the jaw for access to tonsilar and base of tongue carcinomas as being magnifying tissue injury "magnifying tissue injury in the area, and presumably increasing
the risk of osteoradionecrosis. He contrasts this with the median mandibulotomy described in his reference SanGiacomo et al (1992) as a preferred approach that most frequently places this injury to the mandibular bone outside the region of the irradiated field. Altman and Bailey (1996) found that osteoradionecrosis can prevent union of the mandible following mandibulotomy, and review treatment procedures appropriate to osteoradionecrosis in prior mandibulotomy sites. It would appear that many of these (e.g., "defunctioning of the mouth with naso-gastric feeding or gastrostomy") may be associated with greatly diminished quality of life for a period of time. The authors conclude, "mandibulotomy should, whenever possible be avoided if radiotherapy has been used as the primary mode of treatment."

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107 Altman and Bailey (1996) observations:
Five patients demonstrated exposed non-healing irradiated bone with or without extra oral fistulae, and radiologic findings consistent with osteoradionecrosis. In four of the cases osteoradionecrosis developed in mandibles that had been therapeutically irradiated four to nine months earlier; osteoradionecrosis was diagnosed in these patients three to six months following surgery. The fifth patient received therapeutic irradiation in three months following mandibulotomy; osteoradionecrosis developed nine months following irradiation.

108 Shah (1993) evaluated the fixation methods suitable for reduction of mandibulotomies for access to oral pharyngeal tumors.
4. FACTORS THAT MAY PREDISPOSE ORN: SUMMARY

The following compilation of osteoradionecrosis risk factors has two purposes:

a) to gather together most hypothesized ORN risk factors and extraction indications for final review, and

b) to complement previous discussions with additional perspectives.

The list will not be prioritized, includes statistically dependent variables, and omits much significant information and many perspectives and statistics described previously. Otherwise, the list below attempts to consider all potential factors mentioned in the literature. The reader desiring additional perspectives may consider Friedman (1990, in (NIH 1990)) and Stevenson-Moore and Epstein (1993).

Rankow and Weissman (1971) listed potential risk or predisposing factors for osteonecrosis including size of tumor, presence or absence of multimodalities of radiation therapy, the energy/voltage of the radiation source, the field size and number of treatment fields, the oral hygiene potential and the presence or absence of dental trauma including dental extractions, and the presence or absence of post-radiotherapy neck dissection. These factors are updated in more recent, and thus more relevant, literature.

Marx and Johnson (1987) list the following risk and severity factors for osteoradionecrosis:

1. "increasing doses of irradiation above 7000 cGys'

2. "increased dose rates (fractions greater than 200 cGys per day)"

3. "implant sources"
4. "neutron beam'
5. "concomitant surgery'
6. "concomitant chemotherapy or hyperthermy"\textsuperscript{109}

The ADA Oral Health Care Guidelines (1989) state that the incidence of osteoradionecrosis is reduced by

1. adequate healing time of extraction sites prior to radiotherapy (14 days or more)
2. minimizing trauma or irritation to alveolar bone
3. eliminating potential foci of infection or future infection, or other potential sources for future surgical trauma to the area.
4. pre-surgical hyperbaric oxygen.

These factors are included and re-stated in the listing below.

**FACTORS THAT MAY PREDISPOSE OSTEORADIONECROSIS**\textsuperscript{110}

1. **Dose.** (Henk 1985: Factor 1) Morton cites papers as early as Meyer (1958) as relating dose to the incidence of ORN. Henk (1985) cites Watson and Scarborough (1938) as reporting an incidence of 13% osteoradionecrosis in a series of 1819 oral cancer patients treated with irradiation to high dose. Comparability of the technique used with that used today, however, is not assumed so this incidence rate should be regarded as historical.) Another

\textsuperscript{109} See 34. "Simultaneous chemotherapy" below for additional perspectives.

\textsuperscript{110} [Please note: Hyperbaric Oxygen Treatment, being a positive influence on ORN rates, is not listed below. Discussion of treatment and prophylaxis of ORN using hyperbaric oxygen is found in the final part of the Literature Review "3. Clinical Problem": "4. Osteoradionecrosis Pathogenesis, Definition, Diagnosis, Clinical Presentation, and Treatment." ]
study, also not fully relevant to this thesis\textsuperscript{111}, is cited showing no cases of osteoradionecrosis with doses below 6000 cGy, an incidence of 1.8% up to 7000 cGy, and above 7000 cGy an incidence of 9% (Bedwinek, Shukovsky, Fletcher, and Daley 1976).

Beumer, Harrison, Sanders and Kurрасch (1984) state that dosages to bone in excess of 7,500 cGys predispose to high rates of osteoradionecrosis, while those between 6500 and 7500 cGys promote intermediate levels at risk for osteoradionecrosis; this position is echoed by Perrier and Moeller (1994). Marx and Johnson (1987) consider doses of irradiation above 7000 cGys risk and severity factors for osteoradionecrosis. Fujita (1996) considers that an interstitial brachytherapy dose of 6000 cGy appears to be the threshold at which mandibular bone "complication" is induced when the external irradiation dose is 3000 cGys, and found that, "A significant increase in the incidence of bone complication was found at the total dose of 9000 cGys or more, and at the dose rate of 55 cGy per hour or higher.\textit{[p<0.04]}" Yasumoto, et al (1995) considers, as thresholds for the onset of higher incidence and severity of "complications", 7200 cGy for combined external beam irradiation and implant treatment, and 8500 cGy for interstitial implants alone. Pernot, et al (1994) found that " complications" were most influenced by total dose $> 8000$ cGy and treated surface of $>12$ cm\textsuperscript{2}. The ORN relative hazard factors for dose and the equation provided by Withers, et al (1995a,b) could be relevant for

\textsuperscript{111} since it reports on the effects of definitive radiotherapy for squamous carcinoma of the nasal- and oral-pharynx as well as oral cavity
radiotherapy of the tonsil. Dose is a significant factor in the multiple logistic regression equation for necrosis provided in Murray (1980a).

Beumer, Harrison, Sanders and Kurrasche (1984, 825) are of the opinion that "dose to bone is probably the best predictor of [ORN] risk" but that "tumor dose, in and of itself, is not always a reliable indicator of risk for bone necrosis. The number of fractions, the dose per fraction, the time frame of radiation delivery, and the nature of the radiation fields are all important variables that can alter the biologic effects on normal tissues within the field"

Withers et al (1995a,b), previously summarized, offer good current perspectives on these variables as they affect therapeutic tonsil irradiation.

2. **Trauma** as in dental extraction, which places on the bone a demand for bone remodeling and metabolic activity. Moloy, Moran, and Azawi (1991) provided dramatic evidence that the degree of surgical trauma to the mandible may influence the osteoradionecrosis rate. When surgical cancer treatment approach was modified from involvement of the mandible and to assure soft tissue closure following surgery, rates dropped from 100% in the first 5 patients to 0% in the last 7. Nevertheless, a prospective trial in which 112 patients were treated with combined chemotherapy and radiotherapy preoperatively, and 35 received only chemo- and radio-therapy, found ORN rates approximately the same (2.8%) in both groups (Schratter, et al 1991).

Henk (1985) cites his reference Heiss (1971) as stating that the highest incidence of mandibular necrosis occurred in patients having dental extractions immediately prior to radiotherapy.
Trauma can also arise from, e.g., ill-fitting prostheses or rough teeth. Engelmeier and King (1983) state, "To prevent osteoradionecrosis, an intact, infection-free mucosa over the irradiated bone must be maintained."

3. **Infection** via traumatic injuries, tooth extractions, pulpal infection or periodontal infection, which "acts as a mitotic stimulus", increases metabolic demands, and thereby may precipitate necrosis. Radionecrotic ulceration of the overlying mucosa is another route through which infection may manifest.

Robbins, Favrot, Hanna and Cole (1990) identified through logistic regression the following factors as significant in altering the incidence of infection in head and neck cancer patients:

- Wound classification (whether clean, contaminated or intermediate)\(^{113}\)
- Antibiotic regime (use/absence)\(^{114}\)

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\(^{112}\) as discussed also in Subsection 5 of this part (3. "CLINICAL PROBLEM") of the Literature Review.

\(^{113}\) as in Coit and Scalafani (1990, 5) TABLE 2, "CLASSIFICATION OF OPERATIVE WOUNDS", here reproduced:

<table>
<thead>
<tr>
<th>Class</th>
<th>Wound Description</th>
<th>Examples</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>Clean</td>
<td>Non-traumatic, uninfected operative wounds in which respiratory, aliment-ary, or genito-urinary tract is not entered. Usually closed without drains.</td>
</tr>
<tr>
<td>II</td>
<td>Clean-Contaminated</td>
<td>Operative wounds in which the respiratory, alimentary, or genito-urinary tract is entered with only minimal contamination.</td>
</tr>
<tr>
<td>III</td>
<td>Contaminated</td>
<td>Fresh traumatic wounds; wounds with a major break in sterile technique; wounds encountering non-purulent inflammation; wounds made in or near contaminated skin.</td>
</tr>
<tr>
<td>IV</td>
<td>Infected</td>
<td>Wounds in which a purulent infection is encountered.</td>
</tr>
</tbody>
</table>

\(^{114}\) [Interjection by CKC: All studies reviewed by Beumer, Curtis and Harrison (1979b) agree that prophylactic antibiotics are appropriate during surgical procedures. Fleming (1980) suggests, "When a patient has grossly decayed, unsalvageable teeth with periapical pathology or an acutely infected periodontally involved tooth within a previously irradiated treatment field, the method of choice is to treat the patient with antibiotics in an attempt to convert an acute situation into a subacute and eventually chronic situation....The chronically infected tooth root becomes gradually surrounded by granulation tissue, which separates it from the bone, as it is progressively reduced in height by grinding." In contrast, Rothwell (1987) is of the opinion that Rothwell is that there is no evidence of improved outcomes following extractions with the administration of antibiotics in the absence of infection.]
• Concomitant disease (Some possibilities mentioned: Diabetes, chronic pulmonary disease, cardiovascular diseases, other cancers.)

• Neck stage was a "relevant variable."

It should be noted that this article reviews findings from four studies and concludes that the optimal regimen and length of time that antibiotics should be administered to treat infection in head and neck cancer patients remains controversial.

Overall, an infection rate of approximately 20% was found among the four hundred head and neck cancer cases studied prospectively in Robbins, Favrot, Hanna and Cole (1990). Another study, albeit retrospective, of 354 patients found an incidence of wound infection in patients following radiotherapy of 7.6%, not significantly different than the incidence of 6.3% found in patients who had not received prior radiotherapy (Johnson and Bloomer 1989).

Robbins, Favrot, Hanna and Cole (1990) identified through univariate analysis the following factors as significant in altering the incidence of infection in head and neck cancer patients: nutritional status and alcohol consumption, T-stage and N-stage, "duration of surgery, type of surgical wound, complexity of procedure, use of flaps, blood replacement, and the use of drains, nasal gastric tubes, and tracheostomies". However, some of these factors (duration of surgery, complexity of surgery, the use of blood replacement, drains, and tracheostomy) did not show significance in logistic regression; they may correlate with the higher infection rate only because they are associated with
clean-contaminated\textsuperscript{115} procedures in patients with advanced disease.

Please see also the discussions of infections in "33. Extractions", especially; also, "30. Periodontal disease", and "32. Endodontic disease".

4. Invasion of the bone by tumors. Henk (1985) cites his reference Carter (1980) to justify his observation that, "Invading tumors suppress osteoblastic remodeling. [However] if the malignant cells are killed by treatment the bone will attempt to regenerate so that mitotic death of osteoblasts occurs. Consequently, successful treatment by radiotherapy of a carcinoma invading the bone is almost inevitably followed by osteoradionecrosis."

[Please Note: References supporting a factor as a risk for ORN dated 1978 and earlier that were reviewed primarily by Morton (1986) are placed in"{}" below. Others are placed in conventional parentheses "()") ]


Murray et al (1980) found that dentate populations experienced a three-fold rate of osteoradionecrosis relative to the edentulous patients. Factors cited were periodontal disease and trauma from tooth extractions. Henk (1985) comments that improvements in dental management since 1980 have decreased this stated relative risk.

[ The discussions of caries and tooth extraction at the end of this section also have relevance.]

\textsuperscript{115} "Clean-contaminated" operative procedures are those in which the respiratory, alimentary, or genito-urinary tract is entered with only minimal contamination. (Coit and Scalafani 1990, 5)
6. **Circulatory and metabolic vitality. Age. General Care.** The final factors cited by Henk (1985) as increasing the risk of osteoradionecrosis of the mandible is the general care and state of health of the patients. Both systemic health and oral hygiene status are cited as factors predisposing to mucosal ulceration and consequent osteoradionecrosis. Daley and Drane (1974) state that the physical condition and **nutritional status**\(^{116}\) of patients prior to radiotherapy should be considered because impaired constitution may predispose to osteoradionecrosis. Toth, Martin and Fleming (1991) comment that the severity of the morbidity experienced by a therapeutic irradiation patient is related not only to the radiation dose and volume of tissue treated, but the age of the patient when treated. They advocate limitation of elective surgeries to viable patients whose treatment doses were limited.

7. **A site of the tumors close to bone, such as floor of mouth and alveolus:**

{Watson and Scarborough 1938; MacComb 1962; Bedwinek et al 1976}, and (Murray et al 1980a and its multiple logistic regression equation; Murray et al 1980b; Engelmeier and King 1983). Lampe (1971) states that he, along with many others, once adhered to the dogma that treatment of mandibular gingival carcinoma with irradiation to high dose would be followed by an intolerably high incidence of mandibular osteoradionecrosis. However, over the time span 1955 to 1971 he found that \(^{60}\)Co irradiation in these cases resulted in a

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\(^{116}\) Insofar as nutrition is required to maintain host resistance and quality of life and (theoretically) to minimize complication rates including osteoradionecrosis, assessment of the nutritional status and nutritional health promotion efforts are appropriate. Alcohol intake status is also relevant. Both are discussed in (Dwyer 1979); (Barker, Barker and Gier 1994) reference some literature resources.
"remarkably low" incidence of osteoradionecrosis, then went on to advocate routine consideration of therapeutic irradiation for these cancers as an alternative to the then-apparently-preferred surgical resection.

8. **Tumor size [T stage]:** {MacComb 1962; Grant and Fletcher 1966; Rankow and Weissman 1971}, but (Murray et al 1980a; Morrish et al 1981), and (Murray et al 1980b) disagree. Withers et al (1995a,b) found a complex relationship, as indicated in their tables reproduced as Tables 8 and 9 on pages 98-99.


10. **Dental extractions.** Please see 33. below. (Timing is discussed in 20.)

   [Engelmeier and King (1983) tabulate further factors. Omitting duplications from the above and re-ordering the remaining, they state, "The main predisposing factors to osteoradionecrosis are:]

11. **Poor hygiene and inadequate home care** [(Beumer et al 1979a,b), etc.; as discussed in periodontics/dental screening subsection, and a few paragraphs previous to that; 12. "Follow-up", and 15. "Caries Rate", below]

12. **Poor follow-up** [e.g. to ensure proper compliance with recommended home care. Zlotolow (1995) states that the (Dreizen 1977) study of control of radiation caries with fluoride was very significant, and Fleming (1980) states, "After radiotherapy has been completed, patients must comply with a preventive fluoride program." ] Toljanic, Siddique, et al (1996) conducted a double-blind crossover controlled trial that found a weak positive effect of
"salivary peroxidase elements" in controlling gingival disease in patients at risk for ORN, but considered that patient compliance limited the effects observed.

Beumer, Harrison, Sanders, and Kurrasch (1984) considered oral home care compliance levels, along with the nature of the bone exposure, to be a very important predictor of the clinical outcome of existing ORN.

13. Poor patient selection for radiation therapy: for example, poor nutritional status or extensive systemic disease present

14. Inadequate healing time following surgery performed prior to radiation therapy

15. Improper fractionation of the radiation. (Henk 1985) "Dose fractionation prescriptions used in therapy are quite diverse"\textsuperscript{117}. Withers et al (1995a,b) were not able to reach definitive conclusions on a number of fractionation issues. However, as implemented in one regime, hyperfractionation resulted in excessive osteoradionecrosis\textsuperscript{118} (a late complication). The Roos, Dische, and Sunders (1996) CHART regime (3 tx/day @ 1500cGy/fraction on 12 consecutive days), on the other hand, was associated with an acceptable ORN rate.


\textsuperscript{117} (Withers et al 1995a). Two tables from (Withers 1995a,b) are reproduced as Tables 8 and 9 on pages 98 and 99.

\textsuperscript{118} Niewald et al (1986) found a 22.9 % ORN rate in patients treated with two daily fractions of 1200 cGy, 4 hours minimum apart, total 8280 cGy, vs. 8.6% ORN rate in conventional single doses of 2000 cGy, total 6000 to 7000 cGy. (p = 0.029 but dose or dose-dependent/involving relationships could be potential confounders.)
Other factors suggested as impacting the prognosis for osteoradionecrosis directly or indirectly are

17. Combined radiotherapy and radical surgical neck dissection (including branches of the carotid artery). Rankow and Weissman (1971) mention post-radiotherapy radical neck dissection as a predisposing factor for ORN. They mention a plausible pathogenetic mechanism by which this could contribute to osteoradionecrosis, mainly that "baring of the inferior order of the mandible during radical neck dissection results in a decreased periosteal arterial blood supply to the mandible as well as venous congestion...." Quantification of post-radiotherapy radical neck dissection as a risk for osteoradionecrosis may be difficult due to concurrent disease that may confound analysis, but this difficulty need not rule it out as a factor worthy of consideration.119

18. Mandible or maxilla. ["Because the mandible is greater in bone density than the maxilla, the mandible absorbs more radiation energy. This, plus the fact that the maxilla have a more diversified blood supply, apparently explains the lower occurrence of osteoradionecrosis in the maxillae than in the mandible"(Fleming 1980),] etc.

19. Part of mandible (Galler et al 1992), as discussed in periodontology section; etc.

20. Timing of Extractions: Before, or After, therapeutic irradiation, and when:

( Epstein et al 1987a; Beumer et al 1979a; Beumer et al 1979b; Beumer, Harrison, et al 1983a; Beumer, Harrison, et al 1983b; Beumer and Seto 1981)

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119 Shibuya, et al (1993) also cite their references Jesse, Barkley, Lindberg and Fletcher (1970) and Pierquin, Chassagne, Baillet, and Castro (1971) as indicating that elective neck dissection does not improve the overall survival of patients with oral carcinoma.


24. Radiation Fields. Beumer, Curtis and Harrison (1979b) describe soft tissue necroses as being most closely associated with interstitial or peroral cone techniques which allow local high dose irradiation. Soft tissue necrosis is, of course, associated with a higher incidence of osteoradionecrosis. However, Yasumoto et al (1995) conclude that "among our patients with their primary lesion under control, the incidence of bone and or soft tissue complications was evenly distributed in the three treatment modality groups (implant alone, implant plus external radiation and external radiation alone). Unfortunately, with regard to the complication of osteoradionecrosis, the small number of ORN compared do not permit this statement to stand alone as a definitive conclusion. (For further comments, consider cancer treatment discussion of brachytherapy.)

25. Pre-irradiation dental status. (Beumer et al 1979a; Beumer et al 1979b). This is one of three significant variables in the Murray (1980a) multiple logistic regression equation prediction formula for necrosis rate. See also, e.g., 15., 16., and 17. above; also "Caries Rate", "Periodontal /Endodontic Status", below.
26. **Surgical technique:**
   a. during tooth extraction before irradiation
   b. during tooth extraction after irradiation.

27. **Dental prosthetic rehabilitation,** but Beumer, Curtis and Harrison (1979b) cite Beumer, Curtis and Morrish (1976) in which 92 patients edentulous prior to therapeutic irradiation, and of which 87 had dentures extending over the bone in the high dose irradiation volume, did not develop any osteoradionecrosis.

   Soft liners with silicone are not wettable in comparison with hard polymethylmethacrylate; this contributes to mucosal pull and a high rate of osteoradionecrosis (e.g. 8/25, = 32%) (Daley and Drane 1972).  

   Beumer, Curtis and Harrison (1979b) review several papers analyzing the timing of insertion of dental prostheses following therapeutic irradiation. One viewpoint is that there must be sufficient time of healing and recuperation of the irradiated tissues before insertion of dentures. Another view is that the risk of osteoradionecrosis tends to increase with time (Marx 1983a). Given these conflicting views, and the potential for non-comparability of data, the different conclusions reached by different authors is understandable. The opinion that it is unnecessary to wait beyond 6 to 12 months before placing dentures in most patients could seem reasonable. In fact, more recent papers have suggested shorter periods. Beumer, Curtis and Harrison (1979b) provide a fairly

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120 as cited in (Beumer, Curtis and Harrison 1979b)
comprehensive explanation, amounting almost to a protocol, of appropriate full denture technique in these patients.

28. Diet and smoking (Kluth, Jain, Stuchell and Frich, 1988).\(^{121}\) (See pp. 139-141).

29. Caries Rate. Irritation of the pulp resulting from progressive deep caries leads to pulpal death with high potential for periapical inflammation and/or infection, increased risk for osteoradionecrosis, and indication for endodontic treatment (if not extraction, another risk factor for osteoradionecrosis.)

30. Periodontal Status.\(^{122}\) This may be the most important dental consideration aside from acute infections during pre-radiotherapeutic assessment for extractions (Beumer, Curtis, and Harrison 1979a; somewhat echoed by Beumer, Harrison, et al 1984). Epstein, Wong, and Stevenson-Moore (1987) considered periodontal disease sites irradiated to a time dose factor 109 to be at risk for ORN. Toth, Martin and Flemming (1990) considered that teeth with pockets > 7mm predispose infection and should be extracted prior to radio- or chemo-therapy. Local experts (Epstein 1997 private communication) consider as potential indications for extraction, depending on patient characteristics, 5-6 mm. pockets. Molar furcation involvements as small as Class I are of concern in upper teeth. Tooth mobility is evaluated in combination with horizontal bone levels and vertical bone loss and is of particular concern in teeth that may serve as potential abutments for dental prostheses.

\(^{121}\) Also, perhaps, indirectly, (Marunick and Leveque 1989). Of indirect relevance would be the diet and smoking references in "1. ORAL CANCER EPIDEMIOLOGY AND PREDISPOSING FACTORS" Literature Review subsection 1.

\(^{122}\) as discussed in Subsection 5 of this part (3. "CLINICAL PROBLEM") of the Literature Review.
31. **Mandibulotomy** Carlson (1994) describes the mandibulotomy at the angle of the jaw for access to tonsilar and base of tongue carcinomas as being magnifying tissue injury "magnifying tissue injury in the area, and presumably increasing the risk of osteoradionecrosis."

32. **Endodontic Status.**

33. **Dental extractions.** Morton (1986) reviewed the literature to that date:

"The role of extractions as an etiological factor in the development of ORN is not in doubt but there is still uncertainty as to the optimum timing of extractions and indeed to the techniques of extraction. Pre-irradiation dental clearance was favored by Watson and Scarborough (1938) in the pre-antibiotic era. More recently Rankow and Weissman (1971) suggested dental clearance 10-14 days prior to therapy, the extractions being accompanied by alveoplasty. Meyer (1958) advocates pre-irradiation extractions plus alveolectomy and feels it is a reason for his fairly low incidence of ORN (5.3%). Beumer et al (1972), Daley et al (1972), and Bedwinek et al (1976) all showed a higher incidence of ORN with pre-irradiation extractions, but Morrish et al (1981) felt pre-irradiation extractions did not lead to an increased incidence of ORN.

"[The commentary on the Makkonen articles and thesis above are relevant to this point.]" Starke and Shannon (1977) reported one case of necrosis in 62 patients who had pre-irradiation extractions; there was an average healing time of 25.3 days. Beumer et al (1979) suggest that 7-10 days healing is advisable, but where the radiation dose is going to exceed 6500 rads, 14-21 days should be allowed. Grant and Fletcher (1966) and Morrish et al (1981) feel that post-irradiation extractions are more prone to cause ORN than pre-irradiation extractions, while MacComb (1962) felt that there was no difference. Later however, Daley et al (1976) showed the incidence of ORN following post-irradiation extractions to be lower than that following pre-irradiation extractions. There is general [but not unanimous] agreement that antibiotic

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123 as discussed in Subsection 5 of this part (3. "CLINICAL PROBLEM") of the Literature Review.
124 [Epstein, Rea, Wong, Spinelli, and Stevenson-Moore (1987a, 52) provide evidence to support the prophylactic removal of diseased teeth. "Prophylactic extraction of teeth before radiation therapy has been suggested to prevent the development of dental complications that may require extraction and stimulate the development of necrosis. (18,20,21,26) In the present study...twice the risk of osteonecrosis is seen in those in whom teeth were extracted after irradiation (2.2 vs. 1.1%). A comparison of the number of cases of necrosis in relation to the number of patients who had teeth removed shows a higher percentage (7.1 vs. 5.4%) of necrosis in patients with teeth extracted after radiotherapy. These
cover for post-irradiation extractions is advisable but opinion on extraction technique both pre- and post-irradiation is divided. Coffin (1964; 1983) emphasizes a conservative approach with 'atraumatic' non-surgical extraction. Others feel that alveolectomy and removal of all sharp bone, with edge to edge closure of the soft tissues over the socket is preferable (Beumer et al 1972; Horiot et al 1981).

Barker, Barker, and Gier (1990) state that teeth can never be extracted from irradiated bone without the risk of osteoradionecrosis. "More conservative techniques such as endodontics should be considered to alleviate the signs and symptoms of pulpal and periapical disease" (Engelmeier and King 1983). Barker, Barker, and Gier (1990) further suggest that nothing can be done to prevent mucositis, hypogeusia (an abnormally diminished acuteness of the sense of taste), and xerostomia post-radiotherapeutically, and thus recommend only palliative measures, i.e. after the fact. Like previous references, they recommend two weeks healing following extractions prior to radiotherapy. They comment that the guidelines for extraction published by the National Institute of Health Consensus Development Conference do not provide exact guidelines for extraction prior to radiotherapy, and that some judgment is necessary in this regard. Relevant criteria would be the future status of the teeth and the long term survival of the patient. They recommend extractions for any teeth with advanced periodontitis and mobility, and molars with furcation involvement; optional extraction of partially impacted third molars in the field of radiation, but leaving dentate the totally non-symptomatic bony impactions unless three weeks of healing can be allowed.
before initiation of radiotherapy (Barker, Barker, and Gier 1990). Barker, Barker, and Gier (1990) also indicate that the removal of any bony pathology such as periapical infections, odontogenic cysts or tumors, or treatment of same, also would be mandatory.

Rothwell (1987) mentions as factors affecting the decision to extract: gross caries, severe periodontal bone loss, poor periodontal prognosis, low patient dental I.Q., urgency of radiotherapy, and status of eruption. [He recommends extraction of partially erupted teeth, but retention of potential prosthetic abutments, if possible.]

Beumer, Curtis and Harrison (1979a) indicate the following criteria for pre-radiation tooth extraction:

- immediacy of treatment,
- prognosis for tumor control,
- mode of therapy as in whether external or implant or both,
- radiation field,
- the dose,
- condition of the residual dentition, and
- the patient's dental awareness.

Criteria for extraction of teeth in the irradiation field are amplified in Beumer, Curtis and Harrison (1979b): radiographic furcation involvements, significant pain, and/or evidence of pulpal exposure and periapical pathologies are specifically mentioned in this paper.

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125 "Low dental I.Q." is lack of sophistication about the effects and prevention of dental disease, and dentistry in general. Whether due to lack of knowledge or intelligence, or lack of motivation to learn about or care for one's teeth, elevated risk for dental disease and inadequate future compliance with prescribed oral self care is implied.
Perrier and Moeller (1994) list the following indications (if translation suffices) for extraction of teeth prior to therapeutic irradiation:

- large caries
- periapical lesions
- advanced periodontitis
- root remnants,
- partially erupted teeth, and
- impacted teeth.  

Beumer, Curtis and Harrison (1979b) recommended multiple adjacent extractions (i.e. removed in segments”), when indicated because post-surgical closure of flaps easier in this scenario than for individual teeth. Coverage with antibiotics was advocated. 7 to 10 days healing prior to irradiation was considered adequate for healing in most cases, a 1979 recommendation that now might be considered obsolete, Marx and Johnson (1987) having provided evidence that the risk of osteoradionecrosis can be minimized by doing necessary extractions at least 21 days pre-radiotherapy. [Beumer, Curtis and Harrison (1979b) did state, however, that doses in excess of 6500 rads indicated 2 to 3 weeks of healing time to ensure better healing of the wound.]

A tooth extraction technique advocated by Maxymiw, Wood, and Liu (1991) is described on page 137 of the Literature Review.

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127 (p. 394, top right),
Extractions preceding therapy should be done in a non-traumatic manner with alveoplasty bone polishing and primary closure (Epstein et al 1987b; Epstein et al 1987a; Friedman, NIH 1990, 145-49).

Beumer, Curtis and Harrison (1979b) do not recommend extraction of full bony impaction third molars because of the attendant osseous trauma and healing requirements that should predispose to osteoradionecrosis. Indications for extraction of partially erupted mandibular third molars, on the other hand, are considered by Beumer, Curtis and Harrison (1979b) to be stronger, presumably because of a greater chance of infection and somewhat less surgical trauma potential in many cases. Operculectomy (removal of soft flaps partially covering partially erupted third molars, predisposing to plaque and bacterial accumulation and superficial infection) may be advisable in selected cases prior to exposure to osteoradionecrosis-predisposing radiation dosages.

Sonis, Wood, and White (1990) advocate pre-radiotherapeutic extraction of third molars with pericoronitis or other source of infection.

Beumer, Curtis and Harrison (1979b) advise that criteria for dental extraction treatment planning would be different for cases of therapeutic irradiation associated with Hodgkin's Disease than for squamous cell carcinoma, because treatment for Hodgkin's Disease involves dosages only in the range of 4,000 cGy to 5000 cGy. This may lead to the selection of a different type of surgical intervention.
Rodu, Filler and Woodfin (1985) advance orthodontic movement as an alternative to extraction with a rationale that it would reduce extraction trauma that could predispose osteoradionecrosis: "In contrast to the sudden trauma induced by traditional extraction, removal of a tooth by this procedure virtually is atraumatic and promotes continuous and gradual healing, which eliminates an open wound susceptible to infection. Thus, theoretically, tooth extraction can be performed by this technique in an irradiated bone without challenging its tenuous vascular supply, overtaxing its limited potential for repair, or introducing bacterial overload."

34. **Simultaneous Chemotherapy.** Marx and Johnson (1987) consider this an ORN risk variable.

Turner, et al (1996) studied complications following radiotherapy of 333 oral squamous cell carcinomas. Turner, et al found that synchronous MTX chemotherapy contributed to late morbidity rates defined as "late healing soft tissue injuries or bone necrosis" [italics mine].

Archibald et al (1986) concluded "the addition of chemotherapy to the treatment regimen did not increase the incidence of complications (osteoradionecrosis, mucositis, xerostomia, radiation caries, or infection) when compared with historical controls receiving radiotherapy alone." Such conclusions are not definitively established by this paper. The use of historical controls, lack of direct comparability of the four articles cited, particularly in relationship to the ratio of pre- and post treatment tooth extractions, and small numbers of patients reviewed (a total 22 patients...
receiving multimodality cancer treatment) all leave the conclusions in a non-definitive state.

[Schratter-Sehn et al (1991), as in "2. Trauma" above, is of peripheral relevance.]

35. **Neutron beam** (Marx and Johnson 1987). Schultheiss (1990) found rates* of mandibular osteonecrosis:

- between 2000 and 2199 cGy of neutron irradiation, 4.1%;
- between 2200 and 2399, 13.2%;
- between 2400 and 2599, the rate was 35.2%, and
- above 2600 cGy, 41.7%.

* (but the clinically realized observed complication rates would be lower--see Literature Review for explanation.)

36. **Hyperthermy** (Marx and Johnson 1987)
CHAPTER III. METHODOLOGY

THE DELPHI PROCESS 1. RATIONALE AND STRATEGY

To augment the osteoradionecrosis literature, this survey of international clinical experts sought consensus on ORN risk factors, factors relevant to ORN management decision analysis model creation and decision making, quality-of-life-associated outcome surrogates, and the impact of dental management decisions on the prognosis for ORN. To achieve these objectives, open- and close-ended questions, scenarios, and rating scales for confidence in responses and agreement with Delphi statements were presented to the expert volunteers.

Delphi consensus methodology was chosen for the Survey because, among the methods available to achieve consensus (Fink, et al 1984), it permitted analysis of responses from a select group of experts, provided anonymity required to minimize intimidation, and it did not require simultaneous geographical proximity of the experts and involvement of a trained panel-discussion facilitator. Traditional Delphi format was modified, combining traditional Round 1 (open-ended) with a close-ended substitute for Round 2 to minimize the number of times busy experts were bothered. This approach also provided in a single distribution an opportunity for open/close-ended information comparison, permitting evaluation of the face and content validity of the model of osteoradionecrosis risk factors selected by the author for the close-ended items, based on an initial review of the literature, as well as a sense of reliability.
Delphi item statements were designed intentionally to produce a mixture of positive or negative responses, but the systematic repetition throughout the survey of analogous item statements in opposite forms to minimize framing bias (Woltert 1989) and to enable evaluation of one form of reliability was judged to be an undesirable approach because it would add to respondent fatigue in the already 60-page-long survey. (Poorer survey completion due to fatigue would tend to decrease content validity.) However, two pairs of separated Likert response items were included to permit quantitative sampling of test-retest reliability.

The draft of the Survey was pre-tested on two experts (one M.D. and one D.M.D.), then slightly modified.

Experts responding to the Survey indicated that they could not provide certain data required to create a uniformly well quantified decision analysis. Since these data would not be improved over multiple iterations, the objective of gathering data for a decision analysis would not be fulfilled better over multiple iterations. Therefore, the Modified Delphi technique outlined above was modified further by restricting it to a single combined-Rounds-1-and-2-iteration. While this restriction is not a "traditional Delphi" process, it nevertheless is supported by literature.²

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1 Analogous positive and negative item statements will elicit opposite agreement scale responses when responses are reliable. In addition to this form of repetition of statements to test reliability, other techniques may be used, some mentioned in variants of Delphi (Kendall 1977; Rauch 1979; Webler et al 1991).

2 e.g., Linstone and Turoff (1975) cite their reference Brockhoff (1975) as stating that rounds beyond two (the traditional two essentially combined in the present Survey) may actually impair results. Sahal (1975) cites his references Gettys, Kelly and Peterson (1973), Peterson (1973), and Martino (1972), as stating that rounds beyond two may not result in any advantage.
THE DELPHI PROCESS 2. THE SAMPLE

Respondents were selected in the following manner:

1. An initial 14 experts selected on Dr. Epstein's recommendations, and an additional initial 7 references from the preliminary literature review, were asked to participate in the survey in February and March of 1994. Each of these 21 individuals was supplied with a description of the project, an agreement form for participation stating that withdrawal at any time was permissible, and a separate form asking the respondent to recommend other suitable participants for the survey. (For letters and forms, please see Appendix 2.) One solicitation was returned "Address Unknown." 15 of the initial 20 contacted (75%) agreed to participate in the survey.

2. 13 recommendations were made by these first 15 agreeing to participate. One of the 13 (a hygienist with published experience in oncology who was qualified by an M.Sc. but not an M.D. or D.M.D.) was a co-worker with the other expert referring, and therefore did not sufficiently meet Delphi requirements for independence. The remaining 12 were solicited for participation, of which 8 (67%) agreed to participate (a figure ultimately comparable to the initial rate, but achieved only after 3 months.)

3. These 8 "secondary referrals" recommended a further 3 experts, of whom 2 (67%) agreed to participate.

4. These 2 "tertiary referrals" in turn recommended 3 other potential participants, but these were sent the surveys themselves, with apologies for the presumption that they may wish to participate. (Of these, one agreed to participate, and returned the survey.)
THE DELPHI PROCESS 3. RESPONSE RATE

In overview, 28 of 38 experts (74%) solicited for participation in the Delphi Survey agreed to participate. 16 of the 38 (42%) actually returned the 60-page long survey. Response rates were 55% among North American solicitations, 25% among others.

In greater detail, 40 experts in Australia, Canada, the U.S., Great Britain, France, the Netherlands, Germany, and Sweden were solicited to participate in the 60-page-long survey. Of these, one could not be located, and another did not fit the entrance criterion of being an independent expert. Thus, 38 were left.

35 of these experts were solicited by letter. 25 of these (25/35 = 71.4%) agreed to participate in the survey. These 25, along with 3 "final referrals" from those previously contacted, received the survey in July and August of 1994. Of these 28 sent the survey, 16 (16/38 = 42%) participated in, and returned the survey. (Surprisingly, 3 of the 16 surveys returned were lost in the mail. However, 2 participants were able to send Xerox duplicates, bringing total survey returns to 15. The survey irretrievably lost, unfortunately, was from 1 of the 2 radiation oncologist M.D. respondents.)

7 of the 14 experts (50%) recommended by Dr. Epstein, 2 of the 7 (28.5%) experts identified through my own literature search, and 6 of 19 (31.6%) of the expert secondary, tertiary, or final referrals, returned their survey. The letter soliciting agreement sent to the 14 experts recommended by Dr. Epstein mentioned his involvement in the project; this may have resulted in the observed higher rates of return and quick response times, but the average degree of completion of the very long, 60 page, survey

3 Other experts (Joel Epstein and Frances Wong) reviewed the draft survey but were excluded as potential respondents.
among these was less. Perhaps an explanation of this may be that the commitment by some purely as a favor to Dr. Epstein may have been less deep than the smaller proportions agreeing to participation purely through interest; or perhaps the letter sent to the referrals proclaimed their recognition as experts more prominently and dramatically, and the referrals wished to fully demonstrate their expertise recognized by anonymous peers.

Survey response rates of qualified, solicited individuals, by geographic area, were:

- Australia: 1 / 1 ( = 100%; survey completion = fair);
- Canada: 4 / 8 ( = 50%, including 1 lost in mail; median completion = good)
- U.S.: 8 / 14 ( = 57%; median completion = good):
- U.K.: 0 / 7 ( = 0%)
- Non-U.K. Europe (Solicitations = 5 Netherlands +1 each in France, Germany, Sweden & Finland): 3 / 9 ( = 33%; median completion = fair).

Thus, the survey data in many instances is dominated by U.S. and Canadian participation (11 of 15 returns received, usually better completed, and with a 12 / 22 = 55% return rate. These comments particularly apply to items towards the end of the survey, e.g. outcome data, with fewer responses.)

Milholland, Wheeler, and Heieck (1973) indicated that reliability in Delphi surveys reaches a point of diminishing returns with about 13 participants. Thus, the participation of all the respondents in this modified Delphi Survey was very important. This author wishes to express his appreciation for the admirable efforts of the participants in the Survey (one mentioned 12 hours of work, and expressed regret at being unable to finish all items!), and also to express understanding for the non-participation of others.

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4 The Delphi Survey is reproduced as Appendix 3.
Validated quality of life assessments for oral complications of head and neck cancer therapy are essentially lacking at the present time (Browman 1993; Epstein 1997). In the absence of validated instruments for patient-derived QOL utilities to associate with osteoradionecrosis, clinimetric\(^5\) scales were created for evaluation by survey respondents.\(^7\)

One would hypothesize that the dimensions associated in the literature search with the "Functional Assessment of Cancer Therapy Scale" (Cella, David et al 1993b), the "Head and Neck Radiotherapy Questionnaire," (Browman 1993), the symptom check-list of Osaba (1993), and the "Performance Status Scale for Head and Neck Cancer Patients" (List, et al 1990) are positively related to quality of life. Prosthodontic status also influences quality of life. Jacobson et al (1990) found that the characteristics of prostheses most important to quality of life\(^8\) were, in descending order of importance, comfort, function, and appearance.

Integrating the information above with clinical experience in prosthodontics and articles describing the clinical experience of head and neck cancer [e.g. (Dudgeon, DeLisa, and Miller 1980; Dhillon, Palmer, Pittam, and Shaw 1982)], one can hypothesize that an instrument designed to rate the Q.O.L. associated with then-current oral health should involve, in no particular order, the following dimensions:

1. understandability of speech
2. normalcy of diet

\(^{5}\) complementing the discussion of this in the Literature Search
\(^{6}\) The term "clinimetric" in this context is favored by Feinstein (1987). Osaba (1993) advocates the use of ordinal scales until better measures are available.
\(^{7}\) who in this case were health care providers, not patients.
\(^{8}\) as measured by a "feeling thermometer" approach
3. ability to eat in public [assumed to include the functions of chewing and swallowing, lack of drooling, being able to eat without food impacting into the sinuses, etc.]

4. happiness with appearance

5. comfort level associated with the
   a. throat and other tissues potentially affected by oral stomatitis
   b. bone and associated structures
   c. dentition or prosthesis, and supporting and contacting tissues (attached gingiva, oral mucosa, tongue) during rest and during occlusal function (and parafunction?)

6. ease of maintenance of natural dentition or oral prosthesis

All of the above considerations for dimensions of quality of life were combined with practical constraints (potential for respondent fatigue or confusion, etc.; anticipated difficulties in interpreting complex outcome data) to create the clinimetric scales actually utilized in the survey. These scales created were:

| I. PAIN: | P4 = Generally or frequently Excruciating Pain |
|          | P3 = Generally or frequently Severe Pain     |
|          | P2 = Generally or frequently Moderate Pain   |
|          | P1 = Generally or frequently Mild Pain       |
|          | P0 = Generally No Pain                       |

| II. ORAL FUNCTION: |
|                   |
| F4 = Function of jaws severely impaired (either anatomically, physiologically, or due to pain); Use of dentition or dental prosthesis either ineffective or impractical. |

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9 (Epstein & Stuart 1993)
10 The ease of maintenance of natural dentition or oral prosthesis may be an author contribution. Theoretically, it may be possible for any potential utility of prosthodontic status to be dichotomized for the sake of simplicity: capable of prosthodontic reconstruction in the typical scenario, or not, as determined by a survey of clinical experts.
F3 = Function of jaws mildly or moderately impaired  
(either anatomically, physiologically, or due to pain;) Use of dentition or  
dental prosthesis either ineffective or impractical.

F2 = Jaws functional but severely compromised function of dentition or dental prosthesis.

F1 = Jaws and dentition or dental prosthesis all functioning with at least a  
moderate degree of utility.

F0 = Jaws and dentition or dental prosthesis all functioning well.

Some may question the incorporation of both jaw opening and dental  
prostheses/normal dentition masticatory function in a single scale as described in this  
thesis. However, evidence has been reviewed that describes the effects of mastication on  
quality of life. There is a firm positive relationship between good dental prosthetic  
function and proper mastication; poor dental prosthetic function can cause psychological  
problems, impaired nutrition, injury, pain, and impaired function in jaw tissues (local, or  
tempero-madibular joint.) Arguably, the simple jaw/dental prosthesis function scale  
integrates and measures dimensions that overlap markedly, even if they are not  
coincident. Furthermore, quantification and validation of oral prosthesis function is  
extremely difficult, so a subjective and qualitative scale such as the one employed may be  
most appropriate. Gordon (1991) for example considers that "...Indices used to measure  
the oral status of removable dental prostheses generally do not conform to criteria  
essential to high quality measures. Existing indices fail to meet accepted standards of  
reliability and validity, and most lack specified training protocols, use ambiguous  
terminology, are limited to nominal, ordinal or dichotomous level data, and require high  
levels of observer inference".  

11 Gordon suggests that proper measurement of oral status and treatment need among subjects with  
dental prostheses often require not only prosthesis-related data, but measurement of non dental factors.
The two (Pain/Function) scales used as outcome variables in this study also appear to encompass major dimensions of the "Impact of Oral Disorders" conceptual framework presented in Figure 1 of Locker (1992). This figure integrates impairment from anatomical loss, structural abnormality, or disturbance in biochemical or physiologic processes, which can arise as a result of disease or injury, functional limitation, disability ("any limitation in or lack of ability to perform the activities of daily living"), or pain, all of which could contribute to disadvantage and deprivation, which in turn create a handicap.

Pain and function data are gathered in the Delphi survey using the scales above in association with Epstein (1987b) ORN classifications. The definitions of these ORN classes are used as scenarios for the pain and function assessments. (The uses of pain and function associations with categorized ORN are described in the Discussion.)

Dental and facial pain affects quality of life, and effects may depend on the duration and severity of the pain (Hollister and Weintraub 1994), with subjective utilities highly dependent on the final intensities of the pain (Frederickson and Kahneman 1993; Varey and Kahneman 1992; Redelmeier and Kahneman 1996). Although confirmation of the applicability of the latter finding to chronic conditions such as osteoradionecrosis seems lacking at the present time, it may be beneficial that the Delphi survey requested pain and function data for final states of each categorized osteoradionecrosis outcome state.

Epstein and Stewart (1993) stated that pain often increased throughout the course of radiation and persisted following treatment, in some cases continuing for six to twelve months. Given this trend, were any potential single variable proposed to integrate further the survey's pain and function outcome variables, pain should be considered important.

12 [referenced to its citations (World Health Organization 1980; Locker 1988)]
13 Locker defines a handicap as "the disadvantage and deprivation experienced by people with impairments, functional limitations, pain and discomfort or disabilities because they cannot or do not conform to the expectations of the groups to which they belong."
THE DELPHI PROCESS  5. ANALYSIS

A. QUANTITATIVE DATA

Survey data requiring quantitative analysis were from 7-point¹⁴ Likert Scales seeking two responses: agreement and confidence of opinion.

<table>
<thead>
<tr>
<th>My feelings about the last statement are:</th>
<th>I DISAGREE 1 2 3 4 5 6 7</th>
<th>I AGREE VERY STRONGLY [Please circle a number:] VERY STRONGLY</th>
</tr>
</thead>
<tbody>
<tr>
<td>I AM VERY Very strongly</td>
<td>I AM VERY Very strongly</td>
<td></td>
</tr>
<tr>
<td>My confidence in this answer is:</td>
<td>I AM VERY Very strongly</td>
<td></td>
</tr>
<tr>
<td>UNCERTAIN 1 2 3 4 5 6 7 CERTAIN</td>
<td>UNCERTAIN 1 2 3 4 5 6 7 CERTAIN</td>
<td></td>
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</tbody>
</table>

Necessary analyses -- primarily calculation of the median and interquartile (25-75th percentile) range¹⁵, and sometimes the mean-- were calculated from grouped data using the computer program S.P.S.S.6.1.3. These measures were supplemented by the other calculations easily permitted under the S.P.S.S. Statistics Summarize Frequencies command: Mode, Maximum, Minimum, Range, Standard Deviation¹⁶, Variance, Kurtosis, S.E. Kurtosis, Skewness, and S.E. Skew. (For test-retest reliability the S.P.S.S. Statistics Summarize Crosstabs Statistics Kappa command was utilized).

The item "median respondent confidence in opinion" was used¹⁷ as a surrogate for the quality of the opinion data. A preliminary protocol for analyses (developed prior to the receipt of data) suggested classification of Confidence Scale data medians in the following manner:

---

¹⁴ It could be argued that this "7 point" "Agreement" scale is actually two 4-point scales, one for agreement and one for disagreement, and that future surveys could improve reliability if they substituted a 13 point scale.

¹⁵ measures of central tendency and dispersion justified in the Literature Review

¹⁶ The use of many of these calculations would be restricted, because of the small sample numbers, to qualitative ordinal comparisons between comparable data.

¹⁷ as suggested in the Literature Search
• "Little Confidence", if the median is \( \leq x \); "Some Confidence", if the median is \( > x \) and \( < y \),
• "Fair Confidence", if the median is \( \geq y \) and \( < z \), "High Confidence", if the median is \( \geq z \),

where \( x \text{ preliminary} = 2.4 \), \( y \text{ preliminary} = 4.0 \), and \( z \text{ preliminary} = 5.6 \).

Inspection of the data suggested that median confidence less than 4 appeared to associate with low consensus, while no clear relationship was evident with confidence greater than 5. Therefore, another value scheme was employed:

• "LOW CONFIDENCE", if the median is < 4.0
• "FAIR CONFIDENCE", if the median is \( \geq 4.0 \) and \( < 5.0 \),
• "MODERATELY HIGH CONFIDENCE", if the median is \( \geq 5.0 \) and \( < 6.0 \)
• "VERY HIGH CONFIDENCE", if the median is > 6.0.

These classifications sometimes will be modified by combining terms for borderline values.

Descriptors for agreement to items, reported in association with certain items, were:

• VERY STRONG AGREEMENT if the median agreement is \( \geq 6.4 \), \( \leq 7.0 \)
• STRONG AGREEMENT if the median agreement is \( \geq 5.7 \), \( \leq 6.3 \)
• MODERATE AGREEMENT if the median agreement is \( \geq 5.0 \), \( \leq 5.6 \)
• WEAK AGREEMENT if the median agreement is \( \geq 4.3 \), \( \leq 4.9 \)
• NEUTRALITY if the median agreement is \( \geq 3.8 \), \( \leq 4.2 \)
• WEAK DISAGREEMENT if the median agreement is \( \geq 3.1 \), \( \leq 3.7 \)
• MODERATE DISAGREEMENT if the median agreement is \( \geq 2.4 \), \( \leq 3.0 \)
• STRONG DISAGREEMENT if the median agreement is \( \geq 1.6 \), \( \leq 2.3 \)
• VERY STRONG DISAGREEMENT if the median agreement is \( \geq 1.0 \), \( \leq 1.6 \)

\(^{18}\) It is worth noting that the distinction between "high" and "very high" confidence may be moot, given that the probability of a positive response in Likert scale items correlates in sigmoidal fashion with the respondent's attitude. Respondent attitude approaches unity with little \( \Delta y / \Delta x \) slope toward the upper right of a graph on which the probability of positive response is the x-axis. (Rossi, Wright, & Anderson, 1983, p. 253.)
Descriptors for consensus in agreement responses, reported in association with certain items, were:

- "HIGH CONSENSUS" if the interquartile range is \( \leq 2.0 \),
- "MODERATE CONSENSUS" if the interquartile range is \( > 2.0, \leq 3.0 \),
- "LOW CONSENSUS" if the interquartile range is \( > 3.0 \).

Simple measurements (e.g., recommended number of days before radiotherapy) also were analyzed with the S.P.S.S. *Statistics Summarize Frequencies* command. The preferred measure of central tendency in these cases is the mean.

Section V (outcome) data and their group means were illustrated in three dimensions and rotated through two or three perspectives using Excel 5.0 in order to achieve the clearest visualization of trends and comparisons.

**B. QUALITATIVE DATA**

Qualitative data were analyzed using EXCEL rather than SPSS because the EXCEL spreadsheets permitted easy manual sorting of data and the creation of formulae to automatically tabulate the frequency of particular cells (typically response topic categories) and simultaneously print out descriptors for each such cited.\(^{19}\)\(^{20}\) Statistical analyses performed were primarily calculations of simple frequencies and arithmetic means of ranks.

Table 16 provides a sample of the Excel master spreadsheet.

\(^{19}\) Acknowledgment: Mr. Kevin Maloney created these formulas.

\(^{20}\) A list of the several hundred 001-999 topic categories is available.
## TABLE 16. A SAMPLE OF THE EXCEL MASTER SPREADSHEET

<table>
<thead>
<tr>
<th>Survey #</th>
<th>Survey Page</th>
<th>Analysis Type</th>
<th>ItemID</th>
</tr>
</thead>
<tbody>
<tr>
<td>N3</td>
<td>5</td>
<td>2</td>
<td>1030</td>
</tr>
<tr>
<td>N3</td>
<td>5</td>
<td>2</td>
<td>1030</td>
</tr>
<tr>
<td>N3</td>
<td>5</td>
<td>2</td>
<td>1030</td>
</tr>
</tbody>
</table>

The columns in the spreadsheet listed

1. the number and location of the item in the survey, as the survey was distributed
2. the 4-digit computer-reference I.D. Code for the item
3. the 2-digit code for the type of analysis(es) to be performed
4. the 3-digit code for the topic category(ies) associated with the item
5. the potentially biasing personal and practice characteristics of the respondents (columns flagged with a "*" in the top data column of the sample spreadsheet). These were produced via formulas dependent on the number of the respondent entered in that column to the right, but could be fixed when this was necessary to allow sorting of survey data by a personal or practice characteristic.  

6. the number of the respondent providing the data, and 

7. the response data (ranks, topics of primary and secondary responses, agreement and confidence, etc.—including columns not shown). 

The design of this spreadsheet is intended as a model for future surveys. It permits 

- the ability to sort via personal or practice characteristic or other potentially biasing factor, and 

- the ability to sort by the fictional respondent "0" to provide an uncluttered list of items that are associated with a particular topic, facilitating mental consideration of items sorted by topic category. 

These features could not be be not fully employed in the present research because sample examinations of item responses sorted by personal- and practice-characteristics indicated that insufficient numbers were present for significant distinctions to be drawn.

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21 for instance, categorized years of practice, which is associated with the physician determinants of opinion (e.g. institutional and person dependent) that should be considered during consensus studies (Liberati 1986, as discussed in the Literature Review). The Discussion section "Potential Sources Of Bias Survey: Respondent and Practice Characteristics" interprets the findings of the Delphi Survey. Data limitations (small numbers) and the potential for "data dredging" bias will preclude the routine employment of this feature in this thesis. If data permitted, correlation or regression analysis using S.P.S.S. could suggest hypotheses about associations of particular "*" characteristics with particular opinions. 

22 Item (not response) topic data is included in rows associated with the fictional respondent "0".
Where items included requests for rankings, ranks of 1 specified by respondents in open-ended items remained ranked 1 in the analysis. With some sets of data associated with close-ended items, however, reinterpretation of the rankings was required to maximize the comparability of the relative ordinal rankings between respondents. Thus, two ranks of 1 in a close-ended item by the same respondent were pooled during analysis into two ranks of 1.5, and similar pooling performed for other ranks and respondents. (However, because it was apparent in certain items that the respondents were attempting to scale importance rather than ordinal rank, second sets of analyses based on the unaltered, original rank data also are presented.)

As illustrated in the "Table 17: A Sample Tabulation Of Qualitative Data (Item 1050)", ranks by one individual are reported as integers; mean ranks are reported after rounding to the nearest single decimal place. (N.B.: Second decimals of "5", e.g., 1.45, have been rounded downward numerically to the smaller first decimal number, e.g., 1.4, actually representing the higher mean rank.) "Frequency" indicates the number of

---

24 (e.g., in #3180, 3420, 3450, and 3470)
25 typed as "1→1.5 in the "Compilation of Responses'.
26 (e.g., as in Item 3460 data for Respondents 04/ and 08/)
27 Data reported in association with Items #3180, 3240, 3450, and 3470 will be that revised according to the protocol, while the original data will be reported as #3181, 3421, 3451, and 3471.
28 Please Note: Ranks were averaged (arithmetic mean) from available data. Medians also have been calculated conventionally from available data. These measures of central tendency in a sense "extrapolate" data from respondents who did not specify or rank the topic category, and it is recognized that this extrapolation has limited validity with small numbers of respondents. Significance becomes a possibility when a topic is ranked as highly important by a large number of respondents.

An alternative format for calculation of medians that also would be mathematically correct would be that in which a median ranking of a response category not mentioned at all by five of eleven respondents, but ranked 1,1,1,1,1, and 4 by the other six respondents, would be 4, since we can assume that lesser importance would have been assigned to the response category by those respondents who did not mention it. Lack of adequate convergence of responses to open-ended items precluded the use of this approach.
times that the topic was cited within the item. A parenthetical frequency, if present, indicates the different number of times that the topic was ranked within the item.

**TABLE 17: A SAMPLE TABULATION OF QUALITATIVE DATA (ITEM 1050)**

<table>
<thead>
<tr>
<th>Frequency</th>
<th>Mean Rank</th>
<th>Product</th>
<th>Topic Number, Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>10 (8)</td>
<td>1.0</td>
<td>50.0</td>
<td>012. Pain</td>
</tr>
<tr>
<td>6</td>
<td>1.7</td>
<td>25.8</td>
<td>017. Pathological Fracture</td>
</tr>
<tr>
<td>7 (6)</td>
<td>2.7</td>
<td>23.1</td>
<td>646. Inability, or impaired ability, to acquire nutrition,</td>
</tr>
<tr>
<td>7 (6)</td>
<td>2.8</td>
<td>22.4</td>
<td>630. Function of the Bite</td>
</tr>
<tr>
<td>3</td>
<td>2.0</td>
<td>12.0</td>
<td>016. Infection With or Without Drainage</td>
</tr>
<tr>
<td>2 (1)</td>
<td>1.0</td>
<td>10.0</td>
<td>262. Minor surgical interventions necessary (including radical debridement of bone, but not 264 = tooth extractions.)</td>
</tr>
<tr>
<td>2</td>
<td>1.5</td>
<td>9.0</td>
<td>003. Bone Exfoliation</td>
</tr>
<tr>
<td>2 (1)</td>
<td>2.0</td>
<td>8.0</td>
<td>261. Major surgical therapy present or required</td>
</tr>
</tbody>
</table>

Uncertain data, i.e. the few cases of raw rank or categorized topic data where respondent intent was unclear and was flagged with a question mark "?", were excluded from analysis.

Open-ended items could produce two types of responses, as illustrated by reference to a theoretical item about factors that affect mood. Where one respondent responded "color" and another "red", one would be justified in inferring from the second (i.e. the "secondary" or "dependent" criterion "red"), the primary category "color", and state that both respondents responded "color". Only the "primary" factor data are invariably reported in this thesis in association with open-ended items, although selective reference is made to particularly relevant "secondary"("S") data. These secondary data were all analyzed separately in parallel fashion to the "primary" ("P") data.
The importance of responses is suggested within tables in three manners:

1. Presentation of rows with number of respondents > 1, ordered, as above, by *decreasing frequency of citation*.

2. Rows with number of respondents > 1, repeated and *ordered by ascending rank*.
   (As always in this survey, increasing rank indicates *decreasing* importance).

3. Rows with number of respondents > 1, repeated and *ordered by descending product*. The "product" is not employed for items where it is not necessary, i.e. where generally there is apparent convergence between the frequency of citation of a topic and decreasing rank\(^{29}\).

The product, \(\{\text{Frequency times (6 - Mean Rank)}\}\), is an intuitively derived alternate surrogate for importance, and weighting of complex opinions, in open-ended items\(^{30}\). The value "(6-mean rank)" was chosen because practical constraints suggest the desirability of excluding topics from consideration in an introductory decision analysis which for a particular item are regarded as relatively unimportant (e.g., ranks 6.0 and higher.) (Thus, a topic ranked as a mean = 1.0 by four respondents would create a product of \((6-1)*4 = 20\), while a topic ranked as a mean = 6.0 would create a product of \((6-6)*4 = 0\), i.e. be assigned no importance.)

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\(^{29}\) as in the items dealing with potential biasing factors.

\(^{30}\) Rationale: All important topics may not always be remembered by all respondents, although, if asked about the topic, the respondent may have wished to remember it. The "Product" would tend to counter this by integrating the average importance with the frequency of citation. The goal sought would be increased reliability.
Survey findings are presented in "CHAPTER IV. RESULTS." Additional perspectives and integration of Survey data will be offered in the "1. Interpretation Of Findings" part of the DISCUSSION, a section that also reviews in greatest detail the parts of the Survey dealing with potentially biasing factors (personal and practice characteristics, definitions of ORN, etc.). It was concluded that item-by-item sub-group examination of responses by potential biasing factors (e.g. personal or practice characteristic) was inappropriate, and their early presentation would be distracting. A primary rationale was that insufficient numbers were present to indicate clear trends among sub-group responses, notwithstanding potential for data-dredging bias if the analyses were improperly conducted. Respondents also omitted some data intended to clarify bias, seeming disinclined\(^{31}\) to volunteer which factors, from their submitted lists of theoretically-possible biasing factors, could be personally applicable.

As a rule, open-ended items precede close-ended items in the Delphi Survey\(^{32}\), thus enabling the respondents to provide their initial perspectives after only a minimum of item-framing bias. Reporting and analysis of data in the "Results" section mirrors this pattern, for the same reasons. In this manner, tentative models of respondent opinions based on open-ended item data are formed, then further validated by comparison with the opinions expressed in subsequent close-ended and Likert-response items.

Higher quality data will rule over other reported information and form a basis for the conclusions drawn because this may improve the quality of the decision analysis.

\(^{31}\) (Items 1360 through 1410)
\(^{32}\) reproduced as Appendix 3
Open-ended-item responses of higher quality are the categorized topics mentioned frequently and ranked as important (= low mean rank), as these are integrated into the "Product", i.e. Frequency times (6 - Mean Rank). The use of "one-off" data is inappropriate, as a rule. However, relatively rarely, "one-off" data in open-ended items can be an artifact of topic categories that are excessively specific in the context of that item; in these cases their collapsing into more significant groupings may be accepted on an item-specific basis. Also, individual comments sometimes can indicate a reason why a respondent is experiencing difficulty in responding to an item, and a few items related to sources of bias --personal and practice characteristics, etc.-- depended on individual submissions.

Likert scales for confidence accompany some open-ended items; when present, low confidence (< 4.0) indicates relatively lower quality of data.

Higher quality in close-ended item data is associated with adequate numbers\(^{33}\) and the following:

1. for questions asking for respondents' level of agreement with a statement, and confidence level,
   - adequate agreement consensus\(^{34}\), or a clear bimodal distribution with reasonable bimodal consensus, and
   - $\geq$ moderately high median confidence (i.e., $\geq 5.0$; 4.9 = borderline)

---

\(^{33}\) Milholland, Wheeler, and Heieck (1973) suggest that reliability in Delphi surveys reaches a point of diminishing returns at $n = 13$.

\(^{34}\) "High consensus", the ideal here perhaps narrowly drawn, will be defined as an agreement interquartile range $\leq 2.0$. Data of "moderate" consensus, defined here as an agreement interquartile range $\leq 2.9$, $>2.0$, also will be regarded as acceptable for serious consideration and as potentially significant. Agreement interquartile ranges of 2.9 and 3.0 will be regarded as indicating a borderline significance.
• non-neutrality \((\geq 4.3, \leq 3.7)\), or better yet, \(\geq\) moderate median agreement/disagreement (i.e., median agreement \(\geq 5.0\) or \(\leq 3.0\)) (unless clearly bimodal)

2. for questions evaluating relevance: as 1. above, but only agreement permitted.

3. for close-ended lists, majority frequency of citation at \(\geq\) moderately-high median confidence (i.e. \(\geq 5.0\); \(4.9 =\) borderline); also, where applicable, adequate consensus as above.

Individual respondent comments may be presented in association with close-ended items when they express reservations and enhance understanding of the manner in which a respondent accepted a close-ended category, e.g. a tooth extraction treatment planning philosophy. They also will be quoted when they are submitted in place of a numerical choice.

"Higher quality" does not equate with ultimate validity. However, this report does summarize current expert opinion relevant to a theoretical clinical decision analysis examining current assumptions and decision processes, within the limits of reliability permitted by available numbers of respondents and other factors considered in the Discussion.
CHAPTER IV.: RESULTS: DELPHI SURVEY FINDINGS

PREFACE

This section identifies potential radiographic, dental, and medical ORN risk factors, then characterizes their importance, relevance, practicality, and controllability as contributory factors in a clinical decision analysis on minimizing ORN. Potential factors that may bias ORN severity or frequency (e.g. anatomical location), and potential factors relevant to extraction of teeth in the high dose radiation volume are considered. Factors that respondents associate with patient quality of life are compiled. Categorical pain and function scales proposed for patients with ORN are confirmed as ordinally related to quality of life, and the pain and function categories used in these scales are associated in different proportions with each type of osteoradionecrosis outcome category proposed by Epstein, et al (1987b). A summary is provided of types of items that resulted in responses of inadequate consensus or poor quality.

Data will be grouped as follows to facilitate efficient presentation and discussion:

1. Identification and Direct Assessment of ORN Risk Factors
   a. General and Dental
   b. Irradiation To High Dose and Related
   c. Endodontics
   d. Timing of Dental Extractions
   e. Relation of Oral-surgical, Medical, & Prosthetic Technique to ORN Risk
2. Assessment of Characteristics of ORN "Risk Factors"
   a. Perceived Relevance to ORN-Prophylactic Treatment Planning
      [Factor Practicality for Decision Analysis, i.e.:
   b. Quantifiability
   c. Clinical Controllability

3. Factors Relevant to Tooth Extraction


5. Outcomes (and Factors related to Outcomes)
   a. Severity of ORN Lesions
   b. ORN-Associated Factors That May Affect a Patient's Quality of Life
   c. Anatomical Location and ORN Clinical Presentation
   d. Factors Skewing ORN Severity Distributions
   e. Osteoradionecrosis Severity Distributions
   f. ORN Severity Category Associations with Pain & Function

6. Potential Sources Of Bias
   a. Survey: Definition of ORN
   b. Survey: Respondent and Practice Characteristics

7. Responses of Low Data Quality
SURVEY FINDINGS

1. DIRECT ASSESSMENT OF ORN RISK FACTORS
   A. GENERAL AND DENTAL

Data\(^1\) from the group of related items 1140, 1160, and 1170 of the Delphi Survey\(^2\) are presented as Table 18 in APPENDIX 1\(^3\). Item 1140 is an open-ended item, "Case characteristics that I think increase the risk (i.e., expected frequency) of ORN are". Its continuation is Item 1160, "Reviewing my list from the item above, I recognize that certain of the factors listed predispose outcomes relatively more mild or severe than the average", followed by Likert scales for confidence and agreement/disagreement.\(^4\) Item 1170 requests identification and labeling of these factors, where relevant.\(^5\)

Table 19 in this section abstracts from Table 18 the individual ORN risk factors of greatest importance.\(^6\) Although "one-off" citations are excluded from Tables 18 and 19, some do contribute to collapsed (broader) ORN risk topic categories that are presented as A. through I., in descending order of importance, in Table 20.

---

1. excluding "one-off" categorical data.
2. The Delphi Survey itself is presented as APPENDIX 3.
3. ("APPENDIX 1. LARGE TABLES")
4. "7" representing high confidence or strong agreement, and "1" no confidence or strong disagreement. (The agreement/disagreement scale is discussed further in the methodology section, "Quantitative Analyses.")
5. "+" indicates that the factor is thought by the respondent to promote an unusually severe ORN, "-" unusually mild ORN, and "±" either way. (Depending on context, all non-neutral indications could be re-interpreted as "±").
6. The "product" {i.e., "Frequency times (6 - Mean Rank)"} is an intuitively derived alternate surrogate for importance for responses to open-ended items; it is described further in the penultimate part of the Methodology section "Quantitative Data". "6" is chosen to exclude from consideration in a decision analysis factors ranked in importance only rank 6 or lower.
TABLE 19. ITEM 1140.
INDIVIDUAL POTENTIAL ORN RISK FACTORS, RANKED BY "PRODUCT"

<table>
<thead>
<tr>
<th>Product</th>
<th>Topic Description</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>14.1</td>
<td>Radiation Trauma.</td>
<td>The single topic cited most frequently (6 respondents) but ranked only 4.0 in importance.</td>
</tr>
<tr>
<td>12.0</td>
<td>Periodontal disease</td>
<td>Questions raised in the literature about whether periodontal disease is a good surrogate for periodontal infections may bear on the importance accorded this category by the respondents.</td>
</tr>
<tr>
<td>11.2</td>
<td>Caries Rate</td>
<td>(Recent)</td>
</tr>
<tr>
<td>9.9</td>
<td>Specific Part of Mandible</td>
<td>Generally, molar region.</td>
</tr>
<tr>
<td>9.0</td>
<td>Interstitial Therapy</td>
<td></td>
</tr>
<tr>
<td>7.0</td>
<td>Size of Irradiated Volume</td>
<td></td>
</tr>
<tr>
<td>6.9</td>
<td>Periapical Lesions</td>
<td>Periapical lesions often are associated with endodontic disease.</td>
</tr>
<tr>
<td>6.0</td>
<td>Tissue Perfusion Capability</td>
<td>(As anticipated for mandible.)</td>
</tr>
<tr>
<td>4.0</td>
<td>Diet</td>
<td></td>
</tr>
<tr>
<td>3.0</td>
<td>Smoking Status</td>
<td></td>
</tr>
<tr>
<td>0.8</td>
<td>Expected Compliance with prescribed oral hygiene care</td>
<td>Product is low due to the low mean rank of 5.8</td>
</tr>
<tr>
<td>0.0</td>
<td>Excess Alcohol Consumption, and Metabolic State.</td>
<td>Cited by 2 or 3 respondents each at low importance mean ranks of 10. and 6., respectively.</td>
</tr>
</tbody>
</table>

TABLE 20. ITEM 1140.
POTENTIAL ORN RISK FACTORS GROUPED BY CONCEPT.

<table>
<thead>
<tr>
<th>Product</th>
<th>Topic Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>54.6</td>
<td>A. Radiation-Therapeutics-Related Factors</td>
</tr>
<tr>
<td>28.8</td>
<td>B. <em>Non-Radiation</em> Therapeutics-Related Factors</td>
</tr>
<tr>
<td>22.4</td>
<td>C. Caries- and Endodontic-Disease-Related Factors</td>
</tr>
<tr>
<td>14.8</td>
<td>D. Anatomical-Location (of-ORN-related factors)</td>
</tr>
<tr>
<td>11.0</td>
<td>E. Periodontal-Related Factors</td>
</tr>
<tr>
<td>10.2</td>
<td>F. Metabolism-Related Factors</td>
</tr>
<tr>
<td>9.0</td>
<td>G. Overlying-Tissue-Related Factors</td>
</tr>
<tr>
<td>5.0</td>
<td>H. Tooth-Impaction-Related Factors (Σ tooth-impaction + pericoronitis)</td>
</tr>
<tr>
<td>4.8</td>
<td>I. Post-Radio-Tx Dentition-Care-Related Factors</td>
</tr>
</tbody>
</table>
Observations relating to trends in frequency of citation or mean ranked importance in Item 1140, Table 20, may be made, but do not evaluate importance as accurately.

In Item 3200, respondents

1. circle factors in a close-ended list that they consider to be both significant ORN prognosticators and practically assessable (at least qualitatively), then

2. indicate with asterisks the factors in the list that they think are significant prognosticators but that are not routinely assessable.

As presented in Table 21 associated with this item, the indicated frequency is the sum of the factors circled and asterisked by respondents, and the number and percentage inserted parenthetically following the frequency indicate the number and proportion of respondents who thought that the factor was not routinely assessable.

---

7 Item 1140. Perceived ORN Risk Factors Responses Grouped By Concept, as interpreted by

1. Trends In Frequency Of Citation as an ORN risk:
   - Metabolism-Related and High-Dose-Irradiation-Related factors were cited 17 & 13 times, respectively, so these were prominent in the mind-set of the respondents as they considered the item.
   - Dental-Disease-Related factors (Periodontal-Related and Caries & Endo-Related factors) were mentioned 10 and 8 times, respectively.
   - Dental and Medical/Surgical Care-Related ("Non-Radiation-Therapeutics-Related, Post-radiation-Tx Dentition-Care-Related Factors) were mentioned 8 and 6 times, respectively.
   - Other factors, mostly local tissue characteristics, were mentioned less frequently.

2. Trends In Mean Ranked Importance as ORN risk (Rank "1" = most important, higher numbers, lesser importance):
   - Medical and Surgical Interventions ("Radiation-Therapeutics-Related, Non-Radiation-Therapeutics-Related) were ranked highly (mean ranks = 1.8, 2.4),
   - Two respondents considered Overlying-Tissue-Related Factors very important (mean rank = 1.5), and other local tissue characteristic modifiers (Anatomical-Location-Related, Caries- and Endo-Disease-Related, Tooth-Impaction-Related, and Periodontal-Related) were also ranked as moderate to moderately-low in importance (mean ranks = 2.3, 3.2, 3.5, 4.9, respectively).
   - Post-Radiation-Tx Dentition-Care-Related Factors, and Metabolism-Related Factors were accorded overall low mean importance rankings (Mean Rank = 5.2, 5.4)
**TABLE 21. ITEM 3200**
EVALUATION OF FACTORS AS PROGNOSTICATORS FOR ORN FREQUENCY

<table>
<thead>
<tr>
<th>Frequency &amp; Topic Number, Description</th>
<th>n = 14</th>
</tr>
</thead>
<tbody>
<tr>
<td>13 (5, i.e. 40%) The oral hygiene status of the dentition.</td>
<td>520</td>
</tr>
<tr>
<td>12 (5, i.e. 40%) Radiation trauma to tissue and risk for ORN #1</td>
<td>420</td>
</tr>
<tr>
<td>12 (4, i.e. 35%) Dental/oral surgical trauma and risk for ORN.</td>
<td>440</td>
</tr>
<tr>
<td>11 (2, i.e. 20%) Periodontal status</td>
<td>370</td>
</tr>
<tr>
<td>11 (2, i.e. 20%) The patient's smoking status</td>
<td>467</td>
</tr>
<tr>
<td>10 (0, i.e. 0%) The patient's endodontic status.</td>
<td>335</td>
</tr>
<tr>
<td>9 (5, i.e. 55%) The anticipated blood supply, or oxygen perfusion of, the high-dose irradiated mandibular volume [assumed compromised when an assumption is necessary.]</td>
<td>461</td>
</tr>
<tr>
<td>8 (1, i.e. 10%) The salivation or xerostomia status of the patient.</td>
<td>570</td>
</tr>
<tr>
<td>8 (2, i.e. 25%) The dentition's recent caries experience/rate.</td>
<td>401</td>
</tr>
<tr>
<td>8 (3, i.e. 40%) The systemic metabolic state [not circulatory status] [Cf.: 483 = diabetes; 484 = graft vs. host disease.]</td>
<td>463</td>
</tr>
<tr>
<td>7 (3, i.e. 45%) The friability of the oral mucosa in the local area, in combination with local supra-osseous tissue contours</td>
<td>462</td>
</tr>
<tr>
<td>6 (0, i.e. 0%) The restorative status of each tooth in the high-dose radiation volume</td>
<td>415</td>
</tr>
<tr>
<td>5 (3, i.e. 60%) 10 Idiopathic factors</td>
<td>468</td>
</tr>
<tr>
<td>3 (0, i.e. 0%) The patient's age.</td>
<td>777</td>
</tr>
<tr>
<td>3 (1, i.e. 35%) The patient's prognosis for survival.</td>
<td>700</td>
</tr>
<tr>
<td>2 (0, i.e. 0%) The patient's diet (excluding effects on caries rate)</td>
<td>466</td>
</tr>
<tr>
<td>1 (1, i.e. 100%) Occlusion</td>
<td>390</td>
</tr>
</tbody>
</table>

In summary, oral hygiene status, radiation trauma, dental/oral surgical trauma, periodontal status, smoking status, and endodontic status are thought by the majority of respondents to be both prognostic for ORN and assessable. Moreover, in these cases, consensus is clear. The factors marked with the symbol Φ (anticipated blood supply,
salivation status, recent caries experience/rate, systemic metabolic state), are considered by a majority to be prognostic for ORN frequency; of these, a majority consider them assessable also. Thus, these factors also would merit consideration for application in an ORN-prophylactic decision analysis.

The friability of mucosa and supra-osseous tissue contours is considered by half the respondents a risk factor for ORN, although nearly half of these respondents do not consider this variable to be practically assessable. Another factor with borderline consensus is the restorative status of teeth in the high dose radiation volume. An ORN-related decision analysis centered on the research question of whether or not particular teeth should be extracted should include not only factors that modify ORN rate, but those concerned with the desirability of teeth as sound, functional teeth for chewing or for use as prosthodontic abutments. Therefore, "The restorative status of each tooth in the high-dose radiation volume", or another factor better integrating the functional importance of particular teeth, merits careful consideration in a decision analysis.

9 of 16 respondents thought "the anticipated blood supply, or oxygen perfusion of the high-dose irradiated mandibular volume" to be a risk for ORN. However, 55% thought that the anticipated mandibular perfusion in the high dose volume was not assessable routinely, even qualitatively\textsuperscript{11}. Therefore, discussion of this factor in the context of decision analysis will not be further considered in this thesis.

\textsuperscript{11} although dense bone in the elderly suggested as a prognostic factor (Epstein 1996, private communication) may be a surrogate for this.
A minority of the 14 respondents considered idiopathic factors or the patient's age, diet, occlusion, or prognosis for survival to be both prognostic for ORN and practically assessable as prognostic factors. All of these would seem to be unworthy of detailed consideration as factors applicable to a decision analysis until other data indicates the contrary. [Note: Discussion of Item 1140 and 3200 factor relevance to decision analysis continues in the INTERPRETATION OF SURVEY FINDINGS, part of CHAPTER V. "DISCUSSION".]

To repeat, in Item 3200 oral hygiene status, radiation trauma, dental/oral surgical trauma, periodontal status, smoking status, and endodontic status are thought by the majority of respondents to be both prognostic for ORN and assessable. Further, the factors "anticipated blood supply, salivation status, recent caries experience/rate, and systemic metabolic state" merit consideration for application in an ORN-prophylactic decision analysis.

In the 3240-3420 series of items, the root, "This factor, when undesirable, can strongly increase the risk for ORN:" is followed by a series of potential risk factors and Likert response scales on which respondents indicate agreement or disagreement about whether the factor is a risk factor, and their confidence in making the statement. Agreement rankings by respondents for the variables, ranked by descending agreement for all items with confidence \( \geq 5.0 \), are presented in Table 22.

---

12 Likert scale for agreement: \( 7 = \) strongest agreement, \( 4 = \) neutrality, \( 1 = \) strongest disagreement; Likert scale for confidence: \( 7 = \) highest confidence, \( 1 = \) lowest confidence.
### TABLE 22. ITEMS 3240-3420. POTENTIAL ORN RISK FACTORS.

(Please note: Only responses of adequate quality are listed here.)

<table>
<thead>
<tr>
<th>FACTOR</th>
<th>n = 13 to 14</th>
<th>Median Agreement</th>
<th>Agreement IQR</th>
<th>Median Confidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Periodontal status (e.g., periodontal pocket depths, furcation involvements, etc.) of teeth in the high dose radiation volume.</td>
<td>6.0</td>
<td>1.6</td>
<td>6.5</td>
<td></td>
</tr>
<tr>
<td>Vascular and cellular changes induced by high dose therapeutic irradiation</td>
<td>6.0</td>
<td>1.7</td>
<td>6.3</td>
<td></td>
</tr>
<tr>
<td>Level of trauma from therapeutic surgery.</td>
<td>5.9</td>
<td>1.7</td>
<td>6.3</td>
<td></td>
</tr>
<tr>
<td>Endodontic status of each tooth in high-dose radiation volume.</td>
<td>5.6</td>
<td>1.9</td>
<td>6.1</td>
<td></td>
</tr>
<tr>
<td>Oxygen perfusion to the high-dose radiation volume tissue</td>
<td>5.4</td>
<td>-</td>
<td>5.7</td>
<td></td>
</tr>
<tr>
<td>Delicacy/friability of the local oral mucosa, in combination with local osseous contours</td>
<td>5.4</td>
<td>1.5</td>
<td>6.0</td>
<td></td>
</tr>
<tr>
<td>Oral hygiene status of the dentition, independent of caries rate</td>
<td>5.3</td>
<td>1.5</td>
<td>5.9</td>
<td></td>
</tr>
<tr>
<td>Patient’s smoking status.</td>
<td>5.3</td>
<td>2.0</td>
<td>5.9</td>
<td></td>
</tr>
<tr>
<td>Salivary/xerostomia status of the patient</td>
<td>5.1</td>
<td>1.7</td>
<td>6.3</td>
<td></td>
</tr>
<tr>
<td>Systemic metabolic state [NOT Circulatory status]</td>
<td>4.9</td>
<td>1.7</td>
<td>5.6</td>
<td></td>
</tr>
<tr>
<td>Caries experience recently /expected caries rate.</td>
<td>4.6</td>
<td>2.7</td>
<td>6.1</td>
<td></td>
</tr>
<tr>
<td>Mechanical soundness of each tooth in high-dose radiation volume</td>
<td>4.6</td>
<td>2.7</td>
<td>5.8</td>
<td></td>
</tr>
<tr>
<td>Patient’s age</td>
<td>4.0</td>
<td>(Neutrality)</td>
<td>2.0</td>
<td>5.8</td>
</tr>
<tr>
<td>Periodontal disease activity level as estimated through surrogates such as bleeding on probing, microbiological assays, chemical tests, etc.</td>
<td>3.5</td>
<td>3.0</td>
<td>6.1</td>
<td></td>
</tr>
<tr>
<td>Dental occlusion in all manners, including parafunctional habits</td>
<td>3.3</td>
<td>&quot;</td>
<td>2.4</td>
<td>5.6</td>
</tr>
<tr>
<td>Patient's diet (excluding effects on caries rate)</td>
<td>3.6</td>
<td>&quot;</td>
<td>2.1</td>
<td>4.9</td>
</tr>
</tbody>
</table>

All of the responses in this table and the item series 3240-3420 are consistent with the responses of Item 3200, although there is not complete parallelism of the relative rankings in Item 3200 with the degree of agreement in the series 3240-3420. Certain findings of the 3240-3420 series are emphasized:

---

13 The agreement IQR of 3.0 indicates only marginal acceptability of data associated with this factor.
14 The confidence of 4.9 indicates only marginal acceptability of data associated with this factor.
• The survey participants consider conventional measures of periodontal status (arguably, measures of cumulative periodontal disease) to be predictive of risk for ORN (M.A.L., defined as median agreement level, was 6.0) in contrast to surrogates for current periodontal disease activity (M.A.L. = 3.5).

• Surgical trauma (e.g. tooth extraction) is considered (M.A.L. = 5.9) a risk factor for ORN.

• Poor endodontic status (M.A.L. = 5.6), the friability of the overlying tissue (M.A.L. = 5.4), poor oral hygiene status (M.A.L. = 5.3), smoking status (M.A.L. = 5.3), and the salivation status (M.A.L. = 5.1) are considered ORN risk factors.

These bulleted factors are all associated with high consensus levels (= agreement interquartile ranges ≤ 2.0) as well as moderate (= ≥ 5.0) or better agreement levels. Thus, the factors are deemed to be supported adequately as ORN risk factors.

Respondents expressed only fair agreement (M.A.L. = 4.9) at high consensus that metabolic status was an ORN risk factor.

Neither the present caries rate (M.A.L. = 4.6) nor the mechanical soundness of teeth (M.A.L. = 4.6) are ranked particularly strongly as predictors of ORN risk. The caries rate and the mechanical soundness of teeth are associated, like some listed potential factors ranked even lower in importance (diet, occlusion, and periodontal disease activity surrogates), with only moderate consensus (= agreement interquartile ranges > 2.0, ≤ 3.0). Opinion is divided on whether age is a risk factor (M.A.L. = 4.0).

15 (Keratinization, an additional factor suggested by one respondent, presumably would be protective.)
Dental occlusion generally is not considered a predisposing factor for ORN: weak disagreement is expressed at M.A.L. = 3.3).\footnote{Marunick and Leveque (1989) do, however, provide anecdotal reports of mastication and parafunction being associated with ORN.}

Weak disagreement (M.A.L. = 3.6) also was expressed with regard to "the patient's diet (excluding effects on cares rate) as an ORN risk factor. However, median confidence for this item was only 4.9.

In summary, the factors considered in Item 3200 to be prognostic for ORN and practically assessable--oral hygiene status, surgical trauma, conventional periodontal status, the patient's smoking status, and the patient's endodontic status--were identified similarly in items 3240-3420, with adequate consensus and reasonably high confidence. Blood supply, a factor apparently considered prognostic for ORN in both sets of data, but for which practical assessability was not clearly indicated in Item 3200, also is supported as an ORN risk factor. Weak support as ORN risk factors is provided in the 3240-3420 item series for the factors caries rate, mechanical soundness of teeth, salivary status, and metabolic status (the latter two being factors for which practical assessability was not clearly indicated in Item 3200). (Parenthetically, the factor terms "restorative status" in Item 3200 and "mechanical soundness of the teeth" in the item 3240-3420 series are essentially equivalent. This factor was assessed in each set of items as only a marginal ORN risk.)

In Item 3450 respondents evaluated the relative importance, as predictors of ORN risk, of listed conventional indicators of periodontal status. Results are shown in Table 23.
<table>
<thead>
<tr>
<th>Frequency</th>
<th>Mean Rank</th>
<th>Product</th>
<th>Topic Number, Description</th>
<th>n = 10; Median confidence = 5.0</th>
</tr>
</thead>
<tbody>
<tr>
<td>10</td>
<td>1.6</td>
<td>44</td>
<td>353. Periodontal Infection</td>
<td></td>
</tr>
<tr>
<td>10</td>
<td>3.1</td>
<td>29</td>
<td>371. Periodontal Pocket Depth</td>
<td></td>
</tr>
<tr>
<td>10</td>
<td>3.5</td>
<td>25</td>
<td>373. Vertical Bone Loss</td>
<td></td>
</tr>
<tr>
<td>10 (9§)</td>
<td>3.7</td>
<td>23</td>
<td>375. Tooth Mobility</td>
<td></td>
</tr>
<tr>
<td>10 (9)</td>
<td>4.0</td>
<td>20</td>
<td>374. Furcation Classification</td>
<td></td>
</tr>
<tr>
<td>10 (8)</td>
<td>5.9</td>
<td>1</td>
<td>372. Horizontal Bone Loss</td>
<td></td>
</tr>
<tr>
<td>10 (8)</td>
<td>6.7</td>
<td>0</td>
<td>381. Bleeding On Probing</td>
<td></td>
</tr>
<tr>
<td>10 (9)</td>
<td>8.2</td>
<td>0</td>
<td>392. Traumatic Occlusion (Bite)</td>
<td></td>
</tr>
<tr>
<td>10 (9)</td>
<td>8.6</td>
<td>0</td>
<td>391. Tooth Unopposed Occlusion (Bite)</td>
<td></td>
</tr>
<tr>
<td>10 (8)</td>
<td>8.9</td>
<td>0</td>
<td>376. Tooth Root Proximity</td>
<td></td>
</tr>
</tbody>
</table>

* The importance ranks stated first, and used in the calculation of the product, are those revised according to the closed-item re-ranking protocol described in Methodology.
* = original ranks, potentially a better indication sometimes of absolute intended importance
§ Frequency overall is followed in parentheses with the number who actually provided rankings

Respondents assessed periodontal infection as the greatest ORN risk. Those aspects of traditional periodontal status that one could consider predictive or associated with future bacterial entrapment and predisposition to infection, e.g. pocket depth, vertical bone loss, mobility, and furcation involvement, also are ranked highly.

Responses to Item 3450 could support the contention that the respondents are relating periodontal disease as a predictor of ORN risk to its potential for bacterial entrapment and potential for infection.

Noteworthy in Item 3450, and not previously identified, is the high ranking of tooth mobility as a predictor of ORN risk, although "occlusion" (bite) is not. An explanation for the high ranking of tooth mobility is that tooth mobility is associated with deep pocketing in a majority of the older population at risk for ORN.
"Bleeding on probing" is not considered to be a good predictor of ORN risk in either Item 3450 or 3460.

Item 3460 repeats the Item 3450 question root and completion, but the list is supplemented with two additional factors, providing respondents an opportunity to incorporate in their evaluations the importance, as predictors of ORN risk, of two newer (and perhaps more pro-active) indicators of periodontal disease potential. These "newer" indicators are:

- pathologic periodontal flora (e.g., motile Gram negatives/spirochetes)
- chemical test suggestive of periodontal disease activity (e.g. collagenase, hydroxyproline, cyclic AMP, interleukin 1).

The importance rankings associated with this extended list are presented in Table 24. However, the mean ranks presented may be misleading because of strong volunteer bias: there were only 4 respondents to Item 3460 in comparison to 10 to Item 3450, and one respondent who chose not to participate in item 3460 indicated that the two additions to the list were ineffectual. The responses indicate that if a "Gold Standard" for activity of periodontal disease exists, then most Item 3460 respondents would favor this as a predictor of ORN risk, but a clear majority of respondents prefer to depend on traditional indicators of past periodontal disease activity to predict ORN risk.

\[17\] (e.g. sure identification of pathogenic flora, in combination with other hypothetical factors),
### TABLE 24. ITEM 3460
PERIODONTAL PREDICTORS OF ORN RISK, BY IMPORTANCE RANK

<table>
<thead>
<tr>
<th>Frequency</th>
<th>Mean Rank</th>
<th>Product</th>
<th>Topic Number, Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>4</td>
<td>2.6 (2.1*)</td>
<td>14</td>
<td>371. Periodontal Pocket Depth</td>
</tr>
<tr>
<td>3</td>
<td>1.7* (1.7*)</td>
<td>13</td>
<td>382. Pathologic Periodontal Flora (e.g., Motile Gram Neg./Spirochetes.)</td>
</tr>
<tr>
<td>4</td>
<td>2.9 (2.7*)</td>
<td>12</td>
<td>353. Periodontal Infection</td>
</tr>
<tr>
<td>3</td>
<td>2.1 (2.7*)</td>
<td>12</td>
<td>383. Other (Chemical Test Suggestive Of Periodontal Disease Activity (e.g. Collagenase, Hydroxyproline, Cyclic AMP, Interleukin 1))</td>
</tr>
<tr>
<td>4</td>
<td>3.1 (3.0*)</td>
<td>12</td>
<td>373. Vertical Bone Loss</td>
</tr>
<tr>
<td>4 (3 §)</td>
<td>4.3 (3.0*)</td>
<td>7</td>
<td>372. Horizontal Bone Loss</td>
</tr>
<tr>
<td>4</td>
<td>4.8 (3.7*)</td>
<td>5</td>
<td>374. Furcation Classification</td>
</tr>
<tr>
<td>4 (3)</td>
<td>6.0 (4.7*)</td>
<td>0 +</td>
<td>375. Tooth Mobility</td>
</tr>
<tr>
<td>3</td>
<td>7.2 (6.5*)</td>
<td>0</td>
<td>381. Bleeding On Probing</td>
</tr>
<tr>
<td>4 (3)</td>
<td>8.8 (7.0*)</td>
<td>0</td>
<td>392. Traumatic Occlusion (Bite)</td>
</tr>
<tr>
<td>4 (3)</td>
<td>9.5 (7.7*)</td>
<td>0</td>
<td>376. Root Proximity</td>
</tr>
<tr>
<td>4 (3)</td>
<td>10.0 (8.0*)</td>
<td>391. Tooth Unopposed Occlusion (Bite)</td>
<td></td>
</tr>
</tbody>
</table>

* Therefore, strong volunteer bias is present.
* The importance ranks stated first, and used in the calculation of the product, are those revised according to the closed-item re-ranking protocol described in Methodology. In certain cases, e.g. tooth mobility, the product would have been substantially higher if the original rankings had been used.
* Periodontal disease activity predictors— new to Item 3460, not present in Item 3450.
† One non-respondent to this part stated that he was unaware that the additional tests "★" had clinical significance.
§ Frequency overall is followed in parentheses with the number who actually provided rankings.

In the close-ended Item 3470, respondents ranked their perceptions of the relative importance of four different types of dental occlusion (bite) factors as ORN risks:

### TABLE 25. ITEM 3470. OCCLUSAL FACTORS AS ORN PREDICTORS

<table>
<thead>
<tr>
<th>Frequency</th>
<th>Mean Rank</th>
<th>Product</th>
<th>Topic Number, Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>6 †</td>
<td>1.4 ★ (1.5*)</td>
<td>28</td>
<td>394. Trend for bite pressure to be concentrated in one jaw area.</td>
</tr>
<tr>
<td>6</td>
<td>2.4 (2.2*)</td>
<td>22</td>
<td>396. Bruxism</td>
</tr>
<tr>
<td>6</td>
<td>2.9 (2.7*)</td>
<td>19</td>
<td>397. Clenching</td>
</tr>
<tr>
<td>6 (5 §)</td>
<td>3.1 (2.8*)</td>
<td>17</td>
<td>393. Generalized non-working occlusal interferences</td>
</tr>
</tbody>
</table>

† n = 7 respondents, one non-respondent stating with low confidence, "I don't think any are important."
★ The importance ranks stated first, and used in the calculation of the product, are those revised according to the closed-item re-ranking protocol described in Methodology.
* = Original Ranks— may imply absolute importance.
§ Frequency overall is followed in parentheses with the number who actually provided rankings.
The significance of these findings is questionable considering the low numbers, low median confidence, and a comment by a respondent who, while not indicating a numeric importance ranking, stated that he did not consider any of these important. However, pressure concentration in one area of the jaw is rated relatively highly as an ORN risk, a finding consistent with its typical scenario in which there has been tooth loss and the dental prosthesis present would tend to ulcerate the mucosa at the point of pressure concentration.

In Item 3440, respondents ranked their perceptions of the relative importance of different types of infections as ORN risks. Responses are presented in Table 26. However, the differences in ranks are judged to be insignificant. Acute or chronic infections of periodontal or endodontic origin would appear to be ranked equally as predictors of ORN risk.

TABLE 26. ITEM 3440
INFECTION PREDICTORS OF ORN RISK, BY PRODUCT

<table>
<thead>
<tr>
<th>Frequency</th>
<th>Mean Rank</th>
<th>Product</th>
<th>Topic Number</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>15 (11§)</td>
<td>2.6 (2.2*)</td>
<td>51</td>
<td>349.</td>
<td>Acute periapical abscess subsequent to radiotherapy</td>
</tr>
<tr>
<td>15 (11)</td>
<td>2.9 (2.4*)</td>
<td>47</td>
<td>347.</td>
<td>Chronic endodontic infection draining periodontally</td>
</tr>
<tr>
<td>15 (11)</td>
<td>3.0 (2.4*)</td>
<td>45</td>
<td>346.</td>
<td>Acute periodontal infection</td>
</tr>
<tr>
<td>15 (11)</td>
<td>3.1 (2.0*)</td>
<td>44</td>
<td>348.</td>
<td>Endodontic infection draining through buccal bone</td>
</tr>
<tr>
<td>15 (11)</td>
<td>3.4 (2.9*)</td>
<td>39</td>
<td>345.</td>
<td>Chronic periodontal infection</td>
</tr>
</tbody>
</table>

* The importance ranks stated first, and used in the calculation of the product, are those revised according to the closed-item re-ranking protocol described in Methodology.

§ Frequency overall is followed in parentheses with the number who actually provided rankings.

* = original ranks, potentially a better indication sometimes of absolute intended importance.

18 Topic numbers are defined slightly differently in this item than elsewhere.
In summary, factors thought with adequate consensus and reasonably high confidence to be both prognostic for ORN and practically assessable are oral hygiene status, surgical trauma, conventional periodontal status, smoking status, and endodontic status. Periodontal factors appear to be considered prognosticators for ORN in positive relation to their potential for infection. Periodontal infection itself is considered the greatest periodontal ORN risk, and approximately equivalent to endodontic infection in this regard. As measured in terms of Items 3240-3420 agreement, the caries rate, mechanical soundness of teeth, salivary status, and metabolic status are only weakly supported as ORN risk factors; lack of strong support for their inclusion in a decision analysis is further indicated by the only moderate consensus in the assessments of the former two factors, and lack of practical assessability being indicated\textsuperscript{19} for the latter two. Occlusion (bite) is not strongly supported as an ORN risk.

\textsuperscript{19} in Item 3200
1. DIRECT ASSESSMENT OF ORN RISK FACTORS. B. HIGH RADIATION DOSE, ETC.

Pooled responses to Item 1200, "Radiotherapeutic techniques and radiotherapy technical characteristics that I think will reduce the risk of ORN are:", are summarized in Table 27.

TABLE 27. ITEM 1200
RADIOTherAPEUTIC CHARACTERISTICS REDUCING ORN RISK.

<table>
<thead>
<tr>
<th>Frequency</th>
<th>Mean Rank</th>
<th>Product</th>
<th>Topic Number, Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>7 (6)</td>
<td>1.3</td>
<td>33</td>
<td>422. Overall Dosage or Past Hx of a Cumulative Minimum Dose</td>
</tr>
<tr>
<td>8 (6§)</td>
<td>2.0</td>
<td>32</td>
<td>427. Fractionation [in this item, increased number; hyperfractionation.]</td>
</tr>
<tr>
<td>8 (7)</td>
<td>2.1</td>
<td>31</td>
<td>495. Type Of Irradiation*</td>
</tr>
<tr>
<td>6 (5)</td>
<td>1.4</td>
<td>28</td>
<td>429. Shielding/Blocking/Localization Factors/Props</td>
</tr>
<tr>
<td>4</td>
<td>1.5</td>
<td>18</td>
<td>431. The Irradiated Volume</td>
</tr>
<tr>
<td>2</td>
<td>2.5</td>
<td>7</td>
<td>421. Radiation Treatment Plan</td>
</tr>
<tr>
<td>2 (1)</td>
<td>1</td>
<td>10</td>
<td>498. Dose Homogeneity &amp; Measures To Achieve Same.</td>
</tr>
</tbody>
</table>

§ Frequency overall is followed in parentheses with the number who actually provided rankings.

The relative importance of different radiation variables as ORN risks was assessed in the close-ended Item 3180. These data are presented in Table 28.

TABLE 28. ITEM 3180. RADIATION VARIABLES AS ORN RISKS

<table>
<thead>
<tr>
<th>Frequency</th>
<th>Mean Rank</th>
<th>Product</th>
<th>Topic Number, Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>15 (14§)</td>
<td>1.3*</td>
<td>71</td>
<td>422. Overall Dosage, or Past Hx of a Cumulative Minimum Dose</td>
</tr>
<tr>
<td>15 (10)</td>
<td>2.6 (2.3*)</td>
<td>51</td>
<td>424. The Radiation Intensity</td>
</tr>
<tr>
<td>15 (11)</td>
<td>2.7 (2.4*)</td>
<td>50</td>
<td>423. The Time Dose Factor</td>
</tr>
<tr>
<td>15 (13)</td>
<td>3.7 (3.1*)</td>
<td>44</td>
<td>425. Radiation Timing [i.e., sequence; not Time Before XRT.]</td>
</tr>
<tr>
<td>15 (11)</td>
<td>3.8 (3.2*)</td>
<td>42</td>
<td>426. The Source Voltage</td>
</tr>
</tbody>
</table>

* The importance ranks stated first, and used in the calculation of the product, are those revised according to the closed-item re-ranking protocol described in Methodology.

Additional Explanation:
1. Topic category 495 specific comments fall into three categories:
   A. 06/: avoiding interstitial therapy; 13/: technique- interstitial RT;
   12/: combining different types of therapeutic beams;
   B. 08/: Radiation source. Photons vs. neutrons, high energy vs. low energy;
   10/: RT source (Photon, electron, neutron).
   C. 02/: radiation source; 14/: type of irradiation
   03/: availability of various beam sources and strengths.
2. Contributions by 06/, the sole radiation oncologist, are:
   422 Careful dosimetry 495. Avoiding interstitial therapy 498. Dose homogeneity.
However, the only radiation oncologist 06/ commented that *Dose should be ranked 1, Dose per fraction [not listed] should be ranked 2; Radiation timing should be ranked 3*; and Respondent 02/ commented that "*These [last four] are directly inter-related. T.D.F. is an expression of the other [last] three.*" [Therefore all three factors are of importance.]

Item 3190 asked respondents to respond to the statement, "I believe that patients receiving interstitial radiation in addition to external radiation will experience a higher frequency of ORN than patients receiving that same external radiation alone." The median agreement was 5.2 (4.0 representing neutrality) with a median confidence of 6.0.21 Discounting the possibilities of "urge to please" bias, or confusion surrounding lack of the unstated premise "given equal tissue doses", a majority (8) of 13 respondents other than respondent 06/ appear to think that interstitial radiation simultaneously with external radiation increases the risk for osteoradionecrosis.

To Item 3190, the radiation oncologist respondent 06/ stated "Silly question, depends on dose". However, in response to the item #1200, "Radiotherapeutic techniques and radiotherapy technical characteristics that I think will reduce the risk of ORN are;", he commented "avoiding interstitial therapy", which implies that, in respondent 06/'s view, the use of interstitial therapy *does* create an ORN risk.

Radiation variables will be discussed further in the "INTERPRETATION OF FINDINGS" part of the "DISCUSSION".

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21 (If the 06/ response-- an opinion written in the margins that the tissue dose received is the only important independent variable-- is interpreted as A=1, C=7, then the medians would be A= 5.0, C= 6.1.)
1. DIRECT ASSESSMENT OF ORN RISK FACTORS. C. ENDODONTICS, IN DETAIL

A series of Survey items solicited opinion about the impact of endodontic procedures on the risk for ORN.

Item 1630 asked respondents to consider the statement, "I think that endodontic treatment of a tooth carries with it a significant adverse impact on the risk (expected frequency) for ORN." Overall, definite disagreement to this item was expressed (median agreement level = 2.4 (where neutrality = 4.0), with moderate consensus (inter-quartile range 2.3), at a median confidence of 5.9). One respondent who strongly agreed\(^{22}\) with this Item 1630 commented, "Yes, if endodontic treatment was done poorly." Two others agreed with the item,\(^{23}\) one expressed neutrality,\(^{24}\) and 10 strongly disagreed.\(^{25}\) This author interprets all opinions expressed to be consistent with two concepts:

1. that an otherwise healthy tooth upon which endodontic treatment of proven success has been performed will not be an ORN risk factor
2. that endodontic treatment, being extremely technique-sensitive, carries with it a risk of failure\(^{26}\), and that failed cases induce inflammation or infection, predisposing ORN, given enough irradiation.

Item 1670 asked respondents to respond to the statement, "I think that ORN will occur less frequently if a periapically involved but otherwise sound tooth is treated endodontically rather than extracted prior to radiotherapy." Although the dispersion in

\(^{22}\) (A=7, C=7) [Please Note: A = Agreement Response, and C= Confidence Response]
\(^{23}\) at levels of (A=5, C=5) [Please Note: A = Agreement Response, and C= Confidence Response]
\(^{24}\) (A=4 @ C=4); [Please Note: A = Agreement Response, and C= Confidence Response]
\(^{25}\) (A ~ 2 @ C=5,6,7). [Please Note: A = Agreement Response, and C= Confidence Response]
\(^{26}\) Peak (1994) found that endodontic cases treated by Royal Air Force general dentists were definitely successful in 59% of the cases, probably successful in another 27%, and failures in 15%.

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agreement consensus levels and agreement neutrality associated with this item would be associated with insignificance, in this case there would appear to be a true bimodality of responses, of potential significance. The responses are consistent with previously implied respondent views that successful endodontic treatment will not increase or decrease risk for ORN, while the real risk of endodontic treatment failure was considered a significant risk for ORN.

Items 1640 and 1650 and the responses to them were as follows: "I think that endodontically treating selected teeth' 

- 1640. 'prior to' \[median agreement = 4.7 with IQR 3.4; median confidence = 5.4\]
- 1650. 'after' \[median agreement = 5.4 with IQR 2.1; median confidence = 5.6\]

'radiotherapy can decrease the expected future incidence of ORN, compared to no treatment.'

Item 1650 responses but not Item 1640 responses meet criteria for moderate (≥5.0, ≤5.6) agreement and for moderate (agreement IQR >2.0, ≤3.0) consensus. An explanation may lie in the fact that extraction is universally considered an alternative to endodontic treatment only before irradiation with high dose. On the other hand, endodontic treatment after irradiation with high dose (as in Item 1660 below, as well as 1650 above) was thought by more respondents to offer a real atraumatic treatment alternative to extractions, when extractions were considered by some respondents to be strictly inappropriate as an ORN risk.

Responses to this item were agreement responses 1,1,1,2,3,4,4,5,6,6,7,7. Median agreement = 4.0, Agreement IQR = 4.2 = very low consensus. Median confidence = 5.6.
1. DIRECT ASSESSMENT OF ORN RISK FACTORS.  D. RELATION OF ORN RISK TO TIMING OF DENTAL EXTRACTIONS AND TO REPORTED ORN RATES

Item 1530 asked respondents to consider the statement, "I think that extracting certain types of dentally-diseased teeth prior to radiotherapy can decrease the expected incidence of ORN, compared to no extraction." There was strong agreement at high consensus that pre-radiotherapeutic tooth extractions can reduce the expected incidence of ORN. The direct implication of this opinion is that diseased teeth per se are an ORN risk factor; this opinion is strengthened given the dominant position of disagreement expressed in the responses to Item 1480, "I think that patients with teeth can, under some circumstances, be expected to experience a lower frequency of ORN than chronically edentulous patients."

Strong overall disagreement with a minority position was expressed with the Item 1540 statement that post-radiotherapeutic extractions could decrease the ORN rate.  

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28 Item 1530 median agreement was 6.6 and median confidence also was 6.6. [Of 14 eligible respondents, 13 agreed at Agreement = 6 or 7 and Confidence = 6 or 7, although one expressed neutrality (A=4, C=4).]

29 (at least, selective extractions)

Please Note: Dental 'extraction' is defined as the removal of a tooth from a mandible or maxilla.

30 Item 1480: Agreement responses = 1,1,1,1,2,2,2,3,3,4,6,7,7 @ C= U, 5,6,or 7; median agreement = 2.4, Agreement IQR =3.7 (Not low consensus if the distribution is interpreted as bimodal). Median confidence = 6.1. Thus: overall, moderately strong disagreement at low consensus and high confidence.

31 Item 1540: "I think that extracting certain types of dentally-diseased teeth after radiotherapy can decrease the expected incidence of ORN, compared to no extraction." (Agreement responses = 1,1,1,1,1,1,2,2,4,5,5,7 @ C = 5, 6, or 7.) median agreement = 1.8; median confidence level = 6.2 ; Agreement interquartile range was 3.7, i.e. low consensus.

32 As a point for future investigation, a clear majority of respondents to Item 1550 believe, albeit with opinions of unusually low confidence indicating lack of significance (median confidence = 4.0 and quantitative relative risk responses widely dispersed) that post-radiotherapy tooth extractions confer upon an individual about a 4 times greater risk for osteoradionecrosis than do pre-radiotherapy extractions.
Responses to Item 1520,\(^{33}\) the *minimum* time that an extraction socket should be allowed to heal prior to irradiation with high dose, indicate that respondents, while highly confident\(^{34}\) in their opinions, express a wide range of opinions. On average, it was felt that 7 days\(^{35}\) should elapse following tooth extraction prior to irradiation to high dose.\(^{36}\) Responses to Item 1510,\(^{37}\) about the *desired* time that an extraction socket should be allowed to heal prior to irradiation to high dose, are equally confident and slightly less dispersed, with a median of the 14 days, and mean of 11.6 days.

Although both the recommended extraction healing times and the ORN rates reported by the individual respondents have uncertain validity\(^{38}\), it is interesting to display these figures (Table 29\(^{39}\) and scatterplot Charts 1 and 2) to inspect for apparent trends.

### TABLE 29. *Normally Recommended and Absolute Minimum Recommended Pre-Radiotherapy Days of Healing, vs. Reported ORN Rates*

<table>
<thead>
<tr>
<th>RESPONDENT:</th>
<th>01/</th>
<th>02/</th>
<th>03/</th>
<th>04/</th>
<th>05/</th>
<th>06/</th>
<th>07/</th>
<th>08/</th>
<th>09/</th>
<th>10/</th>
<th>11/</th>
<th>12/</th>
<th>13/</th>
<th>14/</th>
<th>15/</th>
</tr>
</thead>
<tbody>
<tr>
<td>ORN RATE ((%))</td>
<td>1.</td>
<td>U*</td>
<td>U*</td>
<td>4.</td>
<td>3.5</td>
<td>1.</td>
<td>7.5</td>
<td>4.5</td>
<td>1.</td>
<td>0.3</td>
<td>4.5</td>
<td>25.</td>
<td>1.5</td>
<td>2.</td>
<td>16.</td>
</tr>
<tr>
<td>Absolute Minimum Healing Time: (Days)</td>
<td>7.</td>
<td>2.</td>
<td>U*</td>
<td>3.</td>
<td>3.</td>
<td>N/A</td>
<td>10.</td>
<td>7.</td>
<td>2.</td>
<td>12.</td>
<td>1.</td>
<td>7.</td>
<td>10.</td>
<td>12.</td>
<td>14.</td>
</tr>
</tbody>
</table>

\(^{33}\) "Assuming that a patient, an otherwise healthy 60 year old male requires mandibular tooth extractions in a future high dose radiation volume, the number of post-extraction days prior to radiotherapy that I would consider the absolute minimum is:"

\(^{34}\) (median confidence = 6.0)

\(^{35}\) (median 7.0, mean 6.9)

\(^{36}\) (Also, one respondent substituted the comment, "for Grade 4 mobility of a mandibular incisor (no bone support) no delay needed")

\(^{37}\) "...the number of post-extraction days prior to radiotherapy that I would recommend is:"

\(^{38}\) due to dispersion of opinions, potential reporting bias, small numbers, lack of data from controlled trials, etc.

\(^{39}\) Table 29 is duplicated in Appendix 1. Tables 30 and 31 in Appendix 1 present Table 29 ORN rate data, and additional data explained in footnotes, in order of increasing recommended healing times. Data in Tables 30 and 31 will be discussed in greater depth later.
FIGURE 5; RESULTS CHART 1.
Recommended MINIMUM Number of Days Post-Extraction Pre-Radiotherapy Healing Time vs. Reported ORN Rate

FIGURE 6. RESULTS CHART 2. Normal Recommended Number of Days Post-Extraction Pre-Radiotherapy Healing Time vs. Reported ORN Rate
Scatterplot Charts 1 and 2 (= Figures 5 and 6), displaying minimally and normally recommended pre-radiotherapeutic tooth socket healing times vs. reported ORN frequency, do not indicate any clear relationship between the tooth socket healing recommendations of the respondents and the ORN rates reported at their institutions. If one excludes reporting and volunteer bias, one may observe, however, that those respondents who follow the most common external literature standard recommended healing time\(^{40}\) of 14 days report ORN rates that vary over the widest range.

\(^{40}\) (whether due to conscientiousness in clinical practice and in reporting ORN rates, or lack of experience, or some other factor. However, categorized years of respondent practice (not displayed here) do not associate in any clear pattern with recommended pre-radiotherapeutic tooth extraction socket healing times.)
1. DIRECT ASSESSMENT OF ORN RISK FACTORS.

E. RELATION OF ORAL-SURGICAL, MEDICAL, AND PROSTHETIC TECHNIQUE TO RISK:

A series of Survey items solicited opinion about the relation of oral-surgical, medical, and prosthetic technique in the high dose radiation volume to ORN risk.

The important open-ended responses to Item 1230, "Dental extraction techniques/principles that I believe are important for minimizing ORN" are tabulated in Table 32.

Responses are consistent with the analogous close-ended item data below.

**TABLE 32. ITEM 1230 DENTAL EXTRACTION TECHNIQUES TO MINIMIZE ORN.**

<table>
<thead>
<tr>
<th>Frequency</th>
<th>Mean Rank</th>
<th>Product</th>
<th>Topic number</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>12 (10)</td>
<td>1.3</td>
<td>56.</td>
<td>451.</td>
<td>Minimize trauma</td>
</tr>
<tr>
<td>9</td>
<td>1.9</td>
<td>37.</td>
<td>443.</td>
<td>Surgical technique --soft-tissue closure (primary)</td>
</tr>
<tr>
<td>6</td>
<td>2.0</td>
<td>24.</td>
<td>452.</td>
<td>Eliminate sharp bony edges; do alveoplasty/alveolectomy.</td>
</tr>
<tr>
<td>3</td>
<td>1.0</td>
<td>15.</td>
<td>282.</td>
<td>Timing of extractions- adequate healing time available prior to initiating XRT.</td>
</tr>
<tr>
<td>4 (3)</td>
<td>2.7</td>
<td>13.</td>
<td>356.</td>
<td>Antibiotic coverage and ORN risk</td>
</tr>
<tr>
<td>2</td>
<td>1.5</td>
<td>9.</td>
<td>453.</td>
<td>Minimize alveoplasty/ alveolectomy. 42</td>
</tr>
</tbody>
</table>

Item 1570 asked for responses to the statement, "To reduce the risk of ORN following the extraction of a tooth, I believe it important to place an intra-alveolar dressing." Item 1570 respondents with high consensus and very high confidence disagree with this statement. 43 Respondents also were emphatic that naso-gastric feeding during tooth extraction socket healing would not reduce the risk for ORN. 44

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41 Frequency overall is followed in parentheses with the number who actually provided rankings (if different). Low rank = High Importance.

42 Item 1230 additional contributions of inadequate quality, being "one-off contributions," are: 290. Factors indicating extractions before, rather than after, radiotherapy: 304. Limit number of tooth extractions; 441. Block anesthesia, not infiltration; 454. Use flaps; 456. Hyperbaric oxygen therapy; 457. Forceps delivery when possible; 458. Do not use flaps; 853. Adequate post-treatment dental care.

43 Item 1570: median agreement = 1.9 (mean = 3.0), agreement IQR = 1.8; median confidence 6.1; individual agreement responses: 1,1,1,1,2,2,2,2,3,4,6,6,7,7, where 7 = strong agreement.

44 Item 1620: "I believe that the risk for ORN could be reduced by requiring patients to undergo naso-gastric feeding while a tooth extraction site heals." Median agreement = 1.5; agreement interquartile range = undefined; median individual agreement responses =1,1,1,1,1,1,1,2,4,5,6 at individual confidences = 5,6,7; median confidence = 6.4.
Item 1580 asked respondents to respond to the statement, "To reduce the risk of ORN following the extraction of a tooth, I believe it important to place an intra-alveolar dressing with topical antibiotic." Practically all respondents disagree with this statement, although consensus is only moderate.\textsuperscript{45}

Item 1590 asked respondents to respond to the statement, "To reduce the risk for ORN following the extraction of a tooth, I believe it important to provide antibiotic coverage prior to, and during, the extraction." Overall, weak agreement with moderate consensus and moderately high confidence\textsuperscript{46} is expressed to this.

Item 1560 asked respondents to respond to the statement, "To reduce the risk of ORN following the extraction of a tooth, I consider that it is more important to achieve primary soft-tissue closure (even if this requires very aggressive osteoplasty), than it is important to minimize osseous trauma." Median response agreement levels were strong, median confidence levels were very high (6.3), but in general agreement was weak due to low consensus. Low consensus in this item would appear to be consistent with bimodal opinion distribution, not poor data quality,\textsuperscript{47} an interpretation supported in the Table 32.

Item 3500 respondents weakly disagreed at moderate consensus with the statement, "I would regard the post-radiotherapeutic use of an old denture to be preferable.

\textsuperscript{45} Item 1580 median agreement = 1.8, inter-quartile agreement range = 2.1, individual agreement responses = 1,1,1,1,1,2,2,2,2,2,2,2,2,2,4,5; median confidence = 5.8.

\textsuperscript{46} Item 1590 median agreement = 4.7 = weak agreement; agreement interquartile range = 2.1. mean agreement 4.4; individual agreement responses = 1,1,1,3,4,4,5,5,5,5,5,5,6,6,6,6- at individual confidence responses of 4, 5, 6, and 7; median confidence = 5.6; mean confidence = 6.6.

\textsuperscript{47} Item 1560: median agreement = 6.3, mean agreement = 4.4; agreement inter-quartile range = 4.0 individual agreement responses: 1,1,1,2,4,5,5,5,5,6,6,6,6,6,7, where 7 = strong agreement.
to the fabrication and use of a new denture, since the old denture would be better tolerated and ultimately less risk for ORN.\textsuperscript{48}

Item 3490 respondents strongly expressed with high consensus the opinion that the extraction of an otherwise healthy tooth with a Class II restoration margin very near the interproximal bone is more risky for ORN than leaving the tooth in place.\textsuperscript{49} Nevertheless, one third of dentist potential respondents did not answer Item 3490, presumably due to respondent fatigue near the end of the 60 page survey.

In summary, achieving primary soft tissue closure and minimizing osseous trauma are the strategies strongly advocated\textsuperscript{50} as ORN risk reduction measures. A policy of prophylactic systemic antibiotic coverage during tooth extractions was advocated weakly\textsuperscript{51}. Respondents to this Delphi Survey did not find the other techniques mentioned in the close-ended items (1560-1590; 3490; 3500) to be relevant to ORN risk.

\textsuperscript{48} Item 3500 median agreement = 3.2, agreement interquartile range = 2.3; individual agreement responses = 1,2,2,3,3,4,4,7,U,U,U,U @ individual confidence responses = 5,6,7, & one entry of (A=4,C=4); median confidence = 5.7.

\textsuperscript{49} The item actually is stated as the converse. The results (strong disagreement) successfully tested an assumption that respondents would disagree with the item if they were paying attention. Item 3490 is: "I would regard the extraction of an otherwise healthy tooth with a Class II restoration margin very near the interproximal bone to be less risky for ORN than leaving the tooth in place." Median agreement = 1.9 = strong disagreement; agreement interquartile range =1.7; individual agreement responses = 1,1,1,2,2,2,3,3,4,U,U,U,U @ individual confidence responses mostly C= 4 - 6; median confidence = 5.5.

\textsuperscript{50} integrating results from Items 1230 and 1560. Another principle advocated in Item 1230, eliminating sharp bony edges via alveoplasty/alveolectomy, is less strongly advocated, as are some other strategies that will be discussed subsequently in the Results and Interpretation.

\textsuperscript{51} weak agreement with moderate consensus and moderately high confidence
2. INDIRECT ASSESSMENT OF ORN "RISK FACTORS"

A. PERCEIVED RELEVANCE TO ORN-PROPHYLACTIC TREATMENT PLANNING.

This section consists of items that parallel, extend or complement the data in Part 1. First, items related to tooth extraction treatment planning are examined, followed by some related factors not addressed previously. In order to be concise, items and responses often will summarized without much commentary. Table 33 summarizing the first data set follows written description of this first set of items.

"1770. Infections of dental origin (whether of endodontic or periodontal origin) affect my treatment planning for ORN-prophylactic tooth extraction." Very strong median agreement and very high median confidence at very high consensus was expressed.

"1820. I need to consider the presence/absence/type of periapical radiolucency and endodontic symptoms/clinical history before establishing a treatment plan for ORN-prophylactic tooth extraction" was considered. Very strong agreement and confidence at high consensus was expressed.

"1780. I need to consider periodontal pockets, furcation classes, mobility, horizontal and vertical bone loss, etc. before establishing a treatment plan for ORN-prophylactic tooth extraction." The responses resulted in median agreement and confidence both extraordinarily strong, and consensus was very high.

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52 Discussion of the implication of these items and the fairly high consistency of these responses displayed relative to items in previous sections will be postponed until the sections "Interpretation of Findings" and "Conclusions".

53 Whenever very high consensus is marked with an asterisk, the obvious consensus was determined by inspection. This occurred when S.P.S.S. was unable to calculate the interquartile range, leaving this undefined. If desired, please see "APPENDIX 5. RESPONSE CLASS GENERATING UNDEFINED QUARTILES", on page 448, for an explanation of these occurrences.
"1860. I need to consider the prognosis for patient compliance with recommended home care therapy and oral hygiene before establishing a treatment plan for ORN-prophylactic tooth extraction." Median agreement and confidence in responses to this item are both very strong, and at high consensus\(^{54*}\).

"1870. I need to consider the prognosis for patient attendance, and compliance with, recommended chair-side dental professional services, before establishing a treatment plan for ORN-prophylactic tooth extraction." Median agreement was very high, confidence very high, and consensus very high.

"1840. I need to assess the presence/absence/type of unbalanced bite, occlusal interference, parafunctional habits e.g. bruxism and clenching, etc. (i.e. subdivisions of the factor, 'Dental Occlusion,' ) before establishing a treatment plan for ORN-prophylactic tooth extraction."\(^{55}\) This item resulted in essential neutrality in agreement/disagreement, at moderate consensus.

\(^{54*}\) Whenever very high consensus is marked with an asterisk\("^*\), then obvious consensus was determined by inspection, the S.P.S.S. calculation of agreement interquartile range having been undefined.

\(^{55}\) Item 1840 median agreement was 4.2, mean agreement 4.0, agreement interquartile range 2.7, individual responses 1,2,2,3,3,3,4,5,5,5,5,6,7 at confidences 3-7, and median confidence 6.0.
TABLE 33. SUMMARY OF RESPONSE ANALYSES FOR SOME ITEMS

<table>
<thead>
<tr>
<th>ITEM</th>
<th>AGREEMENT</th>
<th>MEAN</th>
<th>75 - 25 IQ Range</th>
<th>CONFIDENCE</th>
<th>MEAN</th>
</tr>
</thead>
<tbody>
<tr>
<td>1770</td>
<td>6.6</td>
<td>6.6</td>
<td>*</td>
<td>6.5</td>
<td>6.5</td>
</tr>
<tr>
<td>1820</td>
<td>6.6</td>
<td>6.6</td>
<td>*</td>
<td>6.6</td>
<td>6.6</td>
</tr>
<tr>
<td>1780</td>
<td>6.8</td>
<td>6.8</td>
<td>*</td>
<td>6.8</td>
<td>6.8</td>
</tr>
<tr>
<td>1860</td>
<td>6.6</td>
<td>6.6</td>
<td>*</td>
<td>6.6</td>
<td>6.6</td>
</tr>
<tr>
<td>1870</td>
<td>6.3</td>
<td>6.0</td>
<td>0.3</td>
<td>6.6</td>
<td>6.6</td>
</tr>
<tr>
<td>1840</td>
<td>4.2</td>
<td>4.0</td>
<td>2.7</td>
<td>6.0</td>
<td>5.8</td>
</tr>
</tbody>
</table>

* Inspection of the raw data associated with this item revealed consensus that is high, although S.P.S.S. could not calculate it.
Several items have coincidentally equal medians. These reflect the raw data.

In summary, very strong agreement at high consensus was expressed about the need for consideration of endodontic status, periodontal status, and the presence of infections, prior to treatment planning for ORN-prophylactic tooth extraction. Support also was expressed for consideration of patient compliance with recommended home care measures during treatment planning. Data from item 1250 will be presented later linking patient compliance with oral hygiene status, so oral hygiene status is supported, like the three others above also arising from items 3200 and 3240-3420, as a factor relevant to ORN-prophylaxis. {However, Item 1750 (in Part c below) supports a contention that both oral hygiene status and home care compliance are, for the most part, under patient control, rather than clinician control. This could affect the form of the multifactorial formula incorporating them into a decision analysis as an assumption or a probability node (as illustrated in the final figure in Conclusions).} The bite (occlusion), possibly advanced earlier as an ORN risk in Item 3470 (mostly in the limited context of pressure concentration in one area of the jaw) is not supported as relevant.
2. INDIRECT ASSESSMENT OF ORN "RISK FACTORS"

B. FACTOR PRACTICALITY FOR DECISION ANALYSIS, E.G. QUANTIFIABILITY.

Another advantageous feature for classical decision analysis is the quantification of the factors contributing to the decision analysis directly or through an intermediate variable. The following items gather response data on whether some relevant potential factors identified in the preliminary literature search are quantifiable in a clinically routine manner:

"1790. I can assess periodontal pockets, furcation classes, mobility, horizontal and vertical bone loss, etc., in a quantitative fashion." Median agreement and confidence for this statement on quantifiability of these conventional periodontal status indicators were strong (6.3 and 6.4, respectively), although one of the 14 respondents disagreed, and two others, while agreeing, stated qualifications. Consensus was generally high.

"1830. I can assess the presence/absence/type of periapical radiolucency and endodontic symptoms/clinical history, in a quantitative fashion." The quality of response data is marginal, agreement IQR being 2.9. There was mild agreement with the concept of quantifiability of endodontic status indicators. Thus, inclusion of endodontic status in a decision analysis may require research to develop the suitable measure.

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56 With most of these items, there were only 14 eligible participants, since the physician respondent 06/ was requested to ignore indicated dental items.

57 "What does quantitative fashion mean?", and "There is often not enough time to do an adequate periodontal treatment."

58 Median agreement = 5.0, median confidence = 6.2. 4 of 13 respondents disagreed in Item 1830 and another stated, "Not Sure".

59 Is it possible that there is an element of urge-to-please bias in responses to this item? In any case, quantifiability of endodontic status indicators in relation to prediction for ORN risk would require further research.
2. INDIRECT ASSESSMENT OF ORN "RISK FACTORS"

C. CLINICAL CONTROLLABILITY OF ORN RISK FACTORS

A decision analysis of practical utility would stress variables that are under clinician control, as well as being routinely assessable. Thus, this section complements the earlier Item 3200 discussion of assessability of ORN risk factors.

"1750.a. I consider the following factors postulated to affect the caries rate, and thus the prognosis for ORN and my tooth extraction treatment planning, to be for the most part **under the control of the patient, rather than me:**"

1. diet, [1]
2. oral hygiene status; prognosis for same in the future, and [1]
3. future compliance with recommended home care and therapy. [1]

---

Item 1750 \( n = 14 \). Median Agreement = 6.1 = **Strong Agreement**; Agreement Interquartile Range = 1.4 = **High Consensus**

"b. If you disagree with any of the factors above, please circle the number of the factor."

*(Please see numbers inserted in [brackets] to the right of the Part a. list as a summary of frequency of circled exceptions)*

"Feel free to explain further, or suggest other factors."

Thus, the respondents very strongly agree at high consensus with the contention that diet, oral hygiene status and its future prognosis, and the future compliance with recommended home care and therapy is for the most part under the control of the patient, rather than the practitioner.\(^{61}\)

---

\(^{60}\) Item 1750. Individual agreement responses = 4,5,5,6,6,6,6,6,6,6,7,7,7,7 at individual confidences 6 and 7; median confidence = 6.5 = very high.
"1690 a. I consider all of the following factors postulated to affect dental extraction treatment planning to be largely under my control..." [prior to radiotherapy]:

1. the timing of extractions,
2. dental use of antibiotics,
3. the endodontic/caries/& restorative status of teeth (in the sense that most pathology can be rectified, unless the tooth is unrestorable)
4. the dental treatment plan (including the timing and type of dental prosthesis and liners,) and
5. the dental surgical technique. "

Median agreement = 5.6 = moderate agreement;
Agreement interquartile range = 1.9 = moderately high consensus.62

"b. If you disagree with any of the factors above, please circle the number of the factor. Feel free to explain further, or suggest other factors:"

(Please see Table 34 for these.)

TABLE 34. ITEM 1690.
DENTAL EXTRACTION FACTORS NOT LARGELY UNDER THE CONTROL OF THE DENTIST

<table>
<thead>
<tr>
<th>FACTOR TAKEN AS EXCEPTION TO ITEM 1690 LIST</th>
<th>FREQUENCY (out of n = 13)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. the timing of extractions</td>
<td>4</td>
</tr>
<tr>
<td>2. dental use of antibiotics</td>
<td>1 apparently legitimate</td>
</tr>
<tr>
<td></td>
<td>2 apparent non-sequiturs</td>
</tr>
<tr>
<td>3. the endodontic/caries/&amp; restorative status of teeth (in the sense that most pathology can be rectified, unless the tooth is unrestorable)</td>
<td>0</td>
</tr>
<tr>
<td>4. the dental treatment plan (including the timing and type of dental prosthesis and liners)</td>
<td>1</td>
</tr>
<tr>
<td>5. the dental surgical technique.</td>
<td>0</td>
</tr>
</tbody>
</table>

61 One respondent did, however, stress the role of the practitioner in assisting the patient towards his potential for compliance.

62 Individual agreement responses = 1,1,4,5,5,5,6,6,6,6,7 at individual confidences of =5,6, & 7; median confidence = 6.3 = very high confidence.]
The dental surgical technique was considered unanimously to be largely under the control of dentist. The dental treatment plan was considered to be under the control of the dentist although one respondent stated that it had to fit within radiotherapy timing constraints. That same respondent and three others considered the timing of dental extractions beyond control for the same reason. A statement that dental use of antibiotic is under personal control elicited three objections— one in which the particular respondent implied that he deferred to the surgeon, while the other two, whose objections were on grounds that it was unnecessary, would seem to be non-sequiturs.63

Summarizing, item 1690 indicates that all factors listed (the timing of extractions, dental use of antibiotics, the endodontic/caries/& restorative status of teeth, the dental treatment plan, the dental surgical technique) are under the control of the practitioner involved, unless the dental or oral surgical treatment plan becomes constrained by radiotherapeutic or surgical therapeutic requirements.

"1730.a. I consider all of the following factors postulated to affect dental extraction treatment planning to be beyond my control, at least in the pre-radiotherapy time "window:"
**TABLE 35. EXCEPTIONS TAKEN TO POTENTIAL FACTOR BEING BEYOND DENTIST'S CONTROL**

<table>
<thead>
<tr>
<th>Factor</th>
<th>Number of Exceptions</th>
</tr>
</thead>
<tbody>
<tr>
<td>age</td>
<td>0</td>
</tr>
<tr>
<td>the factors listed the next item suggested to be under the control of the patient</td>
<td>0</td>
</tr>
<tr>
<td>the prognosis for salivary function</td>
<td>1</td>
</tr>
<tr>
<td>the pre-irradiation vitality and healing capacity of the local tissues</td>
<td>1</td>
</tr>
<tr>
<td>the circulatory and metabolic status of the patient</td>
<td>1</td>
</tr>
<tr>
<td>the presence of Black Class II restorations near the bone</td>
<td>1</td>
</tr>
<tr>
<td>smoking status</td>
<td>1</td>
</tr>
<tr>
<td>idiopathic factors</td>
<td>2</td>
</tr>
<tr>
<td>the urgency of radiotherapy</td>
<td>2</td>
</tr>
<tr>
<td>the radiotherapy treatment plan</td>
<td>3</td>
</tr>
<tr>
<td>the post-irradiation vitality and healing capacity of the local tissues</td>
<td>4</td>
</tr>
<tr>
<td>the patient's psychology</td>
<td>4</td>
</tr>
<tr>
<td>the non-restorability of the tooth due to structural loss (e.g., due to caries)</td>
<td>4</td>
</tr>
<tr>
<td>parafunctional habits, if any (e.g., bruxism and clenching)</td>
<td>5</td>
</tr>
<tr>
<td>the periodontal status of the patient</td>
<td>6</td>
</tr>
</tbody>
</table>

Median agreement = 5.3 = *moderate agreement*; Median confidence = 6.3 = *strong confidence*. Interquartile agreement range = 2.5 = *moderate consensus*.

"b. If you disagree with any of the factors above, please circle the number of the factor."

*(Please see numbers inserted in [brackets] to the right of the Part a. list as a Summary of Frequency of Circled Exceptions)*

"Feel free to explain further, or suggest other factors:"

Rather than overdraw conclusions to this Item 1730 (for which data is presented in Table 35), one could state that the responses are consistent with expectation of respondents that they would have significant difficulty influencing all factors listed, with the possible exception of "periodontal status".

---

*64 Arguably, a factor not listed in this Item 1730, endodontic status, is more controllable than periodontal status, and should have been included in this item list.*

*65 Item 1730.a. individual agreement responses = 2,3,4,4,4,6,6,6,6,6,6,7,U,U at confidences = 4 to 7.*
ORAL HYGIENE STATUS AND ITS PREDICTION

The following items also relate to Oral Hygiene Status and its prediction, and are included in this section for the sake of simplicity.

The responses to Item 3160 indicate moderate Likert Scale agreement at moderate consensus and high confidence with the statement "I think that the dentist is able to predict a patient's future compliance with recommended home care therapy", but the moderate consensus and moderately-high median confidence responses to the Item 3170 statement, "I think that the plaque index is a useful predictor of future oral hygiene" indicate that opinions are approximately evenly divided about the ability of the plaque index (alone) to be a predictor of future oral hygiene. The implication drawn is that the dentist often thinks that he has to depend on additional criteria in order to reasonably predict future oral hygiene status. This is supported by responses to the open-ended Item 1240:

"1240. I find that the most clinically useful predictors of future oral hygiene performance are:"

---

66 [Item 3160 median agreement = 5.4, agreement interquartile range = 1.9, individual agreement responses = 3,4,5,5,5,6,6,6,7,7 at confidences of 3 to 7; median confidence = 5.8.]

67 [Item 3170 median agreement = 4.1, agreement interquartile range = 2.4, individual agreement responses = 1,2,4,4,4,4,5,5,6,7,7 at confidences of 4 to 7; median confidence = 5.5.]

221
TABLE 36. ITEM 1240. PREDICTORS OF FUTURE ORAL HYGIENE PERFORMANCE

<table>
<thead>
<tr>
<th>Frequency</th>
<th>Mean Rank</th>
<th>Product</th>
</tr>
</thead>
<tbody>
<tr>
<td>9 (8)</td>
<td>1.0</td>
<td>45.</td>
</tr>
<tr>
<td>4</td>
<td>1.3</td>
<td>19.</td>
</tr>
<tr>
<td>4</td>
<td>2.0</td>
<td>16.</td>
</tr>
<tr>
<td>3</td>
<td>1.3</td>
<td>14.</td>
</tr>
<tr>
<td>3</td>
<td>1.7</td>
<td>13.</td>
</tr>
<tr>
<td>2</td>
<td>1.5</td>
<td>9.</td>
</tr>
<tr>
<td>2</td>
<td>2.0</td>
<td>8.</td>
</tr>
</tbody>
</table>

- 520. The oral hygiene status [e.g., Plaque index] of the dentition.
- 526. Dental attitude and motivation (2); & 525. Dental I.Q. (2)
- 415. Restorative status of each tooth in high-dose radiation volume (3) & 250. Patient's past dental history (1)
- 549. Past history of complying, or not, with prescribed oral hygiene.
- 401. The dentition's recent caries experience/rate
- 578. Oral hygiene instruction before and after radio-therapy(1); & 852. Regular dental (or if appropriate, hygienist) follow-up available.
- 528. I.Q., Intelligence (1); & 713. Education level of patient (1)

Similar but not identical factors predicted compliance with recommended home care therapy (e.g., fluoride mouth rinses) in the open-ended Item 1250:

"1250. I find that the most clinically useful predictors of future compliance with recommended oral home care therapy (e.g., fluoride mouth trays) are:"

TABLE 37. ITEM 1250. PREDICTORS OF COMPLIANCE WITH FLUORIDE, ETC., HOME CARE

<table>
<thead>
<tr>
<th>Frequency</th>
<th>Mean Rank</th>
<th>Product</th>
</tr>
</thead>
<tbody>
<tr>
<td>6 (4)</td>
<td>1.0</td>
<td>30.</td>
</tr>
<tr>
<td>5 (4)</td>
<td>1.7</td>
<td>22.</td>
</tr>
<tr>
<td>4 (3)</td>
<td>1.3</td>
<td>19.</td>
</tr>
<tr>
<td>3 (2)</td>
<td>2.0</td>
<td>12.</td>
</tr>
</tbody>
</table>

- 520. The oral hygiene status of the dentition.
- 525. Dental I.Q. [dental sophistication] (2): dental attitude & motivation (2)
- 549. Past history of complying, or not, with prescribed oral hygiene.
- 528. I.Q., Intelligence

All of these factors should be considered in predicting future compliance.
3. FACTORS RELEVANT TO TOOTH EXTRACTION IN THE “HIGH DOSE RADIATION VOLUME”:

A. GENERAL

This section will proceed from a Delphi process examination of general assumptions about factors potentially affecting for extraction and current treatment policy to an examination of individual factors that currently influence tooth extractions. The findings in this section potentially could be over-ridden by ORN prophylaxis recommendations developed after future research efforts recommended in the Conclusions, but one would expect a clinical decision analysis generally to be consistent with the following.

"1470. Other things being equal, if the risk of ORN from dental causes increases, I will be more likely to extract the teeth involved." Item 1470 respondents generally expressed very strong agreement\(^{68}\) at moderate consensus.

"1460. Other things being equal, if the risk of ORN from non-dental causes increases, I will be more likely to recommend extraction of teeth." Response consensus and data quality was borderline low (3.0), the respondents divided, and median agreement neutral overall\(^{69}\).

\(^{68}\) Item 1470. Median agreement = 6.4, agreement interquartile range = 2.2; individual agreement responses = 1,3,6,6,6,6,7,7,7,7,7 at C=5,6,7, & U (U comment: "Depends upon relationship of teeth to potential ORN"); median confidence = 6.6.

\(^{69}\) Item 1460. Median agreement = 4.0; interquartile agreement range = 3.0; median confidence = 5.9; individual agreement responses = A =1,2,2,2,4,5,6,6,7, @ confidences = 5,6,7, and U (U comment "Depends upon relationship of teeth to potential ORN"), and (A=3, C=4), (A=4, C=4), & (A=4, C=1)(the latter with comment "Are teeth in the field?") Elsewhere in the survey, the respondents were told to assume that the teeth were in the high dose volume, but this may not have been universally assumed for this item, causing some confusion. Nevertheless, the lack of explicit agreement in this item is surprising, and may reflect the borderline quality of the data.
"1490. I favor the extraction of all mandibular teeth in the high dose radiation volume." The median of agreement responses was 1.2 (strong disagreement). Thus, one policy extant in previous decades and still seriously considered in a 1986 French survey, i.e. extracting all mandibular teeth in the high dose radiation volume, was strongly and unanimously rejected at high consensus.*

In item 1500, item policies f., g., i., j., e., and l. were accepted by a majority of respondents:

"1500. The following statements closely reflect my personal treatment philosophies for patients soon to receive radiotherapy involving the mandible:"

**PHILOSOPHIES ACCEPTED BY 93% (13 OF 14) DENTIST-RESPONDENTS:**

f. Extract all mandibular teeth in the high dose radiation volume that have a history of severe periodontal disease.

**PHILOSOPHIES ACCEPTED BY 71% (10 OF 14) DENTIST-RESPONDENTS:**

g. Extract all mandibular teeth in the high dose radiation volume that have a history of moderate periodontal disease.^72

i. Extract all mandibular teeth in the high dose radiation volume that have an infection of endodontic origin.^73

---

^70 Item 1490 median agreement = 1.2 = very strong disagreement; agreement interquartile range = undefined, but interpreted by inspection to be very high; individual agreement responses = 1,1,1,1,1,1,1,1,1,1,1,1,2,3 @ confidences 6 and 7; median confidence = 6.8.

^71 (Peri, Baudet, and Chamard, 1986)

^72 One-off comments included to indicate qualified support for a tooth extraction philosophy:

Comment of 13/: "Retain if there is enough bone support and a healthy gingiva"

Comment of 15/: "sometimes".

^73 One-off comments included to indicate qualified support for a tooth extraction philosophy:

Comment of 13/: "Only if a apectomy is not possible"
j. Extract all mandibular teeth in the high dose radiation volume that have a periapical lesion.\textsuperscript{74}

**PHILOSOPHIES ACCEPTED BY 57\% (8 OF 14) DENTIST-RESPONDENTS:**

e. Extract all mandibular teeth in the high dose radiation volume that have an infection of periodontal origin.

l. Consider retaining a periodontally-involved tooth particularly important for prosthodontic rehabilitation, that otherwise might be extracted.

**50\% RESPONDENT ACCEPTABILITY LINE**

**PHILOSOPHIES ACCEPTED BY 36\% = 5 OF 14 (REJECTED BY 64\%) OF DENTIST-RESPONDENTS:**

m. Consider retaining an endodontically-involved tooth particularly important for prosthodontic rehabilitation, that otherwise might be extracted.

**PHILOSOPHIES ACCEPTED BY 14\% = 2 OF 14 (REJECTED BY 86\%) OF DENTIST-RESPONDENTS:**

h. Extract all mandibular teeth in the high dose radiation volume that have a history of mild periodontal disease.\textsuperscript{75}

**PHILOSOPHIES UNANIMOUSLY REJECTED:**

a. Extract all teeth in the mouth.

b. Extract all mandibular teeth.

\textsuperscript{74} [One-off comments included to indicate qualified support for a tooth extraction philosophy:] Comment of 15/: "RCT"

\textsuperscript{75} Note: One of the two respondents who agreed added the comment, "Rarely."
c. Extract all teeth in the high dose radiation volume.

d. Extract all mandibular teeth in the high dose radiation volume.

k. Extract all mandibular teeth in the high dose radiation volume that have a history of endodontic treatment (even if apparently successful, i.e. asymptomatic and without apparent residual periapical lesion.)

For additional respondent comments, please see footnote 76.

"1130. My major criteria (indications) for extracting teeth in the future high dose radiation volume are:"

(For responses, please see Table , next page)

A Xeroxing error (only partial duplication of a page) when the survey was produced for distribution to the respondents limited the numbers of Item 1130 respondents to 7.

Classification of caries and restorative factors into a single category in Table 38 (Item 1130) occurred in part because some respondents mentioned caries and restorative status simultaneously. The raw data also could be interpreted to indicate also that caries and restorative status each associate with a product of about 14.

---

76 [One-off comments included to indicate qualified support for a tooth extraction philosophy.]
- "Extract all mandibular teeth in high dose field for patient with poor oral hygiene compliance."
- "Extract all teeth in field (high dose) with endo[dontic] involvement of poor prognosis to [for] healing if endo[dontically] treated."
- "NO RULES APPLY AS WRITTEN ABOVE. Treat each patient (extracting teeth) depending on more objective criteria than [tooth extraction philosophy list] "a. - k.""
- "When in doubt about the prognosis of a tooth, extract it."

226
<table>
<thead>
<tr>
<th>Frequency</th>
<th>Mean Rank</th>
<th>Product</th>
<th>Topic Number, Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>2</td>
<td>2.6</td>
<td>29.</td>
<td>417. Non-restorability</td>
</tr>
<tr>
<td>4 (3)</td>
<td>2.0</td>
<td>29.</td>
<td>415. Restorative status of each tooth in high-dose radiation volume</td>
</tr>
<tr>
<td>4 (3)</td>
<td>3.2</td>
<td>overlap</td>
<td>401. The dentition's recent caries experience/rate, &amp; &quot;415.&quot;</td>
</tr>
<tr>
<td>1</td>
<td>2</td>
<td>2</td>
<td>414. Caries in tooth (c.f. 401)</td>
</tr>
<tr>
<td></td>
<td>2.0</td>
<td>18.</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>1</td>
<td>353.</td>
<td>Periodontal infection</td>
</tr>
<tr>
<td>1</td>
<td>1</td>
<td>360.</td>
<td>Periodontal disease and risk for ORN:</td>
</tr>
<tr>
<td>1</td>
<td>1</td>
<td>365.</td>
<td>Severe periodontal disease</td>
</tr>
<tr>
<td>2</td>
<td>3.0</td>
<td>370.</td>
<td>Periodontal status:</td>
</tr>
<tr>
<td>1</td>
<td>2</td>
<td>371.</td>
<td>Periodontal pocket depth</td>
</tr>
<tr>
<td>3</td>
<td>2.3</td>
<td>375.</td>
<td>Tooth mobility</td>
</tr>
<tr>
<td>2</td>
<td>3.0</td>
<td>523.</td>
<td>Oral hygiene status [poor]</td>
</tr>
<tr>
<td>2</td>
<td>2.2</td>
<td>525.</td>
<td>Dental I.Q.</td>
</tr>
<tr>
<td>1</td>
<td>1</td>
<td>550.</td>
<td>The expected compliance of the patient with prescribed home care, such as fluoride rinses</td>
</tr>
<tr>
<td>1</td>
<td>1</td>
<td>540.</td>
<td>Expected compliance of the patient with prescribed oral hygiene home care.</td>
</tr>
<tr>
<td>1</td>
<td>2</td>
<td>530.</td>
<td>Expected compliance with all home care</td>
</tr>
<tr>
<td>1</td>
<td>2</td>
<td>560.</td>
<td>Expected compliance of patient with professional appointments and treatments.</td>
</tr>
<tr>
<td>1</td>
<td>3</td>
<td>852.</td>
<td>Regular dental (or if appropriate to item, dental hygienist) follow-up available.</td>
</tr>
<tr>
<td>2</td>
<td>3.0</td>
<td>334.</td>
<td>Conservative endodontic treatment [c.f.: 223.]</td>
</tr>
<tr>
<td>1</td>
<td>1</td>
<td>222.</td>
<td>Periapical lesion -- see also 332,333</td>
</tr>
<tr>
<td>1</td>
<td>3</td>
<td>352.</td>
<td>Infection of endodontic origin</td>
</tr>
<tr>
<td>2</td>
<td>3.0</td>
<td>233.</td>
<td>Tooth function.</td>
</tr>
<tr>
<td>2</td>
<td>3.0</td>
<td>391.</td>
<td>Tooth unopposed occlusion</td>
</tr>
<tr>
<td>1</td>
<td>7</td>
<td>4.7</td>
<td>171. Mandibular, as opposed to maxillary, location of ORN (as potential ORN incidence risk factor)</td>
</tr>
<tr>
<td>1</td>
<td>4</td>
<td>4.7</td>
<td>399. Tooth location in arch.</td>
</tr>
<tr>
<td>1</td>
<td>3</td>
<td>4.7</td>
<td>232. Tooth position.</td>
</tr>
<tr>
<td>1</td>
<td>4</td>
<td>7.5</td>
<td>231. Tooth particularly important for prosthodontic rehabilitation that otherwise might be extracted.</td>
</tr>
<tr>
<td>1</td>
<td>7</td>
<td>7.5</td>
<td>750. Dental prosthetic treatment plan</td>
</tr>
<tr>
<td>1</td>
<td>7</td>
<td>6.5</td>
<td>752. Oral surgical treatment plan</td>
</tr>
<tr>
<td>1</td>
<td>6</td>
<td>6.5</td>
<td>450. Fractured roots</td>
</tr>
<tr>
<td>1</td>
<td>9</td>
<td>7.5</td>
<td>420. Radiation trauma to tissue and risk for ORN #1</td>
</tr>
<tr>
<td>1</td>
<td>6</td>
<td>7.5</td>
<td>424. The radiation intensity</td>
</tr>
</tbody>
</table>
Table 38 indicates that periodontal factors, endodontic factors, patient compliance, and oral hygiene factors receive further support as being important in the decision to extract teeth in the high dose volume. The rise to relative prominence of caries and restorative factors, and even the degree of dental function in the teeth under consideration, however, is striking. The next item, 1180, requesting an open-ended list of tooth extraction indications, also accords tooth function some prominence.

These factors are all consistent with the set of decision analysis factors hypothesized earlier, then supplemented with the proposed factor dealing with the desirability of retaining the tooth (mechanical integrity, functionality, etc.).

"1180. Foreseeable dental, medical, or surgical cancer treatments in addition to radiotherapy that increase the likelihood that I would extract teeth prior to radiotherapy, as an ORN-prophylactic measure, are:" produced responses tabulated in Table 39.

Similar to Item 1130 ("My major criteria for extracting teeth in the future high dose radiation volume are:"), Item 1180 ("Foreseeable dental, medical, or surgical cancer treatments in addition to radiotherapy that increase the likelihood that I would extract teeth prior to radiotherapy, as an ORN-prophylactic measure, are:" ) produces responses which weigh heavily

- the caries rate and restorative status factors
- periodontal factors
- patient compliance and oral hygiene factors, and
- endodontic factors.

(These will be discussed further.)
### TABLE 39. ITEM 1180. NON-RADIOThERAPEUTIC INDICATIONS FOR TOOTH EXTRACTION

<table>
<thead>
<tr>
<th>Frequency</th>
<th>Mean Rank</th>
<th>Product</th>
<th>Topic Number, Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>□ (2 (1) 1)</td>
<td>53.</td>
<td>419. Tooth Not Anticipated To Be Maintainable (Past Hx Of Poor O.H., Caries, Or Periodontal Susceptibility)</td>
<td></td>
</tr>
<tr>
<td>□ (2 (1) 1)</td>
<td>53.</td>
<td>417. Non-Restorability</td>
<td></td>
</tr>
<tr>
<td>1 (1)</td>
<td>3.0</td>
<td>416. Adequate Structural Integrity [or lack of same]</td>
<td></td>
</tr>
<tr>
<td>2 (1)</td>
<td>1</td>
<td>415. Restorative Status Of Teeth In The High-Dose Rad'n Volume</td>
<td></td>
</tr>
<tr>
<td>5 (4)</td>
<td>1.2</td>
<td>401. The Dentition's Recent Caries Experience/Rate</td>
<td></td>
</tr>
</tbody>
</table>

#### CARIES AND RESTORATIVE FACTORS

#### ORAL SURGICAL FACTORS

<table>
<thead>
<tr>
<th>Frequency</th>
<th>Mean Rank</th>
<th>Product</th>
<th>Topic Number, Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>□ (2 (1) 1)</td>
<td>53.</td>
<td>419. Tooth Not Anticipated To Be Maintainable (Past Hx Of Poor O.H., Caries, Or Periodontal Susceptibility)</td>
<td></td>
</tr>
<tr>
<td>□ (2 (1) 1)</td>
<td>53.</td>
<td>417. Non-Restorability</td>
<td></td>
</tr>
<tr>
<td>1 (1)</td>
<td>3.0</td>
<td>416. Adequate Structural Integrity [or lack of same]</td>
<td></td>
</tr>
<tr>
<td>2 (1)</td>
<td>1</td>
<td>415. Restorative Status Of Teeth In The High-Dose Rad'n Volume</td>
<td></td>
</tr>
<tr>
<td>5 (4)</td>
<td>1.2</td>
<td>401. The Dentition's Recent Caries Experience/Rate</td>
<td></td>
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</tbody>
</table>

#### PERIODONTAL FACTORS

<table>
<thead>
<tr>
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<th>Mean Rank</th>
<th>Product</th>
<th>Topic Number, Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 (1)</td>
<td>1</td>
<td>375. Tooth Mobility</td>
<td></td>
</tr>
<tr>
<td>6 (4)</td>
<td>1.5</td>
<td>364. Mixed Moderate and Severe Periodontal Disease</td>
<td></td>
</tr>
<tr>
<td>□ (2 (1) 1)</td>
<td>53.</td>
<td>419. Tooth Not Anticipated To Be Maintainable (Past Hx Of Poor O.H., Caries, Or Periodontal Susceptibility)</td>
<td></td>
</tr>
</tbody>
</table>

#### METABOLIC FACTORS

<table>
<thead>
<tr>
<th>Frequency</th>
<th>Mean Rank</th>
<th>Product</th>
<th>Topic Number, Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>2 (1)</td>
<td>2</td>
<td>463 Systemic Metabolic State</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>1</td>
<td>459. Bone Marrow Transplant</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>1</td>
<td>243. Cardiac Risk For Sub-Acute Bacterial Endocarditis</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>1</td>
<td>455. Chemotherapy</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>1</td>
<td>461. The Anticipated Blood Supply, or Oxygen Perfusion of, The High-Dose Irradiated Mandibular Volume</td>
<td></td>
</tr>
</tbody>
</table>

#### PATIENT COMPLIANCE & ORAL HYGIENE FACTORS

<table>
<thead>
<tr>
<th>Frequency</th>
<th>Mean Rank</th>
<th>Product</th>
<th>Topic Number, Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1</td>
<td>525. Dental I.Q.</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>1.0</td>
<td>520. The Oral Hygiene Status Of The Dentition.</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>1</td>
<td>530. Expected Compliance With All Home Care</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>1</td>
<td>568. Difficulty Complying With Professional Appointments</td>
<td></td>
</tr>
</tbody>
</table>

#### ENDODONTIC FACTORS

<table>
<thead>
<tr>
<th>Frequency</th>
<th>Mean Rank</th>
<th>Product</th>
<th>Topic Number, Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>5 (4)</td>
<td>1.7</td>
<td>222. Periapical Lesion</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>2.0</td>
<td>330. Endodontic Treatment and ORN Risk.</td>
<td></td>
</tr>
</tbody>
</table>

#### TOOTH FUNCTION FACTORS

<table>
<thead>
<tr>
<th>Frequency</th>
<th>Mean Rank</th>
<th>Product</th>
<th>Topic Number, Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>2 (1)</td>
<td>3</td>
<td>390. Occlusion:</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>1</td>
<td>391. Tooth Unopposed Occlusion</td>
<td></td>
</tr>
</tbody>
</table>

However, Item 1180 also weights heavily some factors that (presumably) do not meet the Item 1130 requirements as being major factors indicating extraction:
• oral surgical factors (particularly the proximity of tooth root surface and alveolar process in relation to site of surgery)
• metabolic factors.

As mentioned previously, tooth function also is accorded some importance in Items 1130 and 1180.

Responses to the open-ended item 1190, "My decision to extract mandibular teeth during the pre-radiotherapy window is influenced by these aspects of the radiotherapy treatment plan:" are tabulated in Table 40.

**TABLE 40. ITEM 1190. RADIOThERAPEUTIC FACTORS AFFECTING DECISION TO EXTRACT MANDIBULAR TEETH IN THE PRE-RADIOTHERAPY WINDOW.**

<table>
<thead>
<tr>
<th>n</th>
<th>Frequency</th>
<th>Mean Rank</th>
<th>Product</th>
<th>Footnote</th>
<th>Topic Number, Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>A. FACTORS RELATED DIRECTLY TO IRRADIATION</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>8-9 (6)</td>
<td>1.2</td>
<td>41.</td>
<td>431. The Irradiated Volume</td>
<td></td>
<td></td>
</tr>
<tr>
<td>9 (7)</td>
<td>1.7</td>
<td>39.</td>
<td>422. Overall Dosage, or Past Hx of a Certain Cumulative Minimum Dose</td>
<td></td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>2.2</td>
<td>23.</td>
<td>495. Type of Irradiation</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>1.7</td>
<td>13.</td>
<td>427. Fractionation</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>1.5</td>
<td>9.</td>
<td>242. Urgency of Radiotherapy = time available prior to XRT</td>
<td></td>
<td></td>
</tr>
<tr>
<td>B. FACTORS RELATED ONLY INDIRECTLY TO IRRADIATION</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5 (4)</td>
<td>1.5</td>
<td>22.5</td>
<td>491. Anatomic Location / Structure Irradiated. {includes 2 (1) &quot;940. Prognosis for salivary function&quot; at ranks U,3.}</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2 (1)</td>
<td>4</td>
<td>4.</td>
<td>265. Prognosis for Complications after XRT if teeth not extracted</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

The irradiated volume is accorded a high importance by the respondents, which suggests that this factor, along with dosage, fractionation, timing, and type of irradiation, must be considered during decision analysis.

---

78 "495." here collapses 6 citations from 6 respondents:
1. 4 citations at mean rank 2.25 of [ "495. Type of radiation"] not defined as to whether
   • "496. Type(s) of electromagnetic and/or particulate radiation employed" or
   • "497. Combination (interstitial brachytherapy and external beam) therapy (in contrast to external beam alone)"
2. 1 citation at rank 3 of topic 496. above; in this case the exact quote is "type of electrons: electrons/photons."
3. 1 citation at rank 1 of topic 428., "brachytherapy"
3. FACTORS RELEVANT TO TOOTH EXTRACTION IN THE “HIGH DOSE RADIATION VOLUME”:

B. SPECIFIC

A series of items evaluates the importance of specific factors as indications for ORN-prophylactic tooth extraction in the high dose volume. This series of items starting with number 1890 is directly analogous to the Item 3240 series, which evaluate ORN risk directly. Both will be presented in a format to permit direct comparison, facilitate understanding, and to gain impressions of reliability.

The 1890-series of close-ended items with the root, "My decision whether to extract teeth depends strongly on my assessment of", produced the following responses (presented in order of decreasing consensus, with the agreement scale digit closest to the item median agreement in bold face and doubly underlined, to provide a visual indication of agreement or disagreement, and the comparable indication from the Item 3240 series (re ORN risk) marked with an arrow "↓"). Details of agreement and confidence medians, means, and interquartile ranges may be found in Table 41 in Appendix 1.

---

79 Data in this section and even the Item 3240-3420 series previously reported may have been compromised slightly by a typographical error in the instructions. Inspection of the raw Likert Scale responses suggests a possibility that two respondents may have been confused in their first few responses, diluting but not changing the agreement trends indicated. For the record, the error in the instructions preceding the Survey Section II. Items 1890-3030 omitted three letters "DIS", underlined below:

"PLEASE NOTE, THAT THE SCALE USED TO THIS POINT -- MY FEELINGS ABOUT THE LAST STATEMENT ARE: [CIRCLE A NUMBER:] I DISAGREE 1 2 3 4 5 6 7 I AGREE VERY STRONGLY I AM VERY MY CONFIDENCE IN THIS ANSWER IS: I AM VERY UNCERTAIN 1 2 3 4 5 6 7 CERTAIN " WILL BE REPLACED WITH A "MINIATURE VERSION" IN THE NEXT TWO ITEMS. THE MINIATURE VERSION SHOULD BE TREATED IDENTICALLY-- I DISAGREE 1 2 3 4 5 6 7 I AGREE AM UNCERTAIN 1 2 3 4 5 6 7 AM CERTAIN " PLEASE RECOGNIZE THAT "1" STILL INDICATES VERY STRONG DISAGREEMENT OR GREAT UNCERTAINTY, AND "7" VERY STRONG AGREEMENT OR CERTAINTY."
"My decision whether to extract teeth depends strongly on my assessment of":

1940 f. - the oral hygiene status of the dentition, independent of the caries rate.

I DISAGREE 1 2 3 4 5 6 7 I AGREE

1890 a. - the "passive" periodontal status (e.g., periodontal pocket depths, furcation involvements, etc.) of teeth in the high dose radiation volume.

I DISAGREE 1 2 3 4 5 6 7 I AGREE

1930 e. - the endodontic status of each tooth in the high-dose radiation volume.

I DISAGREE 1 2 3 4 5 6 7 I AGREE

1910 c. - the dentition's recent caries experience /expected caries rate.

I DISAGREE 1 2 3 4 5 6 7 I AGREE

1920 d.- the mechanical integrity restorative status of each tooth in the high-dose radiation volume.

I DISAGREE 1 2 3 4 5 6 7 I AGREE

1960 h. - anticipated vascular and cellular changes induced by high dose therapeutic irradiation.

I DISAGREE 1 2 3 4 5 6 7 I AGREE

2080 s. - the patient's prognosis for survival [No "↓" ORN risk item applicable]

I DISAGREE 1 2 3 4 5 6 7 I AGREE

— Item 1890-Series (Extraction Indication) —High Consensus ↑ — Moderate Consensus ↓ —

2030 n.-the systemic metabolic state [NOT circulatory status]

I DISAGREE 1 2 3 4 5 6 7 I AGREE

1950 g. - the dental occlusion in all manners, including parafunctional habits.

I DISAGREE 1 2 3 4 5 6 7 I AGREE

1970. i. - anticipated level of trauma from therapeutic surgery.

I DISAGREE 1 2 3 4 5 6 7 I AGREE

These Item 1890-series (extraction indication) data and 3240-series (ORN risk) data demonstrate, for pairs of similar factors, very good consistency, with two exceptions: the "dentition's recent caries experience /expected caries rate of each tooth", and "the mechanical integrity restorative status of each tooth" ...in the high-dose radiation volume. In both these cases, the reason for the discrepancy in agreement levels appears clear: caries or impaired mechanical integrity would indicate tooth extraction to a degree greater than that simply indicated by ORN risk.

Associated with a fall from strong to weak agreement levels within these extraction-indication / ORN-risk medians data pairs, consensus levels also fall-- from high to moderate. For the other factors above, the levels of consensus in Item 3240 (ORN risk) series are high, except for "g. dental occlusion", where it is only moderate.

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The moderately high consensus levels for two items in the 3240 series (ORN risk) are marginally adequate in the Item 1890 series (tooth extraction indication agreement level boldened):

2050  p. - the patient's diet (excluding effects on caries rate)

I DISAGREE 1 2 3  4 5 6 7 I AGREE

The implication of the latter two items is that respondents considered diet and smoking status to be less an indication for extraction than a risk for ORN. The discrepancy associated with diet is explainable; dietary habits could affect dental treatment planning independently of ORN risk. However, considering the known deleterious effects of smoking, e.g. irritation, and association with osteoradionecrosis (Kluth, Jain, Stuchell and Frich 1988), the discrepancy in that matched pair may indicate reliability limitations.

Neutrality in agreement (a moot finding) at adequate consensus is found for

"2040. o. the patient's age" in both series of items.

Agreement levels were comparable within two matched pairs of factors for which consensus levels were high in the 3240 series (ORN risk) but low in the Item 1890 series (tooth extraction indication agreement level boldened):

2000  I. -the anticipated delicacy/friability of the local oral mucosa, in combination with local supra-osseous tissue contours

I DISAGREE 1 2 3  4 5 6 7 I AGREE

1980  j. - the salivary or xerostomia status of the patient.

I DISAGREE 1 2 3  4 5 6 7 I AGREE

This suggests that even some low consensus data (normally not reported, and which does not meet quality standards) may be reliable.
3. FACTORS RELEVANT TO TOOTH EXTRACTION IN “HIGH DOSE VOLUME”:

C. QUALITY OF POTENTIAL INDICATORS FOR ORN-PROPHYLACTIC EXTRactions

In this section, respondents are asked to indicate whether a factor is a "classic" factor indicating extraction. This should assist the identification of criteria that are considered most important as major factors in a theoretical decision tree, given definitions supplied in the item. 81

Table 42 summarizes responses 82 of adequate consensus to the statement root in bold face in the last footnote. Those responses at the top of the list would tend to be suitable for potential inclusion in a decision analysis, and those for which disagreement was expressed, would tend not to be.

TABLE 42. ITEMS 2110-3030. [BY DESCENDING AGREEMENT]:
SUITABILITY OF FACTORS AS CLASSIC INDICATIONS FOR EXTRACTION

<table>
<thead>
<tr>
<th>AGREEMENT LEVEL</th>
<th>FACTOR:</th>
<th>AGREEMENT</th>
<th>CONSENSUS</th>
<th>CONFIDENCE</th>
</tr>
</thead>
<tbody>
<tr>
<td>6.3</td>
<td>Passive/Traditional Periodontal Status 83</td>
<td>1.4</td>
<td>6.3</td>
<td></td>
</tr>
<tr>
<td>5.2</td>
<td>Level of Surgically-Induced Trauma 84</td>
<td>2.9</td>
<td>5.8</td>
<td></td>
</tr>
<tr>
<td>4.1</td>
<td>Systemic Metabolic State 85</td>
<td>2.7</td>
<td>5.8</td>
<td></td>
</tr>
<tr>
<td>↓ DISAGREEMENT →</td>
<td>Patient's Smoking Status</td>
<td>2.5</td>
<td>5.6</td>
<td></td>
</tr>
<tr>
<td>2.8</td>
<td>Anticipated Oxygen Perfusion in high dose vol.*</td>
<td>3.0</td>
<td>5.5</td>
<td></td>
</tr>
<tr>
<td>2.7</td>
<td>Dental Occlusion (Bite) 86</td>
<td>1.9</td>
<td>5.4</td>
<td></td>
</tr>
<tr>
<td>2.4</td>
<td>Present Periodontal Disease Activity 87</td>
<td>2.1</td>
<td>6.0</td>
<td></td>
</tr>
<tr>
<td>2.4</td>
<td>Patient's Age</td>
<td>2.5</td>
<td>5.8</td>
<td></td>
</tr>
<tr>
<td>1.8</td>
<td>Patient's Diet (excluding effects on caries rate)</td>
<td>2.1</td>
<td>5.7</td>
<td></td>
</tr>
</tbody>
</table>

81 "Although distinctions may be arbitrary sometimes, indications for ORN-prophylactic tooth extraction might be divided into two classes:
1. Classic Indication: ideally, an absolute and very sharply demarcated indication, sufficient unto itself, for extraction; in practice, using as an example a "black/white decision," an indication with only a narrow 'gray' area in which other variables need to be considered before deciding whether to extract.
2. Modifying Indication Factor: an indication for extraction which contributes, in combination with one or more other factors considered at the same time, to a decision whether to extract."

82 (from Items 2110 to 3030, with a gap in numbering between 2250 and 3000)

... e.g., periodontal pocket depths, furcation involvements, etc.) of teeth in the high dose radiation volume.

Comment by Respondent 02/: "Cannot anticipate" [level of surgical trauma]

... (e.g., acidotic, diabetic, etc., NOT circulatory status)

... in all manners, including parafunctional habits.

... my estimation of periodontal disease activity through such surrogates as bleeding on probing, microbiological assays, chemical tests, etc."

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4. QUANTITATIVE ESTIMATES OF ORN RISK.

Inspections of the quantitative ORN risk estimates requested in Section IV (44th through 53rd pages) of the Survey (reproduced in the Appendix 3) reveal that most of these scenario-driven quantitative estimates lack sufficient central tendency and quality to merit reporting of medians or means. Therefore findings in this section ordinarily will be limited to a simple report of qualitative findings, or qualitative interpretations of apparent trends when this suggests an understanding of respondents' perspectives. An eventual decision analysis should be consistent with the findings reported unless better quality data indicates otherwise.

6 of the 14 Item 3050 respondents think that all head and neck cancer patients with osteonecrosis must have irradiation as one of the etiologic factors. The distribution of the percentage of osteonecrosis of the mandible in head and neck cancer patients thought by all to occur without irradiation as an etiologic factor was skewed towards zero selected by six respondents, but ranged up to 20% in the "tail".

All 10 Item 3070 respondents consider that ORN of idiopathic origin exists. Individual estimates of the percentage of ORN attributable to idiopathic origin range from ">1%", upwards -- mostly around 10%, with 50% in a "tail". (Of course, some volunteer bias is present in this item 3070, given the fact that only 10 of 15 respondents are

---

88 Item 3730 is an apparent exception to this statement. (This item may be viewed in the Appendix 3 Survey. Its responses may be found in Appendix 1: Tables Summarizing Scenario-Related Management Changes.) Otherwise, "best bets" for potential significance will be ignored because their selection was possible only though "data dredging".

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participating. A similar comment holds for Item 3090, in which only 12 respondents participated.\(^{89}\)

All 12 (of 14\(^{90}\)) Item 3090 respondents thought that dental health factors can contribute to the ORN rate.\(^{91}\) However, individual estimates of the maximum percentage of ORN that theoretically could be accounted for by dental health factors (e.g., given a hypothetical scenario in which teeth terribly diseased are not extracted at-all) ranged from 5% to 90%.

Eventual decision analyses would tend to be validated if they were consistent within reliability limits with the responses to items 3610, 3640, 3670, 3700, 3730, 3790, 3760, and 3820 of the Delphi Survey (Appendix 3). The responses to these items are summarized in, and relegated to, Appendix 1\(^{92}\) because they do not immediately assist understanding of a decision analysis of the clinical problem, their reliability is sometimes open to question (due to small numbers), and some items include variables\(^{93}\) that may not need to be considered in early decision analysis efforts.

---

\(^{89}\) In Item 3090 the "twelfth" respondent did not respond quantitatively, but submitted the comment, "It is extraction that typically precipitates ORN... caries does not precipitate ORN."

\(^{90}\) The physician was excluded from responding to this item.

\(^{91}\) The other two implied that the item was inappropriate due to, e.g., lack of data.

\(^{92}\) 1/3 of the way through the Appendix in the part of the Appendix 1 titled, "TABLES SUMMARIZING SCENARIO-RELATED MANAGEMENT CHANGES"

\(^{93}\) (e.g. tumor stages requiring alternative forms of surgery)
5. OUTCOMES, AND FACTORS RELATED TO OUTCOMES

A. SEVERITY OF ORN LESIONS

Table 52 reports responses for Item 1040, "My important criteria for classifying the medical severity of an osteoradionecrotic lesion are:”. The individual criteria are presented in order of descending importance and product:

<table>
<thead>
<tr>
<th>Frequency</th>
<th>Rank</th>
<th>PROD</th>
</tr>
</thead>
<tbody>
<tr>
<td>8</td>
<td>1.9</td>
<td>32.8</td>
</tr>
<tr>
<td>5</td>
<td>1.0</td>
<td>25.0</td>
</tr>
<tr>
<td>5</td>
<td>2.4</td>
<td>18.0</td>
</tr>
<tr>
<td>5</td>
<td>2.6</td>
<td>17.0</td>
</tr>
<tr>
<td>4</td>
<td>2.2</td>
<td>15.2</td>
</tr>
<tr>
<td>3</td>
<td>1.3</td>
<td>14.1</td>
</tr>
<tr>
<td>2</td>
<td>1.5</td>
<td>9.0</td>
</tr>
<tr>
<td>2</td>
<td>2.5</td>
<td>7.0</td>
</tr>
<tr>
<td>2</td>
<td>2.5</td>
<td>7.0</td>
</tr>
<tr>
<td>2</td>
<td>3.0</td>
<td>6.0</td>
</tr>
<tr>
<td>2</td>
<td>3.0</td>
<td>6.0</td>
</tr>
<tr>
<td>2</td>
<td>3.0</td>
<td>6.0</td>
</tr>
</tbody>
</table>

Table 53: ITEM 1050: FACTORS FOR CLASSIFYING ORN SEVERITY.

Table 53 produced responses involving more than one respondent tabulated in Table 53.
<table>
<thead>
<tr>
<th>Freqency Rank</th>
<th>Topic Number</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>&quot;F&quot;: 11 (9)</td>
<td>1.0</td>
<td>012. Pain</td>
</tr>
<tr>
<td>&quot;R&quot;: 55.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>1.7</td>
<td>017. Pathological Fracture</td>
</tr>
<tr>
<td>&quot;F&quot;: 7 (6)</td>
<td>2.7</td>
<td>23.</td>
</tr>
<tr>
<td>&quot;R&quot;: 26.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&quot;F&quot;: 7 (6)</td>
<td>2.8</td>
<td>22.9</td>
</tr>
<tr>
<td>&quot;R&quot;: 4.1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>2.0</td>
<td>016A. Oro-cutaneous or oro-antral fistula</td>
</tr>
<tr>
<td>2</td>
<td>2.5</td>
<td>7.651. Fear</td>
</tr>
<tr>
<td>2</td>
<td>5.0</td>
<td>2.548. Physical difficulty in maintaining home oral hygiene [Cf.: 641.]</td>
</tr>
<tr>
<td>2</td>
<td>5.0</td>
<td>2.569. Inconvenience associated with professional visits/adjunctive dental or medical therapy</td>
</tr>
<tr>
<td>2</td>
<td>4.0</td>
<td>2.560. Inability/ability to socially interact</td>
</tr>
</tbody>
</table>

The rank and product are suspect for the following because only one respondent ranked the importance:

- 2 (1) 10. 262. Minor surgical interventions necessary (including radical debridement of bone, but not 264. tooth extractions).
- 2 (1) 8. 261. Major surgical therapy present or required

3940 3. I agree that the P4 → P0 [Pain] scale\(^{94}\) would associate positively with quality of life.

Strong agreement with high consensus and at moderately high confidence is demonstrated (\(n = 10\)):

<table>
<thead>
<tr>
<th>ITEM 3940</th>
<th>MEDIAN</th>
<th>75 - 25 IQ Range</th>
<th>MEAN</th>
</tr>
</thead>
<tbody>
<tr>
<td>AGREEMENT</td>
<td>6.1</td>
<td>1.5</td>
<td>5.8</td>
</tr>
<tr>
<td>CONFIDENCE</td>
<td>5.8</td>
<td>1.7</td>
<td>5.6</td>
</tr>
</tbody>
</table>

\(^{94}\) Scales \(\rightarrow\) P4 = Generally or frequently Excruciating Pain. P3 = Generally or frequently Severe Pain.

by Author: P2 = Generally or frequently Moderate Pain

\(\downarrow\) P1 = Generally or frequently Mild Pain

P0 = Generally No Pain
3950.4. I agree that the F4→F0 [Function] scale would associate positively with quality of life.

Individual agreement submissions are: 1, 2, 5, 5, 5, 6, 6, 7, 7, (n = 10)
at confidences 7, 6, 5, 5, 6, 4, 6, 7, 7.

The initially apparent moderate agreement with low consensus [= inadequate data quality] at moderately high confidence --

<table>
<thead>
<tr>
<th>ITEM 3950</th>
<th>MEDIAN</th>
<th>75 - 25 IQ Range</th>
<th>MEAN</th>
</tr>
</thead>
<tbody>
<tr>
<td>AGREEMENT</td>
<td>5.3</td>
<td>3.1</td>
<td>4.9</td>
</tr>
<tr>
<td>CONFIDENCE</td>
<td>5.8</td>
<td>1.7</td>
<td>5.8</td>
</tr>
</tbody>
</table>

is re-interpreted as a bimodal distribution of high consensus and high confidence with peaks of strong agreement and very strong disagreement:

<table>
<thead>
<tr>
<th>ITEM 3950</th>
<th>MEDIAN</th>
<th>75 - 25 IQ Range</th>
<th>MEAN</th>
</tr>
</thead>
<tbody>
<tr>
<td>AGREEMENT 1</td>
<td>5.7</td>
<td>1.5</td>
<td>5.8</td>
</tr>
<tr>
<td>CONFIDENCE 1</td>
<td>5.6</td>
<td>1.8</td>
<td>5.6</td>
</tr>
<tr>
<td>AGREEMENT 2</td>
<td>1.5</td>
<td>1.0</td>
<td>1.5</td>
</tr>
<tr>
<td>CONFIDENCE 2</td>
<td>6.5</td>
<td>1.0</td>
<td>6.5</td>
</tr>
</tbody>
</table>

5. OUTCOMES, AND FACTORS RELATED TO OUTCOMES
C. ANATOMICAL LOCATION AND ORN CLINICAL PRESENTATION

Item 1060. "I believe that the clinical presentation of osteoradionecrotic lesions typical of the maxilla differ from those of the mandible."

Strong agreement with high consensus at high confidence was demonstrated:

F4 = Function of jaws severely impaired (either anatomically, physiologically, or due to pain;) Use of dentition or dental prosthesis either ineffective or impractical.
F3 = Function of jaws mildly or moderately impaired (either anatomically, physiologically, or due to pain;) Use of dentition or dental prosthesis either ineffective or impractical.
F2 = Jaws functional but severely compromised function of dentition or dental prosthesis.
F1 = Jaws and dentition or dental prosthesis all functioning with at least a moderate degree of utility.
F0 = Jaws and dentition or dental prosthesis all functioning well.
The second part of Item 1060, "The difference, if any, is:" produced responses with more than one citation listed in Table 54.

**TABLE 54. ITEM 1060**  
**DIFFERENCES BETWEEN ORN PRESENTATIONS IN MAXILLA AND MANDIBLE**

<table>
<thead>
<tr>
<th>Frequency</th>
<th>Topic Number, Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>5</td>
<td>171. Location = potential ORN incidence risk factor</td>
</tr>
<tr>
<td>4</td>
<td>183. Severity is worse in mandible</td>
</tr>
<tr>
<td>3</td>
<td>181. Location = prognostic factor for consequences of ORN on FUNCTION</td>
</tr>
<tr>
<td>3</td>
<td>191. Location = potential risk factor for incidence of ORN-associ. osseous fracture</td>
</tr>
<tr>
<td>2</td>
<td>174. Location = prognostic factor for consequences other than function or # fractures</td>
</tr>
<tr>
<td>2</td>
<td>194. Location = potential factor affecting function following ORN-associ. osseous fracture</td>
</tr>
</tbody>
</table>

Item 1070. I believe that osteoradionecrotic lesions in the **maxilla** have different effects on the **quality of life** than do osteoradionecrotic lesions in the **mandible**.

Strong agreement with high consensus at strong confidence was demonstrated:

**TABLE 55. ITEM 1070.**  
**DIFFERENT EFFECTS ON QUALITY OF LIFE OF MAXILLARY AND MANDIBULAR ORN**

<table>
<thead>
<tr>
<th>Frequency</th>
<th>Topic Number, Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>5</td>
<td>181. Location = prognostic factor for consequences of ORN on function</td>
</tr>
<tr>
<td>3</td>
<td>167. Treatment is easier in one jaw bone in comparison to the other</td>
</tr>
<tr>
<td>3</td>
<td>187. Function more easily restored in maxillary ORN</td>
</tr>
<tr>
<td>3</td>
<td>174. Location = prognostic factor for consequences other than function or # fractures</td>
</tr>
<tr>
<td>2</td>
<td>183. Severity worse in mandible</td>
</tr>
</tbody>
</table>

The second part of Item 1070, "The difference, if any, is:" produced responses with more than one citation listed in Table 55.
I believe that the clinical presentation of osteoradionecrotic lesions typical of one part of the mandible differ from those typical of some other part(s) of the mandible.

Strong agreement at high confidence and with moderate consensus was demonstrated:

<table>
<thead>
<tr>
<th>ITEM 1090</th>
<th>MEDIAN</th>
<th>75 - 25 IQ Range</th>
<th>MEAN</th>
</tr>
</thead>
<tbody>
<tr>
<td>AGREEMENT</td>
<td>5.7</td>
<td>2.6</td>
<td>5.3</td>
</tr>
<tr>
<td>CONFIDENCE</td>
<td>6.0</td>
<td>1.8</td>
<td>5.8</td>
</tr>
</tbody>
</table>

The second part of Item 1090, *The difference, if any, is:* produced responses with more than one citation listed in Table 56. Volunteer bias and small numbers could limit reliability and validity especially for this item.

<table>
<thead>
<tr>
<th>TABLE 56. ITEM 1090.</th>
<th>DIFFERENCES BETWEEN ORN PRESENTATIONS WITHIN MANDIBLE</th>
<th>(n categorizable responses = 8)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Frequency:</td>
<td>Topic Number, Description</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>157. [Medical] treatment is easier in one part of mandible than another</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>421. Radiation treatment plan can affect the clinical presentation</td>
<td></td>
</tr>
</tbody>
</table>

I believe that osteoradionecrotic lesions typical of one part of the mandible have different effects on the quality of life than do osteoradionecrotic lesions typical of some other part(s) of the mandible.

Strong agreement with high consensus at strong confidence was demonstrated:

<table>
<thead>
<tr>
<th>ITEM 1100</th>
<th>MEDIAN</th>
<th>75 - 25 IQ Range</th>
<th>MEAN</th>
</tr>
</thead>
<tbody>
<tr>
<td>AGREEMENT</td>
<td>6.0</td>
<td>1.9</td>
<td>5.7</td>
</tr>
<tr>
<td>CONFIDENCE</td>
<td>6.2</td>
<td>2.0</td>
<td>6.0</td>
</tr>
</tbody>
</table>

The second part of Item 1100, *The difference, if any, is:* produced responses with more than one citation listed in Table 57. Volunteer bias and small numbers could limit reliability and validity.
TABLE 57. ITEM 1110. DIFFERENT EFFECTS ON QUALITY OF LIFE OF ORN LESIONS IN DIFFERENT PARTS OF MANDIBLE  

<table>
<thead>
<tr>
<th>Frequency</th>
<th>Topic Number, Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>4</td>
<td>177. ORN in one, as opposed to different part of mandible is prognostic factor for</td>
</tr>
<tr>
<td></td>
<td>consequences other than function or # fractures)[in this case, pain, or trauma</td>
</tr>
<tr>
<td></td>
<td>to other structures; etc.]</td>
</tr>
<tr>
<td>3</td>
<td>182. ORN in one, as opposed to different part of mandible is prognostic factor for</td>
</tr>
<tr>
<td></td>
<td>consequences of ORN on FUNCTION)</td>
</tr>
<tr>
<td>2</td>
<td>158. Prosthodontic treatment is easier in one part of the mandible.</td>
</tr>
</tbody>
</table>

5. OUTCOMES, AND FACTORS RELATED TO OUTCOMES
D. FACTORS SKewing ORN SEVERITY DISTRIBUTIONS

Item 3920 requests that respondents who agreed with its statement should list in Item 3930 a list of these skewing factors:\footnote{96}

"3920. Other things being equal, whether the risk of ORN is 0.1% or 30%, I believe that ORN will distribute in similar hypothetical proportions into the severity classifications\footnote{97} just outlined."

<table>
<thead>
<tr>
<th>My feelings about the last statement are:</th>
<th>If *, please see #2. below.</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 DISAGREE 1 2 3 4 5* 6* 7*</td>
<td>I AGREE</td>
</tr>
<tr>
<td>VERY STRONGLY [Please circle a number:]</td>
<td>VERY STRONGLY</td>
</tr>
<tr>
<td>I AM VERY</td>
<td>My confidence in this answer is:</td>
</tr>
<tr>
<td>UNCERTAIN 1 2 3 4 5 6 7</td>
<td>I AM VERY</td>
</tr>
<tr>
<td>CERTAIN</td>
<td></td>
</tr>
</tbody>
</table>

Individual agreement submissions are: 1, 1, 3, 4, 5, 5, 6, 6, 7

at confidences 7, 7, 4, 5, 6, 5, 7, 6, 7

\footnote{96} (comparable to those in Item 1140, previously reported in Table 18 in the Appendix, and for which discussion follows below, also)
\footnote{97} Epstein (1987b) classification scheme for osteoradionecrosis:
ORN 0 = No History of ORN
ORN 1 = Resolved ORN  
1a = No history of pathological fracture
1b = History of pathologic fracture, since resolved.
ORN 2 = Chronic, Non-progressive, Localized ORN (No pathologic fracture or anticipation of same)
ORN 3 = Active, Progressive, ORN  
3a = No pathologic fracture
3b = Pathologic fracture.
The initially apparent weak agreement with low consensus [= inadequate data quality], at very high confidence --

<table>
<thead>
<tr>
<th>ITEM 3920</th>
<th>MEDIAN</th>
<th>75 - 25 IQ Range</th>
<th>MEAN</th>
</tr>
</thead>
<tbody>
<tr>
<td>AGREEMENT</td>
<td>4.7</td>
<td>3.2</td>
<td>4.2</td>
</tr>
<tr>
<td>CONFIDENCE</td>
<td>6.2</td>
<td>1.8</td>
<td>6.0</td>
</tr>
</tbody>
</table>

might also be interpreted as a bimodal distribution of high consensus and high confidence with peaks of strong agreement and strong disagreement:

<table>
<thead>
<tr>
<th>ITEM 3920</th>
<th>MEDIAN</th>
<th>75 - 25 IQ Range</th>
<th>MEAN</th>
</tr>
</thead>
<tbody>
<tr>
<td>AGREEMENT 1</td>
<td>5.8</td>
<td>1.4</td>
<td>5.8</td>
</tr>
<tr>
<td>CONFIDENCE 1</td>
<td>6.3</td>
<td>1.3</td>
<td>6.2</td>
</tr>
<tr>
<td>AGREEMENT 2</td>
<td>1.7</td>
<td>(not calculatable with SPSS)</td>
<td>1.7</td>
</tr>
<tr>
<td>CONFIDENCE 2</td>
<td>6.0</td>
<td>&quot;</td>
<td>6.0</td>
</tr>
</tbody>
</table>

In any case, however, conclusions related to this topic are not easily drawn, due to this dichotomy.

Part "b." of the item series starting with #1140\textsuperscript{98} is Item 1160:

'Theoretically, it may be possible that one condition predisposing ORN may produce ORNs all rather mild and self-limiting, while another may create ORNs that, proportionally, are much more severe or aggressive.'

'Reviewing my list from the item part a. above, ["Case characteristics that I think increase the risk (i.e., expected frequency) of ORN are:" ] I recognize that certain of the factors listed predispose outcomes relatively more mild or severe than the average.'

\textsuperscript{98} Item 1140 (a. "Case characteristics that I think increase the risk (i.e., expected frequency) of ORN are:" ) data was reported previously in Table 18, on page 364, in Appendix 1 ("Large Tables").
Item 1160 responses demonstrated moderate agreement, moderate consensus, and high confidence:\footnote{8 Item 1160 respondents (67\%) agreeing, (contributing 5,6,7,6,6,6,7); 3 (25\%) equivocal (agreements =4,4,4,); and one (8\%) strongly disagreeing ("agreement" =1).}

<table>
<thead>
<tr>
<th>ITEM 1160</th>
<th>MEDIAN</th>
<th>75 - 25 IQ Range</th>
<th>MEAN</th>
</tr>
</thead>
<tbody>
<tr>
<td>AGREEMENT</td>
<td>5.5</td>
<td>2.1</td>
<td>5.2</td>
</tr>
<tr>
<td>CONFIDENCE</td>
<td>6.1</td>
<td>1.5</td>
<td>6.0</td>
</tr>
</tbody>
</table>

In Item 1170, the factors considered by more than one respondent to skew ORN severity distributions were, with small numbers limiting reliability:

- Frequency 3: Radiation trauma, Specific part of mandible, Periodontal disease,
  Expected compliance of the patient with prescribed oral hygiene care;
- Frequency 2: Anticipated blood supply, Systemic metabolic state,
  Interstitial radiotherapy, Caries rate.

Items 3920-3930 requested respondents who did not agree to Item 3920 at levels A= 5, 6, or 7 to describe, "The possible prognostic factors, and/or anatomic locations that would NOT ONLY change the occurrence of ORN, but skew a hypothetical distribution of ORN severity outcomes (i.e., ORN 0...1a...1b...2...3a...3b, above) one way or the other..." Respondent fatigue at the end of the survey apparently limited responses, but two respondents replied that the posterior mandible was worse, a response consistent with #1170.
5. OUTCOMES (AND FACTORS RELATED TO OUTCOMES)

E. OSTEO RADIONECROSIS SEVERITY DISTRIBUTIONS

Responses to Item 3970, which requested respondents to provide data on the relative distributions of severity classes of osteoradionecroses, were widely dispersed. These data would best be gathered from the literature.

5. OUTCOMES, AND FACTORS RELATED TO OUTCOMES

F. ORN SEVERITY CATEGORY ASSOCIATIONS WITH PAIN & FUNCTION

Data in this section are not duplicated in the literature. As explained in the Discussion, data in this section, in combination with ORN severity distribution data, should assist the creation of accurate multi-factorial terminal utilities in a decision analysis. Associations of categorized pain and function with categorized ORN were gathered in two ways, both under the admonishment, "The items below request NOT the information that would be derived from a "cross-sectional" survey, but from evaluations of all patients in equivalent "mature" states of their clinical course" The first set,

"4040. The function and pain classifications that often are associated with each ORN class are:" produced responses tabulated in Tables 58 and 59. (Table 58 summarizes pain and function data separately, while Table 59 presents pain and function associations with categorized ORN side by side, facilitating comparison. Apparent trends will be discussed later.) 3-D Figure 7 ("Results Chart Number 3") illustrates these data.

<table>
<thead>
<tr>
<th>ITEM</th>
<th>CONFIDENCE</th>
<th>MEDIAN</th>
<th>75 - 25 IQ Range</th>
<th>MEAN</th>
</tr>
</thead>
<tbody>
<tr>
<td>4040</td>
<td></td>
<td>5.3</td>
<td>1.8</td>
<td>5.2</td>
</tr>
</tbody>
</table>

100 (or if not these data, improved equivalents or patient-derived analogues, ultimately validated)
101 (derived from the literature, as explained in Section 5.e., above)
102 (positive responses from all respondents for each ORN category, summed)
### TABLE 58. ITEMS 4040-4090. PAIN & FUNCTION CATEGORIES "OFTEN ASSOCIATED WITH" CATEGORIZED ORN

<table>
<thead>
<tr>
<th>ORN Category</th>
<th>P4</th>
<th>P3</th>
<th>P2</th>
<th>P1</th>
<th>P0</th>
<th>F4</th>
<th>F3</th>
<th>F2</th>
<th>F1</th>
<th>F0</th>
</tr>
</thead>
<tbody>
<tr>
<td>ORN3b</td>
<td>5</td>
<td>4</td>
<td>2</td>
<td>0</td>
<td>0</td>
<td>7</td>
<td>2</td>
<td>1</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>ORN3a</td>
<td>1</td>
<td>3</td>
<td>5</td>
<td>1</td>
<td>0</td>
<td>1</td>
<td>6</td>
<td>3</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>ORN2</td>
<td>1</td>
<td>1</td>
<td>4</td>
<td>5</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>6</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>ORN1b</td>
<td>1</td>
<td>0</td>
<td>2</td>
<td>4</td>
<td>3</td>
<td>2</td>
<td>1</td>
<td>4</td>
<td>4</td>
<td>0</td>
</tr>
<tr>
<td>ORN1a</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>6</td>
<td>3</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>6</td>
<td>2</td>
</tr>
<tr>
<td>ORN0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>8</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>8</td>
</tr>
</tbody>
</table>

### TABLE 59. ITEMS 4040-4090. PAIN & FUNCTION CATEGORIES "OFTEN ASSOCIATED WITH" CATEGORIZED ORN

(= TABLE 58 PAIN AND FUNCTION DATA, BUT PRESENTED SIDE BY SIDE):

<table>
<thead>
<tr>
<th>ORN Category</th>
<th>P4</th>
<th>F4</th>
<th>P3</th>
<th>F3</th>
<th>P2</th>
<th>F2</th>
<th>P1</th>
<th>F1</th>
<th>P0</th>
<th>F0</th>
</tr>
</thead>
<tbody>
<tr>
<td>ORN3b</td>
<td>5</td>
<td>7</td>
<td>4</td>
<td>2</td>
<td>2</td>
<td>1</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>ORN3a</td>
<td>1</td>
<td>1</td>
<td>3</td>
<td>6</td>
<td>5</td>
<td>3</td>
<td>1</td>
<td>1</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>ORN2</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>2</td>
<td>4</td>
<td>6</td>
<td>5</td>
<td>2</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>ORN1b</td>
<td>1</td>
<td>2</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>4</td>
<td>4</td>
<td>4</td>
<td>3</td>
<td>0</td>
</tr>
<tr>
<td>ORN1a</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>1</td>
<td>6</td>
<td>6</td>
<td>3</td>
<td>2</td>
</tr>
<tr>
<td>ORN0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>8</td>
<td>8</td>
</tr>
</tbody>
</table>

### FIGURE 7: RESULTS CHART 3

(ITEMS 4040-4090): Pain, and Function, Frequency of Association with ORN Category, Compared
The abscissa in the chart is not a linear scale, but a somewhat discontinuous categorical scale for osteoradionecrosis severity that incorporates a number of dimensions, e.g. presence or absence of fracture, state or rate of necrosis progression:

---

**Epstein (1987b) Classification Scheme for Osteoradionecrosis:**

ORN 0 = No History of ORN
ORN 1 = Resolved ORN: 1a = No history of pathological fracture; 1b = Hx of fracture, since resolved.
ORN 2 = Chronic, Non-progressive, Localized ORN (No pathologic fracture or anticipation of same.)
ORN 3 = Active, Progressive, ORN: 3a = No pathologic fracture; 3b = Pathologic fracture.
---

The axis with categorized pain and function is not linear either. Therefore, discontinuities of trends from one ORN category to the next in the Charts are expected and do not imply flaws in the data due, for instance, to small numbers.

Inspecting the data in Table 59 and Figure 7 (Results Chart 3), one may observe that

- ORN3b, ORN3a, nor ORN2 are not often associated with P0 or F0,
- ORN1b is not often associated with F0, and
- ORN1a is not often associated with P4 and P3.

Pain and function "frequent association curves" also may be imagined for each categorized ORN state.

---

103 [and correlations with quality of life not linear, just ordinal]
104 "imagine" because P4 -> P0 is not a true linear scale, just ordinal, the data and scale are not validated, and small numbers do not permit unqualified assumption of reliability.
105 Trends in frequent association of categorized pain or function with ORN categories:
1. ORN3b: a pain category "frequent association" curve sigmoidally approaching greatest frequencies at P4-P3, and the function association curve peaking at F4.
2. ORN3a: pain and function are mostly P/F3 and P/F2, peaking at P2 and F3 respectively.
3. ORN2: two quasi-normal "frequent association" curves, pain being highly skewed with a mode approaching P1, but function essentially symmetrical with a mode of F2.
4. ORN1b: The pain curve is flatter than any of the other pain or function "frequent association" curves, peaking at P1-P0 but with a long tail to P4. The F4 "tail" portion is even more pronounced in function, which peaks at F2-F1.
5. ORN1a: two highly skewed "frequent association" curves with sharp peaks at P1 and F1.
In contrast with Item 4040, the associations of categorized pain and function with categorized ORN were gathered in a different manner for Items 4160-4260. Items 4160-4260 took the following form:

4160. "Given an opportunity to determine the final Pain and Function correlations for patients in the various ORN severity categories, I would anticipate finding pain and function outcomes in these proportions:"

- for patients classed ORN CLASS "XX":

<table>
<thead>
<tr>
<th>Proportion</th>
<th>100-</th>
<th>80-</th>
<th>60-</th>
<th>40-</th>
<th>20-</th>
<th>0-</th>
</tr>
</thead>
<tbody>
<tr>
<td>of Total in Pain or Function Category</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

Pooled means, medians, and interquartile ranges for Items 4160-4260 are presented in Table 60 of Appendix 1. Understanding of trends may be gained through an examination of the 3-dimensional Figures 8 and 9 (Results Charts 4 and 5).

The "curves" in Figures 8 and 9 (= Results Charts 4 and 5) represent the means of all Item 4160 to 4260 submissions. Charts of high confidence data also were prepared; they do not differ greatly. Given the arguably equivalent quality of all submissions for Items 4160 to 4260, and the need to maximize relative reliability by increasing the sample size, the use of the means of all responses is appropriate to suggest pain and function percentage distributions associated with each ORN category.

106 Overall median confidence for Items 4160-4260 is 5.0 (mean, 4.4). Theoretically, higher average confidence is associated with better data quality, and in fact for the Likert-scale item response data, median confidences lower than 5 generally were associated with decreased consensus. However, a trend toward increased consensus-- and therefore, for higher data quality-- with higher confidence submissions is not evident for the individual Item 4160-4260 submissions. (While the means of ORN2 pain and function inter-quartile ranges, and ORN3a function inter-quartile ranges, is lower when the "confidence = 5 or 6" data is examined, inter-quartile ranges are higher for ORN 1a pain and function inter-quartile ranges. This is interpreted to indicate that for these items 4160-4260, there is no clear or consistent association between increased confidence in an individual opinion and the surrogate for data quality considered to be more important, increased consensus.) Means, medians, and interquartile ranges for items 4160-4260 percentage distributions are presented in the Tables 62, 63, and 64 of Appendix 1.)
FIGURE 8: RESULTS CHART 4. ITEMS 4160-4260
Mean Distributions of Pain in Categorized ORN

FIGURE 9: RESULTS CHART 5 ITEMS 4160-4260
Mean Distributions of Function in Categorized ORN
Items 4160-4260 occurred near the end of the survey, where respondent fatigue probably played a great role in limiting the numbers of responses. It is assumed that volunteer bias in this set of data did not introduce a systematic bias.

In theory, data from the items 4040-4090 is not directly comparable with data from Items 4160-4260. Items 4040-4090 request binary information that might be considered qualitative— in paraphrase, "Is, or is not, this categorized pain or function state often associated with this categorized ORN end state?"— from which the frequency of positive submissions from all respondents is accumulated. In contrast, Items 4160-4260 request analogous, but not equivalent, quantitative data that could be termed "directly assessed final pain or function outcome distributions for patients in the various ORN severity categories". Thus, theoretical differences between the data requested might account for some differences between the two data sets. (However, one could speculate that the magnitude of differences attributable to the non-comparable aspects of the two (#4040-4090 and #4160-4260) item sets may not be great, and that if comparisons do reveal similarities between the two sets of data, then this could be interpreted as evidence of reliability. Pain- and function-category modes in each ORN state should be similar in the two #4040-4090 and #4160-4260 sets of data if the data were reliable and the restriction to "final" states was not applied differently in the two sets of data.

Tabulation of the Item 4040-4090 data could be made "comparable" to tabulation of the Item 4160-4260 data if the Item 4040-4090 pain and function quantities are converted to percentages totaling 100% for each ORN state, as they are in Tables 62, 63, and 64 in Appendix 1. These data are presented for visual comparison in Figures 10 through 21 (= Results Charts 6 to 17) below. Each chart presents 4040-4090 pain and function "Frequent Association" lines in black, #4160-4260 "Distribution" data in white, and another white line representing the mean of these two, in between.
FIGURE 10; RESULTS CHART 6. #4040 FREQUENT ASSOCIATIONS, & #4160 DISTRIBUTION, OF PAIN IN ORN 3b

FIGURE 11; RESULTS CHART 7. #4040 FREQUENT ASSOCIATIONS, & #4160 DISTRIBUTION, OF FUNCTION, ORN3b
FIGURE 12; RESULTS CHART 8. #4050 FREQUENT ASSOCIATIONS, AND #4180 DISTRIBUTION, OF PAIN IN ORN3a

FIGURE 13; RESULTS CHART 9. #4050 FREQUENT ASSOCIATIONS, & #4180 DISTRIBUTION, FUNCTION IN ORN3a
FIGURE 14: RESULTS CHART 10. #4060 FREQUENT ASSOCIATIONS, AND #4200 DISTRIBUTION, OF PAIN IN ORN2

FIGURE 15: RESULTS CHART 11. #4060 FREQUENT ASSOCIATIONS, & #4200 DISTRIBUTION, FUNCTION IN ORN2
FIGURE 16; RESULTS CHART 12. #4070 FREQUENT ASSOCIATIONS, AND #4220 DISTRIBUTION, OF PAIN IN ORN1b

FIGURE 17; RESULTS CHART 13. #4070 FREQUENT ASSOCIATIONS, & #4220 DISTRIBUTION, FUNCTION, ORN 1b
RESULTS FIGURE 18; CHART 14. #4080 FREQUENT ASSOCIATIONS, AND #4240 DISTRIBUTION, OF PAIN IN ORN1a

FIGURE 19; RESULTS CHART 15. #4080 FREQUENT ASSOCIATIONS,& #4240 DISTRIBUTION,FUNCTION,ORN1a
6. SURVEY: POTENTIAL SOURCES OF BIAS

A. DEFINITION OF ORN

This section reports survey data that could indicate a potential for biasing of individual experts' responses to other items in the Delphi Survey. The items are found in Sections B.I and A.I of the survey, and compare respondents' varying perceptions of definitions and pathogenesis of ORN, ORN diagnostic criteria, introductory criteria for outcomes and (clinical severity, presentation, effects on quality of life). Data lending itself to tabular or concise format will be reported here and considered further in the Discussion. Wordy data from a few additional items are simply summarized and integrated directly into the Discussion.

Item 1010, "My current criteria for defining ORN, listed in point form, are:"

produced responses summarized in Table 64.

<table>
<thead>
<tr>
<th>TABLE 64. ITEM 1010. &quot;CRITERIA FOR DEFINING ORN&quot;</th>
</tr>
</thead>
<tbody>
<tr>
<td>Frequency:</td>
</tr>
<tr>
<td>θ 11</td>
</tr>
<tr>
<td>π α 10</td>
</tr>
<tr>
<td>ε 7</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>φ π 4</td>
</tr>
<tr>
<td>θ 2</td>
</tr>
<tr>
<td>π 2</td>
</tr>
<tr>
<td>π 2</td>
</tr>
</tbody>
</table>

However, as previously reported, the analysis elaborated in the Discussion suggests that their consideration during analysis on an item-by-item basis would be inadvisable.

Some other items in this section, on tooth extraction policies, were reported previously.

• Greek letter symbols to the left of the frequencies associate collapsible categories.
• "Frequencies" are the frequencies of citation of the topic.
• Parenthesized frequencies, if present, are the different number ranked.
• Doses of 4000 and 4500 cGy are cited by two respondents for distinguishing osteonecrosis of a radiological origin (perhaps a rather low dosage threshold of risk).
Responses to the open-ended Item 1020, "Very briefly, my description of the etiology/pathophysiology of ORN is:" are reported in Table 65.

| TABLE 65. ITEM 1020. PERCEIVED ETIOLOGIC/PATHOPHYSIOLOGIC FACTORS |
|----------------------------------|---------------------------------|
| Frequency | Topic Number, Description |
| 12 | 461. The anticipated blood supply, or oxygen perfusion of, the high-dose irradiated mandibular volume [assumed compromised when an assumption is necessary.] |
| 9 | 066. Hypocellular. |
| 7 | 420. Radiation trauma to tissue and risk for ORN #1 |
| 6 | 004. Recent History of traumatic insult (non-radiological) |
| 4 | 068. Bone remodeling impaired |
| 4 | 422. The overall dosage or Past Hx of a certain cumulative minimum dose |
| 2 | 069. Bone replacement impaired. |

6. SURVEY: POTENTIAL SOURCES OF BIAS

B. RESPONDENT AND PRACTICE CHARACTERISTICS

Item 1360, "Radiotherapeutic technical factors and clinical management routines that I think realistically could vary from one oncology clinic to another, thus altering clinicians' experience with ORN and potentially biasing perceptions of ORN effects and incidences, are:" produced responses reported in Table 66.

| TABLE 66. ITEM 1360. RADIOTHERAPEUTIC FACTORS THAT MAY VARY AND INFLUENCE CLINICIAN PERCEPTION (Data supplied directly, or implied by "secondary data") |
|----------------------------------|---------------------------------|
| Frequency | Mean Rank | Product | Topic Number, Description |
| ** 8 | 1.9 | 33. | 421. Radiation Treatment Plan |
| * 8 | 2.0 | 32. | 308. Dental Program Present [See also 589.] |
| * 6 | 3.0 | 24. | 589. Changes from standard scenario in level of professional monitoring. |
| * 2 | 1.5 | 9. | 309. Experience/competence of dental personnel |
| ** 2 | 3.5 | 5. | 428. Interstitial Radiotherapy; Brachytherapy. |
| @ 2 | 2.5 | 5. | 880. Demographic characteristics of patient pool. |

Table 67 on the next page reports some personal and practice characteristics of respondents, while Tables 29, 30, and 31 in the Appendix provide additional data on ORN case rates.
### TABLE 67: SOME CHARACTERISTICS OF RESPONDENTS' PRACTICES

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**RESPONDENT NUMBER:**

<table>
<thead>
<tr>
<th>DEGREES:</th>
<th>PRACTICE PROFILE:</th>
<th>YEARS</th>
<th>AREA</th>
<th>ORN:</th>
</tr>
</thead>
<tbody>
<tr>
<td>DENT</td>
<td>Dent Med O.Surg Oncol O.Med Prosth of Practice</td>
<td>Inci</td>
<td>Trd</td>
<td></td>
</tr>
<tr>
<td>DEG. NUMBER:</td>
<td>CATEGORY</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

| 01/ | + - | X | X | 2* | B | 1 | - |
| 02/ | + - | | X | 2 | A | U | - |
| 03/ | + - | X | X | 3 | A | 3 | = |
| 04/ | + - | X | X | 3 | A | 1 | - |
| 05/ | + - | X | X | 1 | A | 1 | - |
| 06/ | - + | | | 3 | A | 1 | U |
| 07/ | + - | X | | 3 | A | 1 | = |
| 08/ | + - | | X | 1 | A | 2 | = |
| 09/ | + - | X | X | 3 | A | 2 | = |
| 10/ | + - | | X | 2 | A | 1 | - |
| 11/ | + + | X | | 2 | A | 1 | - |
| 12/ | + - | | X | 2 | A | 3 | U |
| 13/ | + - | X | X | 2 | B | 1 | U |
| 14/ | + - | X | | 1 | B | 1 | - |
| 15/ | + - | X | X | 3 | A | 1 | = |

--- interpreted from Item l.c, not l.b., for Respondent 01/.

**KEY:** (Characteristics derived from Responses in Section A.II (14th & 15th pages of the Survey).

**CLINICAL DEGREES:** Dental and Medical Degree Categories:

"+" = has particular degree; "-" = does not

**PRACTICE PROFILE:** Categories = Oral surgery; Clinical Oncology; Oral Medicine (including Oral Pathology); and/or Prosthodontics.

(The latter category includes one practitioner who also practices maxillo-facial prosthetics, and another who did not state "prosthodontics," but rather "hospital dentistry.")

**YEARS OF PRACTICE:**

Category 1 = 0-9 years
Category 2 = 10-19 years
Category 3 = 20 years or more
Category U = Undefined.

**GEOGRAPHIC AREA:**

Category A = North America and Australia*
Category B = Europe
Category U = Undefined.

**ORN:** Annual INCIDENCE:

Category 1 = 0 to 5
["Inci"] Category 2 = 6 to 10
Category 3 = ≥11

**TREND:**

Category " - " = Falling Incidence Rate
Category " = " = Stable "
Category " + " = Rising "

*-- The Australian was trained in Texas.

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7. RESPONSES OF LOW DATA QUALITY

Certain Delphi Survey items were associated with responses of low consensus or some other indicator of low quality. For that reason, and also, usually, their association with non-critical issues, they will not be discussed in detail here. Quantitative estimates of risk, and relative risk, of potential ORN risk factors often were low in consensus. Assessments involving either dental occlusion or non-traditional periodontal disease activity measures tended to produce data of lower quality. A number of characterizations of factor suitability for decision analysis were low in consensus or confidence. Open-ended items requesting information about outcomes tended to produce disproportionate amounts of "one-off" topic categorical data.

Further description of the types of items producing lower quality data may assist the framing or focus of future data-gathering efforts. This description is provided in Appendix 4.
CHAPTER V.: DISCUSSION

1. INTERPRETATION OF FINDINGS

The gathering together of data in this survey to create a list of factors suitable for inclusion in an ORN-prophylactic decision analysis will start with hypothesis formation integrating data from Items 1140 and 3200. Some initial comments, and interpretations regarding the utility or applicability of Item 1140 and 3200 ORN risk factor findings in a clinical decision analysis, follow. Small numbers of topic category responses limit their reliability in Items 1140/1160/1170, but these introductory items may be regarded as generating hypotheses for examination and relative validation with subsequent survey data. These variables are consistent with published findings and opinions described in the Literature Review and some major references for these are grouped by similar topic names in the final "Summary" section of the Literature Review.

The collapsed ORN risk factor topic categories in Table 20 must be considered during formation of the decision analysis— or excluded with adequate explanation. The importance of such collapsed topic categories must be interpreted cautiously, since factors of only broadly similar characteristics are being pooled.\(^1\) While subject areas A., C., D., E., F., G. and I. in Table 20 are examined several times in the survey— e.g. in the

\(^1\) Otherwise, misinterpretation may arise through bias. For instance, the construct "Periodontal-related factors" is ranked in importance overall even more lowly (mean importance rank = 4.9, product = 11), than periodontal disease itself (mean importance rank = 4.0, product = 12), since it is diluted by the lesser ranks of other contributory topics (e.g. gingivitis).
next item, #3200—categories H and B are not. Category H, tooth impaction and related factors (specifically, by another respondent, pericoronitis (infection)), might be potentially significant, having been mentioned by two respondents in this early open-ended item that engenders a minimum of bias.

On the other hand, Category B is an aggregation of "one-off" medical/surgical intervention suggestions. While it is worth noting that the respondents think that medical/surgical maneuvers are relevant to ORN prognosis, the significance of particular one-off contributions to the grouping is doubtful due to the small numbers present.

The responses to Item 1140, listing ORN risk factors, are consistent with the literature and will be found to be quite consistent with the responses to related items, e.g. Item 3200 (Table 21, page 191). In Table 21, the number and percentage inserted parenthetically following the frequency indicate the number and proportion of respondents who thought that the factor was not routinely assessable. Factors that are not routinely assessable are difficult to incorporate into a decision analysis, and thus will be dropped from further consideration.

AN INITIAL LIST OF FACTORS POTENTIALLY SUITABLE FOR INCLUSION IN AN ORN-PROPHYLACTIC DECISION ANALYSIS:

1. Radiation Trauma.\textsuperscript{3,4,5,6}

\textsuperscript{2} (Table 18, pages 364-365, as interpreted on pages 188 and 189)

\textsuperscript{3} Please note: The text of footnotes associated with Factors 2-5 are reproduced elsewhere in the main text of this thesis.

\textsuperscript{4} Bernstein et al (1993) consider that there are four treatment factors of particular significance to therapeutic irradiation: the inter-related factors of total dose, total volume treated, fractionation (dose fraction size) and elapsed time during irradiation.
2. Dental/ Oral Surgical Trauma.

3. Periodontal Status.

4. The Patient's Endodontic Status.

Responses to Items 1140 (an open-ended item, "Case characteristics that I think increase the risk of ORN are:), 3200 (a close-ended item asking that those factors in a list that are both prognostic for ORN frequency and practically
assessable be identified), and multiple other survey items suggest "periodontal disease" and "endodontic disease" are key factors in risk for osteoradionecrosis risk. They therefore should be included in a theoretical ORN decision analysis.

5. The recent Caries experience/rate.\footnote{Its linkage in quantitative fashion to outcomes would be difficult and I would suggest that this should enter a decision analysis only after being subsumed under other variables, such as "potential for endodontic infection" implied in the last item above, and, perhaps, the "projected dental desirability of retaining the tooth" variable suggested below. Comparison with the Murray (1980a) use of the term "dental status" also would be appropriate.}

6. The patient's Oral Hygiene status.\footnote{Arguably practical to routinely assess if time is set aside using a dental hygienist or certified dental assistant.}

7. The Patient's Smoking Status. Many Item 3200 respondents think that this is prognostic for ORN and assessable. However, Item 2060 indicates that smoking status probably does not significantly affect the decision to extract, and Item 3240 results do not seem to stress smoking as an ORN risk factor to the degree that responses to item 3200 do. My impression of the literature is that smoking is not emphasized as an ORN risk factor, although Kluth, Jain, Stuchell, and Frich (1988) conclude that alcohol and tobacco are irritants that significantly increase the risk of mucosal breakdown leading to osteoradionecrosis and is also associated with poor oral hygiene and possibly other factors that may contribute to sepsis and tissue irritation.

8. Salivation/Xerostomia Status.\footnote{I hypothesize that xerostomia status may be subsumable as a simultaneous modifier of one or more other decision tree variables: "projected caries rate" and "tendency to endodontic infection"
9. The Friability Of The Overlying Oral Mucosa And Local Supra-Osseous Tissue Contours. A local expert considers this variable important (Stevenson-Moore, 1993). Although only the Item 3350 (ORN risk) item involving mucosal friability meets consensus requirements, respondents support this as a variable, and Beumer (1979a, 302-303) does as well. This suggests that a dichotomous or three-level categorical scale for tissue friability would be practical.

10. The Systemic Metabolic State. Metabolic status was considered to be prognostic for ORN by a majority of Item 3200 respondents but 40% did not consider it practically assessable with regard to ORN prediction. Serious discussion of the applicability of this to decision analysis will be limited until data can be found to relate ORN risk quantitatively to specific metabolic states.

These potential ORN risk factors for hypothetical application to decision analysis are incorporated into Table 68, "Hypothetical Usage in Decision Analysis of Factors That Item 3200 Respondents Indicate as Affecting ORN Rate". (The description following the table explains the symbols "‡", "†", and "•".)
**TABLE 68. HYPOTHETICAL USAGE IN DECISION ANALYSIS OF FACTORS THAT ITEM 3200 RESPONDENTS INDICATE AS AFFECTING ORN RATE:**

<table>
<thead>
<tr>
<th>FACTOR</th>
<th>IRRADIATION TRAUMA. Subdivided into three on advice of Item 3180 radiation oncologist 06/</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>2.</td>
</tr>
<tr>
<td>11.</td>
<td>20%</td>
</tr>
</tbody>
</table>

**CLASS →**

† | † | † | † | † | † | † | † | † | † | † | † | † | § | Θ | ☀ | ☀ |

**CLASS, DESCRIBED**

† could enter decision analysis as independent ORN-rate-modifying "primary" factors.

"◊" also will contribute to a proposed multi-factorial variable, → "projected worth of retaining tooth for dental purposes," integrating combined "◊" effects and projected prosthodontic requirements.

Subsume ORN-rate effects of these † factors under a variable integrating the combined ORN-rate-modifying effects of these.

§ = "◊" Effects = multi-factorial formula?

**KEY:**

"◊"_factors could enter decision analysis as independent ORN-rate-modifying "primary" factors.

"◊" factors should be subsumed under a variable integrating their combined ORN-rate-modifying effects.

"◊" factors also will contribute to a proposed multi-factorial variable "projected worth of retaining tooth for dental purposes," integrating endodontic, periodontal, caries, saliva, oral hygiene status effects, & prosthodontic requirements.

+ Dental prosthesis fit and function could contribute to both these, but only one Item 1140 respondent mentioned this directly.

Θ: Until better quantified, could be omitted from a decision analysis.

§, Θ: Please see table above and explanation on the next page.

* Factors subject to potential refinement as indicated by future considerations of other data.
As observed in Table 68, "f" (caries rate, salivary and oral hygiene status factors) probably should be subsumed to a variable integrating their combined ORN-rate-modifying effects. ORN risk from "§" smoking may vary with the part of the mouth and the individual. Respondents expressed concern with the quantifiability of trauma and metabolic status, so consideration of these "θ" variables in a decision analysis should be postponed until they, or sub-sets, can be better defined.

A local expert, Dr. Joel Epstein, suggested that dental prosthesis fit and function may be a relevant ORN risk variable. In part, this hypothetical variable may relate to the variables above labeled with a "ϕ", i.e. Mucosal Friability and Local Tissue Contour", and "Oro-Dental Surgical Trauma". However, only one respondent (out of 14) directly mentioned this potential variable in Item 1140, so it will not be considered here.\(^\text{13}\)

Each of the $ variables in Table 68 could enter a theoretical decision analysis as an independent modifier of ORN rates-- a so-called "primary" factor. As mentioned earlier, two of them-- endodontic disease and periodontal disease-- may have potential for prior integration into a variable, "potential for infection"\(^\text{14}\). (This remains only a hypothesis for investigation; endodontic disease and periodontal disease could be independent indications for extraction over large parts of their relevant clinical ranges.)

\(^\text{13}\) However, Beumer, Curtis, and Harrison (1979b) discuss concerns about prosthesis fit and ORN risk at length. Also, "pressure concentration in one part of the jaw", which could be associated with an ill-fitting prosthesis, was rated most importantly among the dental occlusion (bite) variables evaluated as ORN risks in Item 3470, ("Occlusal Factors As ORN Predictors"). Parenthetically, respondents weakly disagree at moderate consensus with a policy that it would be preferable for patients to use old, rather than new, dentures post-radiotherapeutically (item 3500).

\(^\text{14}\) Multiple references, e.g. ADA (1989) and NIH (1990) indicate that the elimination of infection prior to radiation therapy is necessary to reduce the risk for ORN. Presumably, elimination of potential for infection also would reduce ORN risk, since some "potential" risk for infection would manifest infection.
Whether or not also considered as "‡" or "†", the "•" variables could contribute to the decision analysis as contributors to a hypothesized variable, "projected worth of retaining tooth for dental purposes", which integrates the combined effects of endodontic, periodontal, caries, saliva, and oral hygiene status effects on future tooth health and desirability. (The latter would include a consideration of projected prosthodontic requirements.) Interactions among the "•" variables would occur particularly between "oral hygiene status", "recent caries rate", and "salivation/xerostomia status".

"Salivation/xerostomia status" is, as a contributor to the "tooth retention worth" factor, a special case, being itself dependent on radiation dose and particular patient circumstances.

A note written in the margins of Item 3190 by the radiation oncologist Respondent 06/ may be interpreted to imply that the tissue dose received is the only important independent variable. In contrast, the same respondent's comments in Item 1200 and the overall respondent responses in Item 3190, imply that the use of interstitial radiotherapy is a risk factor for ORN. {The four therapeutic irradiation factors found by Bernstein et al (1993) to be of particular significance were the inter-related

15 In response to Item 3190, "I believe that patients receiving interstitial radiation addition to external radiation will experience a higher frequency of ORN than patients receiving that same external radiation alone," respondent 06/ had no Likert scale agreement response, merely replying, "Silly question, depends on dose."

16 "1200. Radiotherapeutic techniques and radiotherapy technical characteristics that I think will reduce the risk of ORN are:" produced respondent 06 comments "dose homogeneity(avoidance of a hot spot", careful dosimetry, and "avoiding interstitial therapy".

17 Item 3190 individual respondent agreements (7 indicating strongest agreement) were 2,2,3,3,3,5,6,7,7,7,7 at confidences respectively 6,6,3,5,6,5,6,6,7,7,7; median agreement was 5.2, agreement interquartile range 3.5, and median confidence 6.0.}

Item 3190 ("I believe that patients receiving interstitial radiation in addition to external radiation will experience a higher frequency of ORN than patients receiving that same external radiation alone") respondents were intended to assume an unstated premise, "given equal tissue doses".
factors of total dose, total volume treated, fractionation (dose fraction size) and elapsed
time during irradiation (Bernstein et al 1993). Withers et al (1995a) found a positive
relationship between field size and mandibular necrosis and fracture but not for
complications in muscle or mucosa, and that large dose fractions were an important factor
in the rate of late bone sequelae. Marx and Johnson (1987) found that ORN severity
correlated mainly with the "type of radiation delivered, the total dose, the dose fraction,
and concomitant therapy..." Yasumoto et al (1995) did not find significant variation in
ORN rates with and without interstitial radiation.18

Responses to items 1630 and 1670 are considered consistent with an interpretation
that some respondents consider successful endodontic treatment to lack risk for ORN,
while the real risk for ORN will associate with endodontic treatment failure.

For the most part, responses to the open-ended Item 1230, "Dental extraction
techniques/principles that I believe are important for minimizing ORN are:" are not
surprising. Hypo-traumatic technique, soft-tissue closure, and adequate healing time are
stressed in the literature, while alveoplasty frequently is mentioned to minimize future
soft tissue trauma and maximize chance for soft tissue closure (e.g. Beumer et al 1979).
Counter-arguments about excessive trauma from excessive alveoplasty occasionally also
have been raised. The majority of respondents who advocated antibiotic coverage in Item
1590, and pre- (as opposed to post-) radiotherapeutic extractions in Item 1550, also are

18 Some additional pertinent information may be found in sections of the Literature Search Part 7:

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represented here. The suggestion also has been made in the literature that the number of teeth extracted may influence ORN risk.\textsuperscript{19}

Two responses in Item 1230, "Dental extraction techniques/principles that I believe are important for minimizing ORN:" were "use of dental forceps" and "use of block anesthesia, rather than local infiltrations". These were not stressed in the literature, and although uncorroborated, they may merit consideration as research hypotheses.

The essential neutrality about the need to consider occlusion in ORN-prophylactic treatment planning (in Item 1840\textsuperscript{20}) is consistent with its being discounted relative to other factors in the Items 3240-3420, 3450, and 3470. In addition, its quantifiability is problematic.\textsuperscript{21} There is no current evidence to indicate that dental occlusion per se represents a risk factor for ORN, other than through potential direct injury of opposing gingival tissue. Marunick and Leveque (1989), however, suggest that some "spontaneous cases" of ORN might be traceable to occlusal trauma associated with function or parafunction.

Only 8 respondents would extract all mandibular teeth in the high dose radiation volume that have an infection of periodontal origin,\textsuperscript{22} while 13 out of 14 would extract all teeth that have a history of severe periodontal disease. The lower priorities accorded

\textsuperscript{19} Beumer, Curtis and Harrison (1979b) recommended multiple adjacent extractions "in segments", when indicated, to assist alveolectomy and post-surgical closure of flaps without tension. (Coverage with antibiotics was advocated.) Theoretically, however, multiple extractions may place greater metabolic demands on bone at risk for ORN (due to perfusion limitations).

\textsuperscript{20} "1840. I need to assess the presence/absence/type of unbalanced bite, occlusal interference, parafunctional habits e.g. bruxism and clenching, etc. (i.e. subdivisions of the factor, "Dental Occlusion," before establishing a treatment plan for ORN-prophylactic tooth extraction." Median agreement levels were 4.2 (mean 4.0) at a median confidence level of 6.0. 6 respondents disagreed, 1 was neutral, and 7 agreed, contributing to a median Agreement of 4.2, and mean of 4.0 (neutrality).

\textsuperscript{21} (A finding in the next section of the Survey, that is consistent with the literature.)

\textsuperscript{22} in Item 1500 (personal treatment philosophies about tooth extraction),
periodontal infections here contrast with other states, including severe periodontal disease, that are assumed or found as responses earlier in this report\textsuperscript{23} to be accorded importance by respondents in relation to their consideration as surrogates for potential future infection. For endodontic infections, the apparent discrepancy is less pronounced. (Parenthetically, 10 respondents would extract teeth with an infection of endodontic origin.) This author will assume that these slight discrepancies are artifacts reflecting reliability limitations. (Perhaps an "inertia" bias is present: the Item 1500 periodontal infection category was the first to elicit positive responses after the first four categories failed to elicit any positive responses.)

Reliability is suggested in the essentially identical responses (very strong disagreement) to Item 1490 and Item 1500.d, which deal with the policy of extracting all mandibular teeth in the high dose radiation volume.

Item 1940 indicates that the dentition oral hygiene status strongly affects the decision to extract\textsuperscript{24}. The oral hygiene status was judged relevant to ORN risk in Items 3200 and 3290, but Item 1750 indicates that respondents consider this to be largely under the control of the patient, not much under the influence of the health care practitioner. Therefore this may best enter a decision analysis as an assumption.

Findings in the open-ended Item 1130 {"My major criteria (indications) for extracting teeth in the future high dose radiation volume are"} are appropriately\textsuperscript{25}

\begin{footnotesize}
\textsuperscript{23} (e.g. in the items discussed at the start of this section)
\textsuperscript{24} An unstated assumption for the item was, "prior to radiotherapy."
\textsuperscript{25} Findings are generally compatible, but understandable differences exist. Item 1140 deals directly with ORN risk. Deviations from Item 1140 findings observed in Item 1130 are those one would expect to find associated with consideration of a second criterion for tooth extraction decision making (other than ORN risk), namely the [dental] desirability of retaining the tooth.
\end{footnotesize}
compatible with the findings of Item 1140. The findings for the open-ended Item 1190 ("My decision to extract mandibular teeth during the pre-radiotherapy window is influenced by these aspects of the radiotherapy treatment plan"), e.g. radiation dose, type of irradiation, fractionation, urgency of radiotherapy, and salivary gland involvement in the high dose radiation volume, mostly reinforce the findings of other items. However Item 1190 also places great emphasis on an additional factor— the irradiated volume, suggesting its appropriateness in a decision analysis. This is consistent with the general literature, e.g. Bernstein et al (1993), and Withers et al (1995) found that the field size was a significant factor for rates of mandibular bone complications.

Responses to Item 1180 ("Foreseeable dental, medical, or surgical cancer treatments in addition to radiotherapy that increase the likelihood that I would extract teeth prior to radiotherapy, as an ORN-prophylactic measure) are compatible with other items, but extend the information to include the proximity of the tooth root surface and alveolar process in relation to site of surgical resection and reconstruction (a new factor). Adequate tooth structural integrity, or lack thereof, also was mentioned by three respondents, but ranked only at 3. Two respondents mentioned simultaneous chemotherapy as a variable significantly impacting on whether teeth will be extracted as an ORN-prophylactic measure.26

One respondent questioned the legitimacy of the assumption underlying item 1180 requesting non-radiotherapeutic indications for pre-radiotherapeutic tooth

26 Marx and Johnson (1987) considered that simultaneous chemotherapy adversely affects ORN rates, but the non-definitive Archibald et al (1986) study did not. Turner et al (1996) found that synchronous MTX chemotherapy contributed to late morbidity rates defined as "late healing soft tissue injuries or bone necrosis".
extraction. He stated, "The removal of teeth as an ORN-prophylactic measure must stand alone; irrespective of other treatment modalities. Teeth that are periodontally compromised, that have invasive caries, that have periapical pathoses, that exhibit significant lack of attention (from condition of dental hygiene, calculus, plaque, etc.) -- all create a mandate for pre-radiotherapy extraction. Also, teeth adjacent to surgical cuts in maxilla/mandible might also be at risk for ORN."

However, other respondents indicated that the proximity of the tooth root surface and alveolar process in relation to site of surgical resection and reconstruction, the adequacy of tooth structural integrity, chemotherapy, and tooth impaction are relevant. These are worth consideration for inclusion in a theoretical decision analysis.

Simultaneous chemotherapy was mentioned as a potentially significant ORN risk variable by a minority of respondents (three: 2 of the 13 responding to item 1180,27 and by implication, one other among 14 respondents responding to item 144028). Another respondent volunteered in item 1510 that it would affect the timing of extractions.

As discussed in the Literature Review29, hyperbaric oxygen therapy may be employed with two goals in mind: prevention or treatment of osteoradionecrosis. While still open to critical evaluation, there seems to be a growing consensus that it has merit. In this Delphi Survey, hyperbaric oxygenation was cited by four respondents in response to five open-ended items:

---

27 about factors that potentially could affect the probability of extraction,
28 about the factors that potentially could affect the risk for ORN.
29 The final part of the Literature Review: "3. Clinical Problem: 4. Osteoradionecrosis Pathogenesis, Definition, Diagnosis, Clinical Presentation, and Treatment."
1. Item 1230, dealing with dental extraction techniques important for minimizing ORN: Among 14 respondents, respondent 03/ cites HBO at importance rank 1.

2. Item 1140, dealing with ORN risk: Among 8 respondents, respondent 08/ cites HBO at importance rank 2.

3. Item 1390, dealing with surgical management techniques that could potentially alter the effects and incidences of ORN: Among 9 respondents, respondent 08/ cites HBO at importance rank 2.\(^{30}\)

4. Item 1360, dealing with radiotherapeutic and clinical management techniques that could potentially alter the effects and incidences of ORN: Among 13 respondents, respondent 02/ cites HBO at importance rank 4.

5. Item 1410, dealing with other clinical management techniques that could potentially alter the effects and incidences of ORN: Among 4 respondents, respondent 14/ cites HBO at an unknown importance ranking.

Thus, hyperbaric oxygen is recognized by four respondents (a minority) as having a significant influence on ORN experience.

Close-ended items in a second round are indicated to determine true expert consensus on the relationships of chemotherapy and hyperbaric oxygenation to ORN risk. These data in combination with the literature\(^{31}\) will indicate the degree of contribution of these factors to the decision analysis.

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\(^{30}\) Please note the progression in numbers of respondents (13, 9, 4) in the series of items 1360, 1390, and 1410 is consistent with some respondents having volunteered more information earlier in this progressive series of items. The trend toward lower numbers of respondents here do not necessarily indicate increasing volunteer bias, or even "n" for purposes of analysis.

\(^{31}\) e.g., Marx and Johnson (1987) and Turner, et al (1996) are of the opinion that simultaneous chemotherapy is a factor in ORN rates. Turner, et al (1996) base their conclusion on their own data. Their study, while highly suggestive, is not definitive, and adequate data on chemotherapy dose relationships to ORN risk are lacking.
As explained in the Results, the agreement medians for the Likert scale item series 3240-3420 ("This factor, when undesirable, can strongly increase the risk for ORN:") and (1890-2090: "My decision whether to extract teeth depends strongly on my assessment of") are for most items quite similar, and the differences that exist are appropriate to the different contexts.

The size of the osteoradionecrotic lesion and the pain involved were regarded as highly important in evaluating ORN severity.32 The location of the ORN lesion, and/or a presence of infection33 were rated next in importance, and impairments of function (including compromised ability to acquire nutrition) after that. The age of the patient, the degree of associated soft tissue necrosis, a need for surgical intervention, and, perhaps surprisingly, the persistence/duration of bone exposure, were considered only rather minor criteria for evaluating the severity of the ORN lesion.

"Pain" is ranked most highly as the criterion relevant to patient quality of life in Item 1050. However, "function" assumes greater importance; one aspect or another of function was mentioned very frequently34. If one assigns the topic "function" relatively higher prominence by "collapsing" the two function-related categories 630 and 646, the classes of criteria contributing to patient quality of life could be interpreted as follows:

32 Considering data from Item 1040, "My important criteria for classifying the medical severity of an osteoradionecrotic lesion are:"
33 (presumably for those who would consider ORN with infection still to be ORN, rather than a different entity-- e.g., radio-osteomyelitis.)
34 (see * rows). In fact, 10 respondents mentioned either or both of the function-related topics (630 "Function of the bite", and/or 646 "Inability, or impaired ability, to acquire nutrition"),
Primary: Pain

Secondary: Function; Presence vs. absence of pathological Fracture; (both of these are to some extent interdependent);

Tertiary: Presence vs. absence of Oral-Antral or Oro-cutaneous Fistula;
Presence vs. absence of bone Exfoliation

Other possibilities suggested in Item 1050 data were ease of rehabilitation, and healing rate. Esthetics was mentioned by one respondent directly, and implied by another.

The responses to Items 3940 and 3950 are very consistent with the first two categories of responses to Item 1050. Extremely strong agreement with high consensus and high confidence is expressed that pain, as represented in the custom scale immediately below, is associated with decreasing quality of life.

\[
\begin{array}{ll}
P_4 = \text{Generally or frequently Excruciating Pain.} & P_3 = \text{Generally or frequently Severe Pain.} \\
P_2 = \text{Generally or frequently Moderate Pain} & P_1 = \text{Generally or frequently Mild Pain} \\
P_0 = \text{Generally No Pain} & \\
\end{array}
\]

\[\text{(ca. Product = 45)}\]
\[\text{(ca. Product = 28). Also supported by Epstein (1996) private communication.}\]
\[\text{(ca. Product = 10)}\]
\[\text{5 citations, in one manner or another, from 15 respondents; also, an Epstein (1996) private communication was similar ("possibility or not of prosthetic reconstruction"), but this may have been intended to include medical and dental prosthetic reconstruction.}\]
\[\text{3 citations, in one manner or another, from 15 respondents}\]
\[\text{(and Dr. Epstein)}\]
\[\text{Item 3940 is, "I agree that the P4→P0 [Pain] scale would associate positively with quality of life."}\]
\[\text{Item 3950 is, "I agree that the F4→F0 [Function] scale would associate positively with quality of life." The interquartile range for this item was marginally inadequate (3.1).}\]
Moderate agreement, at equally high confidence, but low consensus, is expressed that function, as represented in the custom scale immediately below, is associated with increasing quality of life.

<table>
<thead>
<tr>
<th>Function</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>F4</td>
<td>Function of jaws severely impaired (either anatomically, physiologically, or due to pain;) Use of dentition or dental prosthesis either ineffective or impractical.</td>
</tr>
<tr>
<td>F3</td>
<td>Function of jaws mildly or moderately impaired (either anatomically, physiologically, or due to pain;) Use of dentition or dental prosthesis either ineffective or impractical.</td>
</tr>
<tr>
<td>F2</td>
<td>Jaws functional but severely compromised function of dentition or dental prosthesis.</td>
</tr>
<tr>
<td>F1</td>
<td>Jaws and dentition or dental prosthesis all functioning with at least a moderate degree of utility.</td>
</tr>
<tr>
<td>F0</td>
<td>Jaws and dentition or dental prosthesis all functioning well.</td>
</tr>
</tbody>
</table>

Items 1060 ("I believe that the clinical presentation of osteoradionecrotic lesions typical of the maxilla differ from those of the mandible."\(^{43}\)), 1070 ("I believe the ORN in the maxilla have different effects on QOL than ORN in the mandible"\(^{44}\)), and 1090 ("I believe that the clinical presentation of osteoradionecrotic lesions typical of one part of the mandible differ from those typical of some other part(s) of the mandible.\(^{45}\)) produced high levels of both agreement and confidence. The second parts of these items indicated that lesions of the mandible generally have greater consequences on function [and on quality of life], are more difficult to rehabilitate, and are more severe, than maxillary ORN lesions. These responses are in agreement with the literature.

The responses to the open-ended part of Item 1090 suggest that the location of ORN within the mandible may be associated with differing: abilities to treat, pain levels, potential for mandibular fracture, and incidence rates.

\(^{43}\) Item 1060: median agreement of 5.8, median confidence = 6.4, interquartile agreement range=1.3.
\(^{44}\) Item 1070 median agreement of 5.9, median confidence of 6.2, interquartile agreement range = 1.7.
\(^{45}\) Item 1090: median agreement = 5.7, median confidence = 6.0, interquartile agreement range = 2.6.
Responses to item 1100 indicate strong agreement and confidence\textsuperscript{46} with a statement that ORN typical of one part of the mandible has different effects on the QOL than ORN typical of some other parts of the mandible, and that a patient's quality of life may be affected by the effects of ORN in different parts of the mandible on:

1. function
2. pain;
3. ease of rehabilitation; and
4. healing rate

In almost all cases the posterior mandible or molar region was cited as being worse in severity and other negative consequences.

Reviewing the format of the final Delphi Survey items, items 4040-4090 request respondents to associate various pain and function categories with specific ORN categories (at the ORN end-state), while items 4160-4260 request quantitative estimations of their distribution in these same ORN categories. When the set of data arising from the item 4040 responses is compared with the mean data from the 4160 series ORN category distribution data, remarkable consistency would appear to be present in the extreme ORN categories--ORN\textsubscript{3b} (progressive ORN with jaw fracture, as in Figures 10 and 11\textsuperscript{47}) and ORN0 (patient at risk, no ORN, as in Figures 20 and 21\textsuperscript{48}). Clearly, the graphs demonstrate similar modes, which is one minimal requirement for reliability, but beyond this, the similarity of the plots of the different (4040 series and 4160 series) data is startling, and imply reliability between two sets of analogous (not identical) data gathered.

\textsuperscript{46} Item 1100: median agreement of 6.0 (interquartile agreement range 1.9), median confidence of 6.2
\textsuperscript{47} = Results Charts 14 & 15
\textsuperscript{48} = Results Charts 16 & 17
in two different ways. Hypothetically similar sets of cognitive biases that might apply in considerations of these two sets of situations would not seem to be an adequate, or even likely, explanation. Is the near-congruency coincidental, or does it represent a real and consistent trend that could be investigated for usefulness in suggesting reliability in similar, presumably readily-recalled clinical situations? Although intuition suggests that coincidence is partly responsible for the near-congruency of the curves, the two methods of data-gathering seem worthwhile in their own right, and future data-gathering employing these approaches could test this suggested research question simultaneously with their primary research objective.

Near-congruency of curves is not demonstrated in the other ORN states. This may indicate difficulty in retroactive recall of health states that may not be easily or accurately cognitively classified, or quantitatively recalled, in a retroactive fashion. The dispersion among the "raw" data is consistent with this supposition, and small numbers.

The Pain and Function curves for ORN3a in Figures 12 and 13 (active, progressive ORN without pathological fracture) are different from each other.49 Perhaps the black line (Item 4050 "pain and function states commonly associated") represents the more-easily-recalled and therefore, the more accurate, data; alternatively, perhaps long consideration of ORN3a in Item 4280 suggests to the respondent a greater range of clinical possibilities and pain/function states (see white line) that one could associate with the definition for ORN3a. (If the latter is true, then future data gathering may be enhanced if a more descriptive system for ORN 3a staging is employed.) These "mean"
percentages presented in Figures 12 and 13 are to some extent "pseudo-means of apples and oranges", but these curves of opinion data may represent the best present expert-
cognitive synthesis of Pain and Function distribution in categorized ORN, over a range of clinical experience. Further, they may be the most appropriate for use in the proposed theoretical decision analysis until "harder" data are gathered in a prospective fashion. However these data, even when gathered in different centers in a prospective fashion in the future and internally validated, may continue to reflect different clinical experience and thus will not necessarily be wholly generalizable.)

In ORN2, the mode for pain from the two sets of data (Figure 14) is coincident. The function mode varies, being skewed to better function (= lower F #) in the white line (Item 4200 " % Distribution" data) in comparison with the black line (Item 4060). In fact, in ORN Stages 1b and 1a, both pain and function modes vary with a consistent rightward shift of pain and function to the better state, i.e. lower P/F number, in the white line (Items 4160-4260). An explanation for this shift is lacking.

To repeat, it is suggested that the "pseudo-means" represent the best present estimates for pain and function associations with osteoradionecrosis outcomes. As explained below, these could assist the assignment or weighting of outcomes used in the terminal branches of a theoretical decision analysis.

---

50 where not in opposition to the Item 4040-4090 frequency of association curves (which are intuited as more reliable than the Item 4160-4260 distribution curves) if and where a choice between the two must be made.
A theoretical ORN "utility" weighted for the ORN severity distribution associated with a particular set of patient state and therapeutic intervention assumptions could be modeled by the following formula:

**WEIGHTING OF THEORETICAL ORN "UTILITIES"**

Given validated utilities for ORN 3b, ORN 3a, ORN 2, ORN 1b, and ORN 1a, the average utility of ORN could take the form

\[
U_{ORN} = \left( \frac{P(ORN3b) \times \text{Utility}(ORN3b)}{\text{Utility}(ORN3b)} + \frac{P(ORN3a) \times \text{Utility}(ORN3a)}{\text{Utility}(ORN3a)} + \frac{P(ORN2) \times \text{Utility}(ORN2)}{\text{Utility}(ORN2)} + \frac{P(ORN1b) \times \text{Utility}(ORN1b)}{\text{Utility}(ORN1b)} \right)
\]

where \( P \) is the proportion of ORN in that classification, given the particular set of patient state and therapeutic intervention assumptions.

This formula would not apply directly to the non-linear pain and function state data gathered in this thesis. However, inspection and interpretation of the thesis' ordinal pain and function associations with ORN categories, in association with data on the probabilities of the various ORN categories for the particular situation at hand, could 1) suggest the mean of weighted pain and function experiences in ORN, for which utilities could be assigned for use in theoretical decision analyses until better data are gathered, and 2) provide information assisting informed consent and patient education, by better explaining the potential for the patient to experience debilitation in particular situations. Further research is indicated for implementation of these suggestions.

The gathering of pain and function distribution data in association with particular Epstein (1987b) ORN classifications was useful on methodological grounds since the precise ORN classes were, in effect, scenarios on which the assessments could be based.
2. POTENTIAL SOURCES OF BIAS

A. OVERLAP OF DELPHI RESPONDENTS WITH CITED AUTHORS

Many surveyed topics are not duplicated in the literature. Other topics are discussed in the literature (e.g. the epidemiology of ORN); for these, comparisons between survey data and that in the literature would be appropriate. However, in these comparisons, tautology, or circular logic, could develop if and to the extent that, the articles cited for comparison are authored by survey respondents. Bias would enter analyses that were based on assumptions of independence of such sets of data.

8 of 15 Delphi respondents are not cited in the thesis as authors and could be considered to represent opinions “independent” of the literature. To this extent, the potential for bias outlined above would not exist. 2 (two) other survey respondent / literature review authors are represented by only one reference each, dealing with different, and very specific, topics; thus, their surveyed opinions would be heavily outweighed by the opinions of the others on the relevant items, and the potential for tautology arising from this during comparisons of survey and literature data would be minimal. The remaining five respondents, however, could contribute to tautology during some comparisons of data in the survey and literature (assuming that their opinions were dominant in their articles).

Further, among these five respondents, two pairs co-authored articles, and this could create a further potential for some dependence in their submitted opinions.

51 for instance, characterizations of the suitability of potential ORN prognostic factors for a decision analysis
52 The ethical review and study protocol for this survey research requires anonymity of survey participants.
53 The literature cited in this thesis emphasizes ORN epidemiology rather than clinical routine. At least two of the 8 "uncited" experts are published.
54 The average survey completion of this group of respondents is equivalent to that of the balance.
55 represented by 2, 3, 3, 5, and 7 citations each
56 These 5 survey respondents were primary or sole authors only in 40% of these cited articles, and the mean number of authors in these papers was 3.
Some tautology exists even under ideal circumstances when Delphi surveys of this type are compared with the literature. Experts are expected to be knowledgeable about the literature and to remember significant articles. Thus, absolute independence of thought is neither expected, nor desirable. The undesirable extent of potential tautology that could exist and contribute to bias when respondents also are “cited authors” is reduced by the fact that discussions of most topics in the thesis usually involve multiple citations, diluting the influence of particular authors. In addition, very few respondent/authors are cited multiple times on multiple topics; this further reduces the opportunity for excessive tautology in comparisons between the survey data and that from the literature. Therefore, bias in Delphi survey discussions or conclusions due to tautology would tend to be restricted to the very few issues of relevance to the decision analysis in which the survey and literature opinion consensus is marginal, and where the tautological influence would hold potential for sway. No issues and discussions in this thesis that were examined satisfied all of these requirements for significant adverse influence due to tautology. Thus, although a potential for the tautology outlined above exists, the conclusions of this survey research are not considered to have been significantly adversely affected by tautological influence.

2. POTENTIAL SOURCES OF BIAS

B. DEFINITION OF ORN

Further to the data reported in Section 6 of the "Results", most of the factors mentioned in Table 64 (Item 1010. "Criteria for Defining ORN") are consistent with the literature and would not bias survey responses by particular respondents. However:

55 Two exceptions could have been Robert Marx and Robert Johnson, but they chose not to participate.
• Respondents 01/ and 14/ (two of the three European respondents, the other being 013/) both included as criteria for defining osteoradionecrosis the concept of pathological fracture. If this were considered a necessary criterion, then of course it would bias the reporting of rates, and in fact the ORN incidence rates reported by these practitioners are very low.56

• Infection was cited as a criterion for defining ORN by four respondents (the three Europeans, and one non-European who implied infection with the word "drainage"), while an absence of infection was considered a criterion for definition of ORN by one other non-European. Both positions may be rationalized—osteoradionecrosis can proceed to a radio-osteomyelitis, while one may wish to distinguish ORN from this— but the differing definitions could influence the data supplied by the respondents.

The differing durations of bone exposure assumed for ORN definition in Item 1430 also would bias reported ORN rates.

Responses to Item 1030, the open-ended item "My important criteria for diagnosing ORN are", indicate that the respondents assume criteria for diagnosing ORN similar to the criteria that they use to define ORN.

The literature suggests that the practitioner characteristic "years of practice" (YOP) is frequently associated with variations in practice (Liberati 1986; Palmer and Reilly 1979; El-Mowafy and Lewis 1994). Reviewing Item 1010 (ORN definition criteria) and sorting by categorized years of practice, some potential associations are apparent. If these associations are truly present, then these could bias reported ORN rates, over and above

56 (as described in the 2 and 2' ORN incidence rates reported in Tables 30 and 31 in Appendix 1. (Please consider comparison with Respondent Practice Characteristics listed in Table 66.)
57 Significance may be negated by the small numbers present and an apparent usual tendency of this survey's respondents in their middle years of practice to volunteer slightly more data. It also is possible that other respondents may assume some factors without mentioning them, biasing the analysis.
the other potential sources of errors already reported. The apparent associations are:

- Topic 20 ("an exposure of non-viable irradiated bone") was mentioned increasingly frequently with ascending Years of Practice.
- Topic 14 ("radiographic signs, density changes") was mentioned increasingly frequently with ascending Years of Practice.

The responses to Item 1430 ("I think that ORN is better defined as:", followed by a series of categories and bone exposure durations\(^{58}\) for respondents to choose among) indicate confident agreement with a statement that ORN definition should be associated with a bone exposure of specific duration, but the durations chosen by the respondents were widely dispersed, with three apparent clusters of responses around zero, 2 1/2, and 6 months (median duration 2.4 months, mean 2.5). Thus, the adoption of an intermediate duration of bone exposure, such as the 3 months favored by Beumer, et al (1984), and Epstein, et al (1987a), would seem to be appropriate to adopt as a standard. (However, when the forthcoming International Classification of Diseases 10th Edition definition for ORN is known, it should take precedence.)

Digressing slightly from the discussion of potential sources of bias, the description of the pathophysiology of ORN provided by the responses (Table 65) to the open-ended Item 1020, "Very briefly, my description of the etiology/pathophysiology of ORN is:" is consistent with the contemporary literature and indicates general acceptance of the (Marx and Johnson 1987a) pathogenetic model.\(^{59}\)

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\(^{58}\) described fully in Appendix 3 ("Delphi Survey"), where this item is reproduced in entirety.

\(^{59}\) Confirmation of the respondents' belief in elements of the Marx and Johnson pathogenetic model for ORN is provided by their generally confident acceptance, as ORN risk factors, of:

- trauma (Item 3320: 12 respondents positive agreement, 1 neutral, 1 negative),
- anticipated vascular and cellular changes induced by high dose therapeutic irradiation (Item 3310: 11 positive agreements, 3 negative), and
- anticipated oxygen perfusion to the high-dose radiation volume (Item 3340: 8 positive agreements, 1 neutral, 3 no response, 2 disagreement.)
2. POTENTIAL SOURCES OF BIAS

C. RESPONDENT AND PRACTICE CHARACTERISTICS

Practice and personal characteristics of respondents can bias the perceptions and survey feedback away from high external validity, as discussed in Liberati (1986), Palmer and Reilly (1979), and El-Mowafy and Lewis (1994). In order to enable examination of such potential relationships, relevant data were compiled in one part of the Survey (Section A.II, where it would not be in a potentially "off-putting position of prominence). A summary of these data is provided in Table 66, "Some Characteristics Of Respondents' Practices". The two association trends observed clearly were not significant, however, due to small numbers.

ORN case rates ranged from 1% to 25%, and average 3 to 5%, depending on how they are defined, among the 25 to 800 patients at risk for ORN per respondent. No obvious correlations were noted between respondents' reported ORN rates and survey responses, and concerns discussed elsewhere about the apparent face validity limitations in some reported ORN rates, and also the size of the sample, would limit any conclusions. The relevance of applying potentially biasing factors identified below

However, the mention of infection as a pathogenetic factor by a respondent associated with a prestigious European institution may imply incomplete acceptance by him of the model, and it is not entirely clear whether isolated respondents mentioning fibrosis, local nutrition impairment, and immune function impairment intended to subsume these under the Marx and Johnson (1987) model, or to emphasize these characteristics to a greater degree.

Other sources of bias exist; they are discussed in the Literature Review (Delphi) and Discussion. Numbers did not permit routine analysis (e.g. cross-impact analysis) for confounders. If these were performed, explicit data on the case load referral status would have assisted elimination of bias.

1. Oral Medicine specialist respondents: - Generally longer years of practice
2. Oral Surgeon respondents: - Generally fewer years of practice, relatively more European, and associated with clinics reporting lower ORN incidences. The low ORN incidences reported by oral surgeons may themselves be biased. Surgeons may mostly see the cases needing surgical treatment, i.e. not the full range treated conservatively, and ORN definitions by oral surgeons may be skewed to serious cases, as in (Coffin 1983).

E.g., one respondent probably provided data reversing z and z' rates. For additional explanations and details, please see Tables 30 and 31 in Appendix 1.
to re-interpretation of ORN rates to eliminate confounders and achieve comparability of ORN rate data, also would be limited. These potential sources of bias nevertheless should be addressed in any future data-gathering study of ORN rates around the world.

A first factor that could bias in respondent-reported ORN rates is a differing definition of ORN. This could contribute significantly to bias in reported incidence rates, both in absolute and relative terms. For instance, the inclusion by two (01/ and 14/) of the three European respondents (all of whom reported low ORN incidence rates) of the factor "spontaneous fracture" (or "pathological fracture") in their ORN definitions63 may be significant.

Other potential sources of bias in reported ORN incidence rates could include the surgeons' perspective bias discussed previously,64 the potential for some practitioners to wish to minimize the rates reported at their institutions, and inclusion or absence of infection or tumor in their definitions of ORN.

Items 1360 to 1410, dealing with major potential factors for potential bias of radiotherapeutic, dental, surgical, or other origin, requested that respondents circle the factors possibly applicable to them. This expected process of expert respondent self-identification of factors relevant to them (e.g., practice characteristics varying from others or the average, that might be associated with bias in their perceptions and the opinions expressed in this survey) was intended to be a major source of these data for this thesis. However, only one respondent responded.

The lack of respondent inclination either to decide or to indicate which clinical factors might bias personal responses, is disappointing but perhaps not surprising since

63 (Item 1010 responses)
64 To repeat, surgeons mostly see the cases needing surgical treatment, i.e. not the full range treated conservatively, and ORN definitions by oral surgeons may be skewed to serious cases, as in Coffin (1983).
most clinicians do not consider their opinions biased. These data also might have been considered sensitive, potentially implying the possibility of undesirable personal or practice variations from the norm. The general absence of these data in some respects limits the anticipated interpretation of Survey data in a manner designed to recognize bias and attempt to correct for it. Thus, attempts to maximize the external validity and comparability of data will be limited, although other data relevant to bias will be commented upon.

The Survey provides other data about sources of bias. Item 1360, "Radiotherapeutic technical factors and clinical management routines that I think realistically could vary from one oncology clinic to another, thus altering clinicians' experience with ORN and potentially biasing perceptions of ORN effects and incidences, are: " produced responses reported in Table 67 which may be collapsed into broad categories that are consistent with the literature:

- dental program characteristics
- radiation therapy treatment plan
- patient demographic characteristics, and
- all other factors (e.g. case characteristics)

These may be compared with the responses from the sole radiation oncologist return not lost in the mail. Although he emphasizes dose homogeneity more strongly, fairly strong agreement between the opinions of the radiation oncologist and the others is evident.

---

65 [as in * rows in Table 67],
66 [as in ** rows in Table 67],
67 [as in @ rows in Table 67]
68 listed in Table 67, and if the entry "fractured roots" is considered as a surrogate for surgical trauma)
69 Respondent "06/", incidentally associated with a large clinic reporting low ORN incidence, and who represents special expertise in this subject area. His responses were:
Rank = 1: Pre-treatment dental consultation & intervention
Rank = 2: Dose homogeneity
Limitations in the ORN rate data provided by respondents in this survey preclude conclusions about associations of ORN incidence with particular irradiation methodologies. Volunteer bias may exist and the numbers are small.

Item 1370, "Major dental management practices that I think could vary from one oncology clinic to another, thus altering clinicians' experience with ORN, and potentially biasing perceptions of ORN effects and incidences, are:" produced responses recognizing the possibilities for different protocols or experience in:

1. Absence and/or type and sophistication of pre-radiotherapy dental diagnostic, treatment planning and prophylactic routines
   - Variations in oral hygiene and oral health promotion routines
   - Variations in caries and periodontal disease control philosophy (e.g., one respondent emphasizes not being fooled by patient resolve to improve oral hygiene
   - Variations in tooth extractions
   - protocols for selecting teeth for extraction
     - tooth disease thresholds for extraction in high dose vol.
     - radiation dose thresholds for extraction in high dose ".
   - timing of tooth extractions
     - before or after irradiation to high dose
     - time for healing prior to irradiation to high dose
   - surgical technique, as in Item 1390 below

2. Degree of integration of services-- teamwork among H & N surgeon, radiotherapist, and dentist, and dental hygienist, etc.

---

Rank = 3: Good dosimetry
Rank = 4: Fluoride prophylaxis.
3. Follow-up
   - degree of reinforcement of oral hygiene and treatment of dental complaints
   - variation in dental prostheses chosen and delivered
   - varying availability of dental services to patient

4. Availability of payment for dental services

   All of these responses are in agreement with the literature. However, absent from the list are ORN-rate-influencing factors on which institutional protocols could have been believed by respondents to be standardized—e.g. measures for prevention or resolution of infection. Reliability limitations mentioned at the conclusion of this section also apply.

   Item 1390, "Surgical management practices that I think could vary from one oncology clinic to another, thus altering clinicians' experience with ORN and potentially biasing perceptions of ORN effects and incidences, are:" produced responses recognizing the possibilities for:

1. Tooth extraction treatment planning variation
   - criteria for selecting teeth to be extracted
   - multiple vs. single extractions at one time

2. Surgical technique variation
   - skill of surgeons
   - e.g. tissue handling, soft tissue closure, alveoplasty
   - post-surgical follow-up and debridement

3. Variation in degree of integration of oral surgical services with head and neck cancer program

4. Relative use or absence of
   - Hyperbaric oxygen therapy
   - Microvascular anastomosis surgery
   - Mandibulotomy
5. Neck dissections—radical, modified, [none?]

Item 1410, "Clinical management practices not mentioned in 7., 8., 9., or 10. above, that I realistically think could vary from one oncology clinic to another, thus altering clinicians' experience with ORN and potentially biasing perceptions of ORN effects and incidences, are:" produced responses mirroring the above, including one factor, alveoplasty, inserted in the responses to the last item.

All responses above are consistent with the literature. However, microvascular surgery or microvascular anastomosis achievability was mentioned in Items 1370, 1390, and 1410 by two or three different respondents—two directly, and a third (probably) by implication of his item 1390 comment "use of vascularized flaps". Microvascular anastomosis as a variable potentially affecting the rate of osteoradionecrosis is not emphasized in the osteoradionecrosis literature. A rationale for this approach is, however, provided by statements in the literature advancing the desirability of maintenance of a proper mandibular periosteal blood supply.70

Numbers of responses prevent the responses described for Items 1360, 1370, 1390, and 1410 from being considered a highly reliable representative sample of expert opinion. They may serve as hypotheses for further testing, however. A second, close-ended Delphi round or would be indicated to confirm whether all factors listed above should be present, and to clarify relative importance.

70 (The Z' ORN Incidence Rates for these respondents was not significantly different from the mean.)
3. INTEGRATION: FACTOR SUITABILITY FOR AN ORN DECISION ANALYSIS

Further to the "Table 68. Hypothetical Usage in Decision Analysis of Factors That Item 3200 Respondents Indicate as Affecting ORN Rate", a second table (Table 69, at the end of this section) summarizes data from throughout the survey. It organizes the data in a similar manner to facilitate intra-factor observations in columns, and inter-factor comparisons in rows. This, along with observations about other potential factors made in the right-hand column, facilitates revision of the factor assumptions. Based on the data presented in Table 69, the following factors should be appropriate for further consideration for inclusion in the decision analysis, whether as assumptions or as factors within it:

- Radiation Dose, Dose/fraction, Radiation Timing, and Simultaneous Interstitial Radiotherapy, Irradiated Volume, or some integral of combined effects, perhaps as threshold categories. (These would tend to be decision analysis assumptions since these would not be under control of dentist.)

- Endodontic Status, however defined, or some integral of combined effects (potential for infection)

- Traditional periodontal status indicators, bearing in mind anatomic location, or some integral of combined effects (potential for infection)

- Projected oral hygiene status, caries rate, patient compliance, and salivation status effects: integral of effects. (Could this be analogous to the factor "presence or absence of teeth" mentioned by Murray (1980a) in his ORN risk equation?)
• Tooth mechanical integrity (but difficult to quantify) integrated with other factors mentioned in Table 68, p. 266, to contribute to the proposed variable, "Projected worth of retaining tooth for dental purposes."

• Surgical trauma (but difficult to quantify?)

• Anatomic location (posterior mandible or not, possibly the proximity of teeth or root to surgical cuts).

• Tumor proximity to bone is supported as a pertinent variable in the literature.

Each of the above factors or multifactorial integrals could contribute as probability nodes, or as assumptions in a decision analysis in which the major decision is simply, "Should this tooth be extracted, or not?" Inclusion of the effects of the following factors would be more problematic: oral mucosal friability in combination with local contours, smoking status, circulatory status, and metabolic status.

The important factors that would appear to skew the distributions of severity of ORN are:

• radiation dose

• posterior mandible

• periodontal disease

• compliance of patient with recommended procedures.

The Conclusions abstract the above, then supplement them by reference to the literature.

71 particularly by Murray (1980a), who includes it in his equation for ORN risk. Although this variable is not supported directly by the survey results, it is related to mandibular dose, which is supported. It also is associated with increased potential for mandibular invasion.
**Table 69. Modifying Data in Subsequent Items, For Factors Postulated for Inclusion in Decision Analysis in Table 68.**

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<tbody>
<tr>
<td>OTHER FACTORS AND OBSERVATIONS</td>
<td>(Note: These notes do not supercede better notes found in the results, and interpretation of same)</td>
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<td>Observations, and Items that support or impair inclusion of the factor in a decision analysis:</td>
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<td>Item 1200 confirms this.</td>
<td>Item 1200 confirms this.</td>
<td>Considered important by #1140, 3200, etc.</td>
<td></td>
<td>Please see next page.</td>
<td>1860/70 Patient compliance with home and professional care important; 1750 indicates that this is in control of patient (not caregiver.)</td>
<td>Item 1190: Salivary glands in beam influence decision to extract.</td>
<td>Please see next page.</td>
<td>Please see next page.</td>
<td>Please see next page.</td>
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<tr>
<td>#1140, 3200: Radiation trauma important.</td>
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<td>See also text following table.</td>
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<tr>
<td>Item 1180. Additional factors mentioned by some respondents as lowering the decision threshold for tooth extraction, which potentially have significance worthy of future investigation, but for which present survey evidence is not strong enough to merit immediate inclusion of the factor in decision analysis:</td>
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<td>• The proximity of the tooth root surface and alveolar process in relation to site of surgical resection and reconstruction.</td>
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<td>• Apicoectomies (especially molar)</td>
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<td>• Tooth impaction</td>
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<td>• Simultaneous chemotherapy</td>
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Note: Box = Interjection

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These are not control, ORN under but risk.

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Item 1190: Irradiated Volume is extremely important, and should be considered as a factor.

[Cf.: Type of particles photon/electron/ neutron were clearly cited by only 2 R in Item 1200.)

[Cf.: Type of particles photon/electron/ neutron were clearly cited by only 2 R in Item 1200.)

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These are dentists greatly affect

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Item 1190: Irradiated Volume is extremely important, and should be considered as a factor.
### Table 69, Cont. Modifying Data in Subsequent Items, for Factors Postulated for Inclusion in Decision Analysis in Table 68.

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<td>(Note: These notes do not supersede better notes found in the results, and interpretation of same)</td>
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<tr>
<td>Observations, and Items that support or impair inclusion of the factor in a decision analysis:</td>
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<tr>
<td>Supported by 3240 series at 6.0/7 (4.0 = neutral re ORN risk), &amp; also 1780</td>
<td>Supported by 3240 series at 5.6/7 (4.0 = neutral re ORN risk)</td>
<td>Supported by 3240 series at 5.4/7 (4.0 = neutral re ORN risk)</td>
<td>Supported by 3240 series at 4.6/7 (4.0 = neutral re ORN risk)</td>
<td>Supported by 3240 series at 5.1/7 (4.0 = neutral re ORN risk)</td>
<td>Supported by 3240 series at 4.9/7 (4.0 = neutral re ORN risk)</td>
<td>Supported by 3240 series at 5.9/7 (4.0 = neutral re ORN risk)</td>
<td>Supported by 3240 series at 5.3/7 (4.0 = neutral re ORN risk)</td>
<td>Supported by 3240 series at 4.6/7 (4.0 = neutral re ORN risk)</td>
<td>Supported by 3240 series at 5.1/7 (4.0 = neutral re ORN risk)</td>
<td>Supported by 3240 series at 4.9/7 (4.0 = neutral re ORN risk)</td>
<td>Supported by 3240 series at 5.9/7 (4.0 = neutral re ORN risk)</td>
<td>Item 1180: Adequate tooth structural integrity is mentioned by 3 Item 1180 respondents (ranked @ 3 by 2R), This is suggested for inclusion in the decision analysis proposed multifactorial variable 'desirability of retaining tooth':</td>
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<td>1800: Disease activity surrogates not supported.</td>
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<td>1890: Periodontal status strongly affects decision to extract; except for 1990 occlusion</td>
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<tr>
<td>1920: Smoking status does not much affect decision to extract.</td>
<td>1940: Oral hygiene status strongly affects decision to extract.</td>
<td>1980: Salivary/xerostomia status of patient affects decision to extract.</td>
<td>2060: Metabolic status may affect decision to extract.</td>
<td>1910: Recent caries rate strongly affects decision to extract.</td>
<td>2030: Informed consent for extraction required.</td>
<td>1140: Other possibilities assoc. with increased ORN rates: posterior mandible, interstitial therapy; size of irradiated volume, Tissue Perfusion</td>
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<tr>
<td>1920: Mechanical integrity of tooth strongly affects decision to extract.</td>
<td>1940: Oral hygiene status strongly affects decision to extract.</td>
<td>1980: Salivary/xerostomia status of patient affects decision to extract.</td>
<td>2060: Metabolic status may affect decision to extract.</td>
<td>1910: Recent caries rate strongly affects decision to extract.</td>
<td>2030: Informed consent for extraction required.</td>
<td>1140: Other possibilities assoc. with increased ORN rates: posterior mandible, interstitial therapy; size of irradiated volume, Tissue Perfusion</td>
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<td>1140: Other possibilities assoc. with increased ORN rates: posterior mandible, interstitial therapy; size of irradiated volume, Tissue Perfusion</td>
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<td>1140: Other possibilities assoc. with increased ORN rates: posterior mandible, interstitial therapy; size of irradiated volume, Tissue Perfusion</td>
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Note: Observations, and Items that support or impair inclusion of the factor in a decision analysis: See also text following table.
### Table 69, cont.  Modifying Data in Subsequent Items, for Factors Postulated for Inclusion in Decision Analysis in Table 68.

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<tr>
<td>Observations:→</td>
<td>Note: Box= Interjection</td>
<td>3470: Occlusion irrelevant but 1840: Occlusion may be factor</td>
<td>1630: EndoTx→ORN risk (#1670 &amp; 1680 results not significant)</td>
<td>1790: Yes to normal perio status indicators at right to ORN risk prediction</td>
<td>1830: Endo mildly yes.</td>
<td># 3450: Relevance of perio status indicators at right to ORN risk prediction</td>
<td>[Is quantification of perio status indicators at right to ORN risk prediction?/Yes to traditional status and to bite</td>
<td>4040 and 4160: Pooled data can suggest relative distributions of categorized pain and function in categorized ORN severities, as in final table &amp; chart in Results.</td>
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<td>Is Factor Quantifiable?</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>Partially?</td>
<td>Item 1130: periodontal factors, patient compliance and oral hygiene factors, endodontic factors, the caries rate, and the restorative status of particular teeth in the high dose volume are highly important in the decision to extract. The functionality of the teeth, their anatomical location, prosthodontic treatment planning factors, oral surgical treatment planning factors, and radiation factors also are considered.</td>
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<tr>
<td>Is Factor Controllable by Dentist? (1690-1760 Series):</td>
<td>No also to tumor control technique.</td>
<td>Partially yes to traditional status and to bite</td>
<td>No; under patient control; See info in Results</td>
<td>No; although Partial yes to post-irradiation vitality of local tissues</td>
<td>No; also to age, circulatory, and patient psychology</td>
<td>No; also to the pre-irradiation vitality of local tissues, &amp; patient prognosis</td>
<td>Pooled data can suggest relative distributions of categorized pain and function in categorized ORN severities, as in final table &amp; chart in Results.</td>
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See also text following table.
4. RELIABILITY

Comparisons between Items 3920 and 1160, and between Items 1790 and 1810 (reproduced in Appendix 3, "Delphi Survey") are appropriate for analysis of test-retest reliability.

In Item 1160, 8 respondents (67%) agreed at a level of 5 or higher (A=5,6,7,6,6,6,6,7); 3 (25%) were equivocal (A=4,4,4), and 1 (8%) strongly disagreed (A=1) with this item {(as he did to Item 3920). In contrast, another respondent indicating "1" in Item 3920 while also commenting about "exhaustion", stated "7" in Item 1160. If the Item 3920 response was assumed to result from exhausted confusion, one could substitute a "7", then examine the effect on reliability calculations. This is done in Table 70 in Appendix 1.

Sample estimates of Likert-scale-item intra-rater reliability were calculated from comparable numeric data in Items 3920/1160, and Items 1790/1810. These data pairs and calculated "Kappa" values are listed in Table 71 in Appendix 1. Reliability in agreement is 0.3 (poor) for unmodified Item 1160/3520 data, and reliability in confidence, good. Reliability in agreement is fairly good in items 1790/1810 and reliability in confidence, very good.

Reliability estimates were calculated using the S.P.S.S. STATISTICS SUMMARY CROSSTABS STATISTICS KAPPA command. This calculation was

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72 compared with corresponding Agreements of (A=U,6,7,5,3,U,4,1) in Item 3920
73 compared with corresponding Agreements of A=U,6,U in Item 3920
74 after collapsing of the 7 categories to 4 in order to achieve a symmetrical data array required for the weighted Kappa calculation. Kappa values > 0.75 represent excellent agreement, and between 0.4 and 0.75, fair to good agreement, and <0.4, poor agreement. (Fleiss, 1981) in (Armitage and Berry, 1994)
chosen because it incorporates representation of the magnitude of the categorized
differences during test-retest reliability comparison in the same respondents.

The reliability estimate associated with Items 1160 and 3920 represents sampling
near the beginning and end of the 60 page original survey. On the other hand, the
estimate associated with 1790/1810 compared responses to identical items on the front
and back of the same sheet of paper, and may be compromised in this regard if some
respondents recognized the repetition and consciously duplicated their responses.

Based on this very limited sample, it can be seen that

- there is moderately good consistency in response medians from similar items
  near the beginning and end of the survey. (This consistency is greater when
  the "outlier" submission of the self-identified "fatigued" respondent is not
  included, and may have been better yet if others had not also been fatigued.)

- Intra-rater agreement test/retest reliability appears to range from poor (or
  marginally poor) to good.

These data suggest that the Survey data are adequate for reliable reporting of
qualitative opinions. This opinion is supported by the marked consistency among a few
open-ended items requesting similar qualitative data (e.g., the parts of Items 1140 and
3930 requesting the identification of factors that could skew the distribution of severities
of osteoradionecroses, and Items 1490 and Item 1500.d, which deal with the policy of
extracting all mandibular teeth in the high dose radiation volume) and consistency among
the responses to same, that have been discussed elsewhere. One possible contrasting
example of lower reliability among qualitative responses was mentioned previously: the
lower apparent importance assigned periodontal infection in Item 1500, as compared to others. Nevertheless, almost all survey responses (intra-rater, especially) to open-ended items are both reasonable and consistent from item to item.

An argument could be made that future Surveys would benefit from inclusion of a greater number of close-ended item pairs from which reliability can be estimated. Although this may be true, the counter-argument that dominated the construction of items in this Survey (that it was essential not to include excessive repetition that could reduce the credibility of the Survey in the minds of the Respondents, or to add to respondent fatigue) also could be true.

5. VALIDITY CONSIDERATIONS AND LIMITATIONS

The osteoradionecrosis outcome data gathered in clinimetric scale form for this thesis is an introduction to the data necessary for objective evaluation. Although some observations already have been made in the discussion regarding an impression of reliability in parts of the outcome data, and a need for further research elsewhere, proper interpretation and clinical implementation of these health indices would require that they be evaluated as to their characteristics for discrimination, prediction, and evaluation, and that reliability and validity be demonstrated. (Kirshner and Guyatt 1985) discusses methodologies and perspectives appropriate to these types of assessments of health indices, and their Table 1 (p.29) discusses major issues in index construction and validation.
After validation of a scale to measure outcomes, there must not only be statistical validation; one also must determine the minimally significant clinically important difference. (Jaeschke, Singer, and Guyatt 1989; Redelmeier and Lorig 1993)

A confidence scale was used to assist evaluation of the "quality" of the data supplied. However, some respondents were always confident in their opinions, so few items generated median confidences less than 5.0. These cases, however, were noteworthy. Confidence as a surrogate for data quality is dependent on the conscientiousness of the respondent, and in one apparently unusual case, an impression of haste and inattention in a somewhat poorly completed survey was accompanied by indications of high confidence in responses. High consensus seemed the better indicator of higher data quality.

Item 3970 requested respondents to provide data on the relative distributions of severity classes of osteoradionecroses. Three respondents commented that such responses would simply be guesses, and this may be reflected in the large measures of dispersion associated with these pooled estimates, but the 6 respondents who did reply averaged a fairly high confidence of 5.0. Therefore, median respondent confidence is not always an adequate measure of overall data quality.

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75, a surrogate for data quality discussed in the Literature Search,
76 This is also consistent with the sigmoidal operating characteristic of the Likert Scale. (Rossi, Wright, and Anderson 1983, 253)
77 Thus, high confidence and high consensus often were independent of each other. However, low median confidences (<4) frequently were associated with low consensus, and low consensus with low median confidence.
A slight difficulty in interpreting items of the Item 1730 format arose from the format itself, which was intended to avoid respondent fatigue by excessive repetition in a series of similar individual items. This format depends on the conscientiousness of respondents in circling objections, and respondents rushing or suffering fatigue may not choose to respond in an ideal manner. On the other hand, parts of the item are subject to checking of face validity—e.g., objections to idiopathic factors being beyond personal control (as done by 2 respondents).

Most clinical experts responding to this survey have published extensively in the field, and some are of international status. They should fairly represent opinion with two exceptions--authors of important research articles on osteoradionecrosis, Robert Marx and Robert Johnson, who did not respond to requests that they participate. Nevertheless, given the range of open-ended opinions supplied by the world experts, relatively good content validity is suggested for item construction in the survey. The potential for tautological influence on this conclusion is discounted, as explained on pages 281 and 282.

The extent to which the ultimate goal of quantitative estimates of ORN risk in different circumstances, is realized, depends on the validity of the responses. Respondents in the "4. Quantitative Estimates of ORN Risk" section of Results expressed reservations about their contributions due to their lack of knowledge. This, along with low consensus and small numbers, tended to suggest that data in Section 4 of the Survey were not truly quantitative and should be gathered from the literature instead.

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78 (1730. "I consider all of the following factors postulated to affect dental extraction treatment planning to be beyond my control, at least in the pre-radiotherapy time "window"."
[1730. "I consider all of the following factors postulated to affect dental extraction treatment planning to be beyond my control, at least in the pre-radiotherapy time "window": [List of 16 factors] [Likert scale for agreement and confidence]"
"b. If you disagree with any of the factors above, please circle the number of the factor"

79 although generalizing a lack of face validity of part of the item, to the whole, may be inappropriate
In Item 4040, and with moderately strong confidence (5.3), ORN0 is almost exclusively associated with $P_0$ and $F_0$. This contrasts with the results of the Locker (1990) study of the "The Burden of Oral Disorders in a Population of [Ontario] Older Adults" and suggests that the normal background burden of pain and dysfunction reported by Locker in his potentially comparable population\(^80\) was ignored by the respondents to Items 4040-4090. If so, this would have the beneficial effect of increasing the sensitivity of the reports above to alterations from the norm for the population at risk for ORN, but one would have to recognize the potential limitations in external validity in particular, of these data.

It must be noted that the abscissa in the item 4040-4090 graphs is not a linear scale, but a discontinuous categorical scale for osteoradionecrosis severity that incorporates a number of dimensions\(^81\), e.g. presence or absence of fracture, state or rate

\(^80\) 95% of B.C. oral cancer patients were over 55 years of age in 1993. (B.C. Cancer Agency Annual Report). This group prior to cancer may experience a burden of oral disorders similar to that of a group of adults surveyed by Locker. Locker (1992) concluded that for a population of Ontario adults aged 50 years and over, living independently, "24.1% were edentulous, 30.5% were unable to chew one or more foods, 37.2% reported oral and facial, or facial, pain in the previous four weeks, and 67.5% experienced one or more other oral symptoms. One third reported problems with eating and communication-social interaction, 18.7% worried a great deal about their oral health, and 30.8% were dissatisfied with some aspect of their oral health status".

Locker (1992) measured oral disorders in a population of older adults using the following types of scales:
1. A dichotomous scale relating to the presence or absence of teeth, the number of missing teeth and the number of natural functional units and periodontal attachment loss.
2. Indexed chewing capacity (asking which of six ranges of foods could be chewed.)
3. Pain and other symptoms (using a modification of previous pain inventories supplemented with a 13-item inventory for oral symptoms and complaints other than pain)
4. Disability and handicap (using an 11-item multidimensional scale of social and psychological impact of oral disorders, and satisfaction with oral health. The items measuring social and psychological impact requested information about eating and communication social interaction. These dimensions were derived from previous literature.)

\(^81\) Epstein (1987b) classification scheme for osteoradionecrosis:
ORN 0 = No History of ORN
ORN 1 = Resolved ORN
  
1a = No history of pathological fracture
1b = History of pathologic fracture, since resolved.
of necrosis progression. The axis with categorized pain and function is not linear either\textsuperscript{82}. Therefore, discontinuities noted in the charts of the data need not imply flaws in the data due, for instance, to small numbers. They also would not associate linearly with patient preference.

Items 4160-4260 requested that respondents estimate directly the proportions of ORN Severity Stage patients in the various pain and function categories. In them, graphing of quantitative data by respondents and conversion back to quantitative data could have created small inaccuracies, but these potential inaccuracies were presumed to have been outweighed by their enabling of respondents to perform a "visual check" on the data, confirming intended relative proportions even if an arithmetic mistake was made and the absolute proportions indicated did not sum to unity. Another potential limitation in Items 4160-4260 is that the required recall of quantitative data by respondents may have been a challenge, especially at the end of the survey.\textsuperscript{83} Variability between respondents in the raw data for Items 4160-4260 may be consistent with these suppositions, with inter-rater variability possibly reflecting more than differences in clinical experience.

Earlier remarks that the 4040-series and 4160-series data for Pain and Function

\begin{itemize}
\end{itemize}

\textsuperscript{82} [and correlations with quality of life even less linear]

\textsuperscript{83} although the recall required for Items 4040-90 could have served as useful preparation for 4160-4260.

\begin{itemize}
\item ORN 2 = Chronic, Non-progressive, Localized ORN
  (No pathologic fracture or anticipation of same)
\item ORN 3 = Active, Progressive, ORN
  3a = No pathologic fracture
  3b = Pathologic fracture.
\end{itemize}
distribution in categorized ORN should be used until "harder" data is gathered in a prospective fashion, then validated, carried with them an unstated qualification. The qualification was that these data, even when gathered in different centers in a prospective fashion in the future and internally validated, would continue to reflect different clinical experience and would not be wholly generalizable. Thus, at the present time, center-to-center variation would tend to limit the external validity and generalizability of pooled data, in or out of a decision analysis, to any particular center.

6. BIAS, RELIABILITY, AND VALIDITY CONCLUSIONS AND APPLICATIONS

Numbers of responses to close-ended items routinely were sufficient to satisfy the requirement of a group size of about 13 suggested for maximal quality of Delphi responses (Millholland, et al 1973, and its Reference “1”.)

Variations present in respondent personal and practice characteristics, definitions, or diagnostic criteria for osteoradionecrosis, may bias the responses of particular respondents to particular items in this survey. The effects of these were difficult to determine via open-ended questioning due to the small numbers of respondents present, and thus the small size of data subsets. (This is a basic limitation of the Delphi methodological approach employed.) Therefore, data subsets associated with potentially biasing respondent or practice characteristics were not always be considered routinely. This routine discounting of potential biases in the Survey was further justified on the following bases:

84 thought most reliable if pooled, although, if only one set of data had to be chosen, the Item 4040-4090 frequency of association curves are intuited as the more reliable.
1. Since no clearly significant associations of respondent characteristics with bias were suggested, and inspection of the data presented suggested that the respondents sampled somewhat randomly many respondent and practice characteristics, then any respondent biases present would tend to cancel each other.

2. The exact intentions of some respondents sometimes were unclear (e.g., when they included pathological fracture among ORN diagnostic criteria). Thus, a determination whether or not a bias existed (e.g., from different ORN definitions) was difficult to perform in many cases.

Thus, potential biases that were difficult to identify and that probably would not affect results anyway, were ignored. This maximized numbers and, in that regard, maximized potential for validity.

Potential future efforts to gather and compare ORN rates worldwide should gather data on the potential biasing and confounding factors listed in the preceding sections and must take them into account before true comparability can be achieved.

One premise of this modified Delphi Survey was that the experts would indicate when the data requested could not be estimated properly. Survey experts did this, whether due to lack of data, or due to recognition of bias, is not clear. This may support an observation made in the literature that experts are more likely to recognize sources of bias in their own field, if not in themselves.

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85 Experts apparently are less influenced by cognitive biases when dealing within their specialty (Winkler 1986; Woltert 1989 reference 42).

86 as evidenced by respondents' reluctance to indicate sources of bias personally applicable in Survey Items 1360 to 1410.
Sources of potential bias in this modified Delphi Survey extended beyond the practice and personal characteristics of respondents. The internal and external validity of this research will be limited by the extent and quality of the existing research and the low numbers of experts surveyed—the latter involving invitational and acceptance bias, recall bias, the potential for subjects' wish to please (or to hide embarrassing statistics), effects of uncertainty on subjective analysis (and thus on statistical validity,) and lack of blinding during analysis and interpretation of the results. Incidence-prevalence bias, interviewer bias, and volunteer bias all may affect validity indirectly. Cognitive illusions mentioned in the Literature Review (due to framing, anchoring, and availability effects, as well as conjunctive and disjunctive bias) could lead the respondents to this survey to make inconsistent or biased probability estimates. A recently recognized tendency for choice-makers not to decide in the face of excessive numbers of choices may affect responses given to certain items. Delphi surveys suggest but do not confirm the construct and content validity of the new scales and dimensions, and a degree of tautology may have been present when survey responses were compared with the literature. The potential errors in estimation of effects of prognostic variables are not limited to separate effects, but combined effects, which may not be independent, but additive, subtractive, synergistic, etc. These relationships may be difficult to elucidate.

Best available data, whether in the literature or the Survey, must, of course, take precedence. In the absence of better data, the opinion data in this survey are a legitimate starting point for scientific discussion.

87 explained and referenced in the Literature Review
88 (probably non-significant. Please see, if desired, the explanation on pages 282-283)
CHAPTER VI.: CONCLUSIONS

1. CONCLUSIONS

This study should be regarded as exploratory with respect both to the survey process and its effort to identify decision analysis factors for a clinical problem of considerable real world complexity. Conclusions reached will have significance to other researchers contemplating further work in decision analysis of osteoradionecrosis or, in certain contexts, contributory oral risk factors. The future database for all types of studies on the dental management of osteoradionecrosis will be enhanced if "Recommendations" included in the third section are implemented.

The combining of rounds one and two Delphi technique in the survey was practical due to the body of literature on the subject, which allowed framing of close-ended as well as open-ended items, and the successful comparison of responses. The combining of Delphi Rounds one and two minimized the number of times busy experts were bothered. Subsequent rounds proved unfeasible because experts indicated that they were unable to supply, with accuracy, all of the data necessary for a clinical decision analysis; thus, multiple rounds would not improve this. In any case, increases in reliability theoretically arising from multiple Delphi rounds would have been negated if busy experts refused to participate in further rounds, and one expert indicated this.
12 of 22 experts solicited in the U.S. and Canada participated in the Delphi survey, in contrast to only 4\(^1\) of 16 in Europe and Australia. The size of the 60 page long survey tended to limit participation rates and increase respondent fatigue, decreasing validity in some respects, but increasing reliability and validity in other respects. Overall, most advantages of Delphi technique were realized, but its practicality for a problem of this complexity is open to question.

Dental factors proposed for inclusion in the decision analysis were assessed and characterized as to their suitability (i.e., quantifiability, controllability, and degree of independence). This approach was indicated by the nature of the dental variables potentially relevant to the clinical problem.

Expert opinion consensus revealed that major risk factors for ORN were Radiation;\(^2\) Periodontal Status;\(^3\) and Endodontic status.\(^4\) Anatomical site \{ a) mandible; b) posterior part of mandible; perhaps c) proximity of roots to surgical cuts\} also were considered by respondents to be highly relevant to ORN risk. [Tumor site for irradiation (proximity to bone) is considered relevant to ORN risk in the Murray (1980a) ORN risk equation. Although Morton (1986) found a positive association between tumor stage and ORN rate, Withers et al (1995) did not.]

---
\(^1\) (from Australia, the Netherlands, and Sweden)
\(^2\) particularly dose, dose per fraction, the timing of radiation, the osseous volume irradiated to high dose, and the presence or absence of interstitial therapy;
\(^3\) as assessed using conventional static indicators, e.g. pocket depth
\(^4\) (although quantifiability of periodontal and endodontic status as these contribute to ORN risk may be difficult. Research needs to determine relevant clinical ranges over which they could be included in a variable integrating tendency to infection.)
The oral hygiene status of the dentition, projected caries rate, patient compliance, and salivary status were considered relevant to ORN risk but are presumed to be mathematically dependent and to need to contribute to the decision analysis as a multifactorial integral indicating their combined ORN risk.\(^5\)

Surgical trauma, particular metabolic states, anticipated mandibular perfusion capability, and mucosal friability were considered by respondents to be relevant to ORN risk or the decision to extract, but either they, or their effects, were regarded as difficult to quantify.

The importance of hyperbaric oxygen as a variable affecting ORN experience was recognized by only four respondents responding to open-ended items.\(^6\) Potential implications of this limited recognition are discussed below in "2. Limitations: Data Quality", and "3. Recommendations."

Simultaneous chemotherapy was mentioned as a potentially significant ORN risk variable by 3 respondents (2 of the 13 responding to item 1180,\(^7\) and by implication, one other among 14 respondents responding to item 1440\(^8\)). Another respondent volunteered in item 1510 that it would affect the timing of extractions. If further research confirms and quantifies the opinions of Marx and Johnson (1987) and Turner et al (1996) that simultaneous chemotherapy is a factor in ORN rates, then it should enter the decision analysis.

---

\(^5\) This integrated variable may relate in some manner to the \("Is the patient dentate?\) factor in the Murray (1980a) ORN risk equation.

\(^6\) For details of results pertaining to hyperbaric oxygenation and chemotherapy, please see the 10th and 11th pages of Part I., "INTERPRETATION OF FINDINGS", of CHAPTER V.: DISCUSSION.

\(^7\) about factors that potentially could affect the probability of extraction,

\(^8\) about the factors that potentially could affect the risk for ORN.
On average, expert opinion regarded the 1) minimum, and 2) desired times that an extraction socket should be allowed to heal prior to high dose irradiation were 1) 7 days, and 2) 14 (median; mean 11.6) days. Although low consensus levels were of concern in these responses, they could serve in practice as a complement to the 21 day ideal suggested by Marx and Johnson (1987).

A decision analysis on ORN-prophylactic tooth extraction should not only include factors related to ORN risk, but factors related to the desirability of retaining teeth in the high dose radiation volume. A set of factors integrating caries rate, tooth mechanical soundness/restorability, and tooth functionality into a multifactorial variable "desirability of retaining the tooth" should enter the decision analysis, probably as a contributor in turn to a multifactorial utility variable integrating the effects of factors relevant to the quality of life.

The proposed scales for ORN-associated pain and function were supported as related to quality of life. Pain was regarded as the primary contributor to quality of life, while function and pathological fracture were regarded as secondary. Others, some perhaps also function-related (as even fracture might be considered) were suggested. Function levels in various ORN categories clearly appeared to be associated negatively with pain, suggesting that quality of life utilities could, if only validated pain data were available at some particular time in the future, be related (as an approximation) at first to pain alone.

---

9 Item 1100 data of inadequate numbers suggest that fistulae, healing rate and ease of rehabilitation should be considered, and Epstein (1996, private communication) also mentions the "possibility or not of prosthetic reconstruction", presumably intending this to include both medical and dental prosthetic reconstruction.
Once improved, the decision analytic outcome indicators suggested in this thesis would be suitable for incorporation within frameworks for quality improvement\textsuperscript{10}, cost-benefit analysis\textsuperscript{11}, or both.

Figures 22 and 23 concluding this section illustrate two introductory, theoretical decision analytic models\textsuperscript{12} proposed as consistent with this research. The first model is simplified (possibly overly simplified\textsuperscript{13}) to a structure similar to the tree illustrated in the introduction by moving complexity away from tree structure to multivariable ORN risk matrixes and multiple trees. As illustrated in Figure 22, simple decision trees \#1 to \#x for each potential time of intervention could be created, each of which have separate "$b''", "$b^{''}$, "$d''$, & "$d^{''}" multifactorial utility formulas, and $a''$ & $c''$ ORN risk probabilities, where

- "$x" is the number of assumption sets involving an interacting "$y" number of variables relevant to ORN risk, suitable for decision analysis (as determined by this thesis and the literature). The employment of $x$ number of decision trees is intended to make more practical, to the point of diminishing returns, simplicity and symmetry in the trees. (Tree symmetry eliminates a form of bias otherwise present during sensitivity analysis (Wellman, et al 1989). Other things being equal, simplicity is

\textsuperscript{10} e.g., that of Maxymiw et al (1995)
\textsuperscript{11} Peterson (1994) emphasized the need for cost-benefit analysis further to the study of Sonis, Woods and White (1990).
\textsuperscript{12} The tree should not be used to guide clinical practice until it, and its data assumptions, are validated.
\textsuperscript{13} The probability node would be more comprehensive if the "ORN present" category was subdivided into Epstein Classes ORN 1a, ORN 1b, ORN 2, ORN 3a, and ORN 3b, and utilities associated for each of these with no treatment, conservative treatment, and radical treatment. However, after folding back, these values could enter the decision analysis in the simplified way illustrated.
considered by Weinstein, Fineberg, and Elstein (1980) to be desirable, and also should encourage routine use of the tree.)

- "a" and "c" ORN risk probabilities are found in cells in an \((n - y)\) dimensional matrix, where \(n\) = the number of total variables relevant to ORN risk and suitable for decision analysis (as determined by this thesis and the literature), and \(y\) is the number of variables already taken into account in the multiple trees, and

- Different trees would be employed for different times of tooth extraction.

Were conjoint probabilities to arise from ORN risk factors other than the caries rate/salivation/home care compliance/oral hygiene status interactive variable, then this approach, using ORN risks gathered for each multiple-assumption circumstance independently, and entered in the appropriate cell as an isolated datum, would avoid potential problems of synergism, negative interaction, etc. (This would, of course, require an improved database.)

An alternative approach, traditional tree structure, is illustrated in Figure 23. Its models the overall decision-making process. Due to the complexity of the decision process and need for both relative simplicity and symmetry, the tree has been put into a modified "reduced" form (Weinstein, Fineberg and Elstein 1980) that, while not modelling the temporal sequence of decision-making, is mathematically equivalent.

Please note that special symbols on the master decision analysis indicate in that location the presence of (a) sub-branch(es) that are illustrated and identified on succeeding pages. Given the survey results, hyperbaric oxygen and chemotherapy are, for the time being, at least, absent from the tree. Node "divisions" were chosen by reference to the literature,
but some data are lacking to confirm their external validity, and similar comments would apply to the external validity of some of the assumptions made elsewhere in the tree.\textsuperscript{14}

(The generalizability of some of the source literature is open to question due to differences in therapeutic protocols, case distributions, etc.) For this reason, quantitative probabilities will not be assigned, nor threshold and sensitivity analyses performed, until meta-analytic or other suitable procedures outlined in Jaeschke and Sackett (1989), Droitcour, Silberman, and Chelimsky (1993), etc., can be applied to an adequate database. The tree may be considered, however, as a framework illustrating a suitable decision making process to which ordinal risk values may be assigned by experienced clinicians, some values anchored as absolute risk probabilities, and initial implications assessed.

---

\textsuperscript{14} The radiation categories proposed as initial categories for branches in the decision analysis assumed rough generalizability and comparability of the data from multiple sources:

A. for Total Dose: 6000 cGy, 6000-7500 cGy, \( >7500 \) cGy: (Beumer, Harrison, Sanders, Kurrausch 1984; Epstein, Rea, Wong, Spinelli, Stevenson-Moore 1987a; Fujita, et al 1996; Marx and Johnson 1987; Perrier and Moeller 1994; Yasumoto, et al 1996 [the last = combined radiation, too])


C. for Type of Radiation: (Schultheiss, et al 1990 [Netutron radiation threshold for mandibular ORN \( \approx 2400 \) cGy]; Shibuya, et al 1993 [\( \approx 2 \) times ORN when radioactive irridium used rather than radioactive radon, gold, or radium]).

D. for Field Size: (Pernot, et al 1994 [Treated Surface \( > 12 \) cm\(^2\)], Withers, et al 1995 [Radiation Treatment of Tonsil \( \rightarrow \) Relative Hazard for ORN of 1.15])


The categories in the Figure 23 decision analysis are proposed for discussion purposes. More refined future analyses could suggest alterations.
Osteoradionecrosis is a persisting clinical problem. ORN-prophylactic tooth extraction clinical decision analysis assists in understanding the problem, reviewing current assumptions and theory, and supporting decision making by both the patient and by health care providers. It also promotes the determination of patient-centered utilities, quantification of the consequences of treatment choices for informed consent, and identification of health-impacting areas requiring further research. The "Recommendations" made in Part 3. below will further all of these goals, and have merit in their own right. Improved decision making will result from implementation of these recommendations and continuation of research in areas addressed in this thesis.

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15 despite isolated reports to the contrary:

a) Makkonen, Kiminki, Makkonen, and Nordman (1987) report that for a series of 224 patients (135 with squamous carcinoma) treated between 1974-77, in which 45 teeth were extracted preradiotherapeutically and 94 after radiotherapy, no cases of osteoradionecrosis were observed. They conclude, "It is evident that the repairing of patient's teeth before radiation treatment, coupled with continuous preventive care of caries, will prevent serious complications from arising."

b) Patel, Raybould, and Maryuyama (1989) infer, "With present management methods at the University of Kentucky, ORN is not a problem."

c) Maxymiw, Wood and Liu (1991) associate a suggested tooth extraction management protocol with low reported ORN rates.

The concerns expressed near the end of the Discussion about generalizability of data, and bias due to different definitions for ORN, are relevant to article a) above. In articles b) and c), the case distributions and dosage protocols present may be responsible in large measure for the observed ORN rates. (For details, please see Literature Review.)
2. LIMITATIONS: DATA QUALITY

Qualitative data supplied on important topics generally were quite consistent from item to item. Although small numbers of categorized responses were of concern in a range of open-ended items, similar responses in overlapping items generally implied the presence of reliability. Relatively poor qualitative data quality was associated primarily with a small number of items dealing with non-critical issues. Most pooled Likert agreement scale responses to Delphi statements were adequate in consensus, which ultimately appeared to be more sensitive to the quality of the pooled data than the median confidence in the responses. Likert scale test-retest reliability was estimated for one pair of items as "good", for another, "marginal". Although quantitative expert opinion estimates of ORN risk were judged to lack adequate quality, quantitative estimates of pain and function associations and distributions in categorized ORN end-states demonstrated a degree of consistency when gathered in two ways. Seemingly remarkable consistency was present the extreme ORN categories-- progressive ORN with jaw fracture, and patient at risk (no ORN).

Content validity for the Delphi Survey's close-ended items was implied by widespread agreement between responses to the open-ended items and the content of, and responses to, the close-ended items. The design of the combined Delphi rounds would have been improved by the inclusion of close-ended items about the effects of

16 Interpretation and details will be found in "METHODOLOGY".
17 Comparisons of data from these related Item 4040 and 4160 series of items is interesting methodologically, and suggests the possibility of using analogous sets of items to examine the potential for reliability arising from the use of the technique. More complete considerations of bias, reliability, and validity limitations in this research may be found in the Discussion sections 3., 4., 5., and 6.
chemotherapy and hyperbaric oxygen therapy on the risk for ORN. The scant discussion of these topics by experts responding to open-ended items raises three possibilities:

1. that the frequency of responses involving these factors are biased by some special nature of the variables themselves--e.g., hyperbaric oxygenation "falling between [medical/surgical/oral surgical discipline] stools", not immediately rising to mind when factors affecting ORN rates are requested

2. that the sample is biased, e.g. by low numbers or lack of mention of the factors elsewhere in the survey.

3. that a large proportion of experts, while employing hyperbaric oxygen because it is now accepted practice, harbor private qualms about its efficacy.

Further information about expert opinion in these matters (surveys of experts using close-ended items) is indicated. Another randomized prospective controlled clinical trial (possibly where hyperbaric oxygen is not universally available) may be indicated if possibility 3. above is supported.

These Conclusions are subject to the reliability and validity constraints elaborated in the Results, Interpretation, and Discussion. In overview, the internal and external validity of this thesis research and conclusions are limited by the extent and quality of the existing research, the low numbers of experts surveyed, biases present (e.g. invitational and acceptance bias, cognitive bias during responses, bias potentially associated with personal or practice characteristics of respondents), the effects of uncertainty on subjective analysis, and lack of blinding during analysis and interpretation of the results. Tautology may affect conclusions about comparison.
A minor overlap between the survey respondents and authors cited in the literature Delphi surveys will suggest but not confirm the construct and content validity of the new scales and dimensions. Potential errors in estimation of effects of prognostic variables are not limited to separate effects, but combined effects, which may not be independent, but additive, subtractive, synergistic, etc. These relationships are difficult to elucidate.

The lack of respondent inclination or ability to supply with confidence some data requested in this survey for a decision analysis implies the presence of some weak assumptions in the current theory that guides practice, as well as the possibility of occasional poor recall or fatigue. Therefore, the continuation of the research started in this thesis would be useful. However, while a second round of the present survey would likely clarify the relatively few issues where consensus was lacking, further clarifications of opinion would not remedy underlying weaknesses in the quality of consensus data. Rather, a step-by-step examination and research related to each of the individual factors or factor groups arising from the results, in which the limits of opinion are complemented with appropriate epidemiological, clinical trial, and quality of life research, where possible, would clarify the database, assist in validating the theoretical decision analysis model, and assist in moving it toward real-world applicability. Thus, recommendations are made below to facilitate this process.
3. RECOMMENDATIONS

The following actions are advocated to enhance the database for future studies on the dental management of osteoradionecrosis:

A. Shorter Term

I. **Adoption, in future studies, of a standardized definition for osteoradionecrosis of the jaws.**

*Rationale:* Standardized definitions should increase the generalizability of osteoradionecrosis data.

II. **Application to the Canadian Institute of Health Information to recommend the adoption by the "International Classification of Diseases" of a specific diagnostic code for osteoradionecrosis of the jaws.**

III. **Initiation of ongoing collection of ORN epidemiological data from non-experimental databases if and when the "International Classification of Diseases" nosology distinguishes ORN as a separate entity.**

*Rationale:* Future comparison of rates of jaw osteoradionecrosis will be facilitated by non-experimental hospital and registry data gathered in accordance with classification changes possible in the "International Classification of Diseases".
IV. Initiation of further prospective data gathering in patients at risk for ORN, with detailed recording of treatments employed, ORN prognostic factors, and ORN outcomes, including a) oral hygiene, b) prophylactic- and post-irradiation tooth extraction,\(^{18}\) and c) other factors found in the Conclusions.

Rationales.

1. As indicated by Withers, et al (1995) in the footnote, these data are best gathered in a prospective fashion.

2. Improved ORN risk estimates, in association with knowledge of particular treatment circumstances and outcome consequences, and comparisons between centers (after taking into account the potentially biasing factors\(^ {19}\) revealed by expert opinion in this thesis), would serve to validate, or promote the evolution of, particular treatment policies.

3. The data could contribute to evidence-based decision analyses\(^ {20}\), clinical algorithms, practice guidelines, and quality control frameworks.

4. Improved risk estimates, in association with knowledge of particular treatment circumstances and outcome consequences, will assist understanding, communication, and patient [and physician] recall of risks associated with particular procedures or factors (Hughes 1993; Timmermans 1994).

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\(^{18}\) A notable 9-center study of post-radiotherapeutic complications in 676 patients, Withers et al (1995a), strongly implies advocacy for such detailed prospective data gathering. It concludes, "Other factors such as oral hygiene, and 'prophylactic' tooth extraction, or post-radiation trauma, especially tooth extraction, are important determinants of normal tissue sequelae that were not analyzed here only because they are not amenable to accurate retrospective analysis."

\(^{19}\) For details, please see Discussion.

\(^{20}\) A decision analysis is valuable because it develops quantified probabilities and effects within a decision analytic framework, permitting identification of decision thresholds in classes of patients. However, being constrained to a model, it may require modification for specific cases, and therefore is considered as an intermediate support for clinician decision making, not a substitute.
V. Adoption of a common standard for categorization of ORN outcomes.

Rationale.

1. The range of ORN experience is of concern to both clinicians and patients. The comparability of present literature suffers because a number of schemes exist for classifying ORN severity. As reviewed in the Literature Search, osteoradionecrosis can be categorized epidemiologically in a number of ways. The Epstein (1987b) classification scheme used in this Delphi survey would appear to assess severe osteoradionecrotic lesions the most accurately. Some other literature utilize schemes that do not to provide as much detail. (For instance, Morton (1986), classified ORN into cruder groups (bone at risk for ORN, "minor ORN", and "major ORN").) An argument could be made for worldwide adoption of the more accurate and better defined ORN classification scheme, especially in clinics with a large ORN case rate.

VI. Integration (meta-analysis?) of existing data on the distribution of ORN severities in particular circumstances.

Rationale: Better understanding of existing ORN severity data, comparability, and generalizability limitations, would occur. A proportion of the literature now extant provide data based on three-level ORN classification schemes. Fortunately, most represent "lower common denominators" roughly compatible with the Epstein (1987b) scheme. Although pooling epidemiological data from all articles would lose worthwhile data provided in the articles that used the more complex schemes, an argument could be made that this sacrifice would be countered for some short term uses of the data by increases in data numbers and generalizability.
VII. A series of close-ended Delphi Survey items to determine further the expert consensus on the relationships of chemotherapy and hyperbaric oxygenation to ORN rates and healing.

Rationales:

1. The reliability of the responses to related open-ended items in the thesis research would be assessed, and proven if responses to the close-ended items demonstrated agreement. If hyperbaric oxygen prophylaxis is not widely perceived to be a very significant influence on ORN rates, as is implied by the responses to the open-ended items, then a new randomized, prospective clinical trial would appear to be helpful in resolving issues, although ethical constraints might restrict its location to a facility where HBO is available, in any case, only to some of the patients.

2. The use of hyperbaric oxygen as a therapeutic or prophylactic measure is widely advocated in the literature, but remains a matter of some controversy. Some criticize the evidence cited for its efficacy (Sheps 1992; Zlotolow 1995); another (Clayman 1997) critiques some of the "evidence" and criticizes the cost-benefit ratio of employing HBO universally, as prophylaxis for ORN; yet another (Lambert, Intriere, and Eichstaedt 1997) advocates its universal use and criticizes its restriction to selected cases, as in Stevenson-Moore and Epstein (1993).

VIII. Employment, in analogous contexts, of the two methods outlined in the thesis to gather ORN severity distribution data.

Rationale: To determine overall reliability of the approach.

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21 Some literature is reviewed in the final part of the Literature Review, "3. Clinical Problem: 4. Osteoradionecrosis Pathogenesis, Definition, Diagnosis, Clinical Presentation, and Treatment. "HYPERBARIC OXYGEN"
B. Intermediate Term

I. Creation of validated patient-derived outcome scales for osteoradionecrosis.

Rationales:

1. Patients should be the ultimate judges of the success of medical treatment.

2. Non-validated utilities could lead to incorrect understanding, incorrect treatment decisions, and incorrect decision thresholds in clinical decision analyses.

3. Validated ORN utilities would assist informed consent.

II. Refinement of existing decision trees, once the data base improves, e.g.:


2. dividing the "master" decision tree into simpler trees with different sets of assumptions suited to particular patient education or clinical circumstances

3. creating new trees related to prosthetic and functional rehabilitation, etc.

4. considering whether multi-factorial probability formulas (as made possible by "C. Long Term" below) could take the place of certain tree nodes.
C. Long Term

I. Validated clarification of interactions and effects of potentially dependent ORN risk variables.

Rationale. Some ORN risk variables thought relevant to decision analysis probably are mathematically independent, and others interdependent such that they would best contribute to a decision analysis through an intermediate factor that integrated their combined effects. The validation of such combination factors would require further research based on the enlarged database advocated above. (Until such time, decision trees of clinical utility would use simplifications.)

---

22 This concept also could apply to dependent sub-variables, such as periodontal pocket depth, furcation involvement, and tooth mobility sub-variables associated with potentially independent ORN risk variables, e.g. periodontal disease. Similarly, interactions among endodontic sub-factors could be considered, perhaps in relation to potential for infection. (Survey responses from Item 1830 indicated mild general agreement with the concept of quantifiability of endodontic status indicators.)
A FIRST ORN-MINIMIZING TOOTH EXTRACTION
THEORETICAL DECISION TREE MODEL SUGGESTED BY THIS RESEARCH

ORN-PROPHYLACTIC TOOTH EXTRACTION DECISION TREES --NOS. 1 - "x", FOR TIME "z"

Should Tooth Be Extracted?

"Yes": Extract Tooth

Average probability of ORN occurrence, given "Yes," = \( a \)
Utility given "Yes" & ORN, = \( b \)

Average probability of no ORN, given "Yes," = \( 1 - a \)
Utility given "Yes" & no ORN, = \( b' \)

"No": Do Not Extract Tooth

Average probability of ORN occurrence, given "No," = \( c \)
Utility given "No" & ORN, = \( d \)

Average probability of no ORN, given "No," = \( 1 - c \)
Utility given "No" & no ORN, = \( d' \)

Decision Trees #1 to #x, with Different Assumptions, each of which have separate "\( b \)", "\( b' \)", "\( d \)", & "\( d' \)" multifactorial utility formulas, and \( a \)" & "\( c \)" ORN risk probabilities. Please see section 1 text for explanation.

**KEY:**

Decision Node:

Probability Node:
FIGURE 23  A MODIFIED REDUCED FRAMEWORK FOR AN ORN-MINIMIZING DECISION ANALYSIS

- **Extract tooth 1wk. preRTX**
  - **A₁**
  - **B₁ =** BrachyTx cGy
    - **C₁ =** None
    - **D₁ =:** ≤ 200
    - **D₂ =:** > 200
  - **E₁ =:** Field Size
    - **Small**
    - **Large**

- **Extract tooth 2wks. preRTX**
  - **A₂**
  - **B₂ =** Total Dose
    - **≥6000, <7500 cGy**
    - **B₃ =** Total Dose
      - **≥7500 cGy**

- **Extract teeth 3wks. preRTX**
  - **A₃**

- **Do Not Extract teeth**
  - **A₄**

- **Extract teeth Post-RTx**
  - **A₅**

- **ASSESS PERIODONTAL STATE (as on next page)**
  - **F₁ =:** Adequate
    - **F₂ =:** Inadequate

- **ASSESS ENDODONTIC STATE (as on next page)**
  - **G₁ =:** Adequate
    - **G₂ =:** Inadequate

- **ASSESS LOCATION**
  - **H₁ =:** Maxilla
    - **H₃ =:** Non-Poster Mandible
  - **H₂ =:** Mandible

- **ASSESS f(CARIES RATE; SALIVATION; PATIENT COMPLIANCE; TISSUE CHARACTERISTICS)**
  - **I₁ =:** ORN CI
    - **I₂ =:** ORN 2b
    - **I₃ =:** ORN 2a
    - **I₄ =:** ORN 1b
    - **I₅ =:** ORN 1a

- **p = probability**
- **u = utility**
FIGURE 23  A MODIFIED REDUCED FRAMEWORK FOR AN ORN-MINIMIZING
DECISION ANALYSIS, continued

ASSESS PERIODONTAL STATUS → $Q_1$

ASSESS FURCATIONS
Mandib. Class I
→ $R_1$

ASSESS MOBILITY
Cl I Max $S_1$ = ≤ 5 $T_2$

POCKETS
mm.

> 5 $T_1$:

INFECTION

Furcation Max Cl. I or Mn. Cl. II
→ $R_2$

INFECTION

PRESIDENT

Furcation Max Cl. II or Mn. Cl. III
→ $R_3$

FURCATION

SYMPTOMS

ASSESS ENDO-DONTAL STATUS → $W_1$

ASSESS ENDO STATUS
RADIO-LUCENCY PRESENT
→ $X_1$

ASSESS

SYMPTOMS

Present $Y_2$

Absent $Y_1$:

RADIO-LUCENCY ABSENT
→ $X_2$

INFECTION

Present $Z_2$

Absent $Z_1$:

POCKETS

$P_{ORN,v2}$

$P_{ORN,v1}$

$P_{ORN,z2}$

$P_{ORN,z1}$
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### TABLE 18. POTENTIAL ORN RISK FACTORS. All Item 1140 Responses.

Grouped by concept, with product subtotal for each concept group.

<table>
<thead>
<tr>
<th>Product F(6-R)</th>
<th>Topic Number</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>A. RADIATION-THERAPEUTICS RELATED FACTORS</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Frequency</strong></td>
<td><strong>Mean Rank</strong></td>
<td></td>
</tr>
<tr>
<td>3+++</td>
<td>1.3</td>
<td>14.1</td>
</tr>
<tr>
<td>1+</td>
<td>2</td>
<td>4</td>
</tr>
<tr>
<td>1+</td>
<td>1</td>
<td>5</td>
</tr>
<tr>
<td>2++</td>
<td>1.5</td>
<td>9.0</td>
</tr>
<tr>
<td>2+</td>
<td>2.5</td>
<td>7</td>
</tr>
<tr>
<td>1+-</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>1</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>1</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>1+</td>
<td>2</td>
<td>4</td>
</tr>
<tr>
<td><strong>B. NON-RADIATION THERAPEUTICS RELATED FACTORS</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>2.4</td>
<td>28.8</td>
</tr>
<tr>
<td>1+</td>
<td>1</td>
<td>5</td>
</tr>
<tr>
<td>1+</td>
<td>2</td>
<td>4</td>
</tr>
<tr>
<td>1+</td>
<td>2</td>
<td>4</td>
</tr>
<tr>
<td>1+</td>
<td>1</td>
<td>5</td>
</tr>
<tr>
<td>1+</td>
<td>5</td>
<td>1</td>
</tr>
<tr>
<td>1+</td>
<td>4</td>
<td>2</td>
</tr>
<tr>
<td>1+</td>
<td>2</td>
<td>4</td>
</tr>
<tr>
<td>1</td>
<td>2</td>
<td>4</td>
</tr>
<tr>
<td><strong>C. CARIES- AND ENDODONTIC-DISEASE RELATED FACTORS</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>3.2</td>
<td>22.4</td>
</tr>
<tr>
<td>4+-</td>
<td>3.2</td>
<td>11.2</td>
</tr>
<tr>
<td>3-</td>
<td>3.7</td>
<td>6.9</td>
</tr>
<tr>
<td>2</td>
<td>4.5</td>
<td>3</td>
</tr>
<tr>
<td>1 (0)</td>
<td>301. Tooth-related</td>
<td></td>
</tr>
</tbody>
</table>

---

1. Responses are tabulated by frequency of citation, by mean rank, and by "product". Factor importance is implied by any of the following: high frequency, low rank, and high "product". The frequency is the number of clear citations of the topic. If the topic was ranked in importance a lesser number of times, this is inserted parenthetically. The "product" \( (\text{Frequency times } (6 - \text{Mean Rank}) \) ), is an intuitively derived alternate surrogate for importance for responses to open-ended items; it is described further in the final part of the Methodology section.

2. (i.e. 8 only, because Xeroxing error prevented full distribution of item.)
<table>
<thead>
<tr>
<th>Frequency</th>
<th>Mean</th>
<th>Product Rank</th>
<th>Topic Number</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>4</td>
<td>2.3</td>
<td>14.8</td>
<td>D.</td>
<td>ANATOMICAL-LOCATION-OF-ORN RELATED FACTORS</td>
</tr>
<tr>
<td>1</td>
<td>1</td>
<td>5</td>
<td>171. Mandibular, as opposed to maxillary, location of ORN (as potential ORN incidence risk factor)</td>
<td></td>
</tr>
<tr>
<td>±±±</td>
<td>2.7</td>
<td>9.9</td>
<td>172. Specific part of mandible, location of ORN (as potential ORN incidence risk factor)</td>
<td></td>
</tr>
<tr>
<td>10</td>
<td>4.9</td>
<td>11.0</td>
<td>E.</td>
<td>PERIODONTAL-RELATED FACTORS</td>
</tr>
<tr>
<td>1</td>
<td>13</td>
<td>0</td>
<td>359. Gingivitis and risk for ORN [C.f.: 379.]</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>4.0</td>
<td>12.0</td>
<td>360. Periodontal disease and risk for ORN</td>
<td></td>
</tr>
<tr>
<td>- +</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>2</td>
<td>4</td>
<td>353. Periodontal infection</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>8</td>
<td>0</td>
<td>390. Occlusion:</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>2</td>
<td>4</td>
<td>375. Tooth mobility</td>
<td></td>
</tr>
<tr>
<td>17</td>
<td>5.4</td>
<td>10.2</td>
<td>F.</td>
<td>METABOLISM-RELATED</td>
</tr>
<tr>
<td>3 - ~</td>
<td>4.0</td>
<td>6.0</td>
<td>461. The anticipated blood supply, or oxygen perfusion of,</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>the high-dose irradiated mandibular volume [assumed compromised when an assumption is necessary.]</td>
</tr>
<tr>
<td>3 (2)</td>
<td>6.0</td>
<td>0.0</td>
<td>463. The systemic metabolic state [not circulatory status]</td>
<td></td>
</tr>
<tr>
<td>+ +</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 (0)</td>
<td></td>
<td>-</td>
<td>469. Patient's race</td>
<td></td>
</tr>
<tr>
<td>3(2) +</td>
<td>5.0</td>
<td>3.0</td>
<td>467. The patient's smoking status</td>
<td></td>
</tr>
<tr>
<td>2(0) +</td>
<td></td>
<td>-</td>
<td>465. The patient's age</td>
<td></td>
</tr>
<tr>
<td>2 (1)</td>
<td>4</td>
<td>4.0</td>
<td>466. The patient's diet (excluding effects on caries rate)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>[c.f. 648 = excessive alcohol consumption]</td>
<td></td>
</tr>
<tr>
<td>2 (1)</td>
<td>10</td>
<td>0</td>
<td>648. Excessive alcohol consumption</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>3</td>
<td>3</td>
<td>649. Smoking and alcohol consumption</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>1.5</td>
<td>9</td>
<td>G.</td>
<td>OVERLYING-TISSUE-RELATED FACTORS</td>
</tr>
<tr>
<td>1 ±</td>
<td>1</td>
<td>5</td>
<td>473. Quality of periosteum/soft tissue overlying</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>2</td>
<td>4</td>
<td>475. Keratinization; fibrosis</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>3.5</td>
<td>5.0</td>
<td>H.</td>
<td>TOOTH-IMPACATION-RELATED FACTORS</td>
</tr>
<tr>
<td>1 +</td>
<td>3</td>
<td>3</td>
<td>369. Pericoronitis [infection in soft tissue overlying partially impacted tooth]</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>385. Impacted tooth (teeth)</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>5.2</td>
<td>4.8</td>
<td>I.</td>
<td>POST-RADIO-TX DENTITION-CARE-RELATED FACTORS</td>
</tr>
<tr>
<td>1, -</td>
<td>5</td>
<td>1</td>
<td>853. Adequate post-treatment dental care, i.e. BOTH 560 AND 852.</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>3</td>
<td>3</td>
<td>550. The expected compliance of the patient with prescribed home care, such as fluoride rinses, other than oral hygiene. 550=404.</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>5.8</td>
<td>0.8</td>
<td>540. Expected compliance of the patient with prescribed oral hygiene home care.</td>
<td></td>
</tr>
<tr>
<td>+ ± -</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Whenever the potential for skewing of distribution of severities is indicated by a respondent, these are indicated: "+" = relatively more severe; "-" = relatively less severe, and "±" = skew in either direction.
TABLE 29. [DUPLICATED]  
NORMALLY RECOMMENDED AND ABSOLUTE MINIMUM 
RECOMMENDED PRE-RADIOThERAPY DAYS OF HEALING, VS. REPORTED ORN RATES

<table>
<thead>
<tr>
<th>RESPONDENT:</th>
<th>01/</th>
<th>02/</th>
<th>03/</th>
<th>04/</th>
<th>05/</th>
<th>06/</th>
<th>07/</th>
<th>08/</th>
<th>09/</th>
<th>10/</th>
<th>11/</th>
<th>12/</th>
<th>13/</th>
<th>14/</th>
<th>15/</th>
</tr>
</thead>
<tbody>
<tr>
<td>ORN RATE (±; %)</td>
<td>1. U</td>
<td>U</td>
<td>4.</td>
<td>3.5</td>
<td>1.</td>
<td>7.5</td>
<td>4.5</td>
<td>1.</td>
<td>0.3</td>
<td>4.5</td>
<td>25.</td>
<td>1.5</td>
<td>2.</td>
<td>16.</td>
<td></td>
</tr>
<tr>
<td>Absolute Minimum Heating Time: (Days)</td>
<td>7.</td>
<td>2.</td>
<td>U</td>
<td>3.</td>
<td>3.</td>
<td>N/A</td>
<td>10.</td>
<td>7.</td>
<td>2.</td>
<td>12.</td>
<td>1.</td>
<td>7.</td>
<td>10.</td>
<td>12.</td>
<td>14.</td>
</tr>
</tbody>
</table>

or, in greater detail:

TABLE 30. ITEMS 1520 AND 1320.1330. &1340. ABSOLUTE MINIMUM RECOMMENDED PRE-RADIOThx TOOTH SOCKET HEALING TIMES VS. REPORTED ORN FREQUENCY

<table>
<thead>
<tr>
<th>RESPONDENT:</th>
<th>01/</th>
<th>02/</th>
<th>03/</th>
<th>04/</th>
<th>05/</th>
<th>06/</th>
<th>07/</th>
<th>08/</th>
<th>09/</th>
<th>10/</th>
<th>11/</th>
<th>12/</th>
<th>13/</th>
<th>14/</th>
<th>15/</th>
<th>03/</th>
<th>06/</th>
</tr>
</thead>
<tbody>
<tr>
<td>Absolute Minimum Recommended Healing Time (Days):</td>
<td>1</td>
<td>2</td>
<td>2</td>
<td>3</td>
<td>3</td>
<td>7</td>
<td>7</td>
<td>7</td>
<td>10</td>
<td>10</td>
<td>12</td>
<td>12</td>
<td>14</td>
<td>U</td>
<td>N/A</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Reported z ORN Rate (%):</td>
<td>4</td>
<td>U</td>
<td>1</td>
<td>4</td>
<td>3</td>
<td>1</td>
<td>5</td>
<td>25</td>
<td>7</td>
<td>1</td>
<td>0.3</td>
<td>1</td>
<td>U</td>
<td>U</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Reported z' ORN Rate (%):</td>
<td>5</td>
<td>U</td>
<td>1</td>
<td>4</td>
<td>4</td>
<td>U</td>
<td>4</td>
<td>E</td>
<td>8</td>
<td>2</td>
<td>U</td>
<td>3</td>
<td>16</td>
<td>U</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Best available estimate (z &amp; z'):</td>
<td>4.5</td>
<td>1</td>
<td>4</td>
<td>3.5</td>
<td>1</td>
<td>4.5</td>
<td>25</td>
<td>7.5</td>
<td>1.5</td>
<td>0.3</td>
<td>2</td>
<td>16</td>
<td>U</td>
<td>1</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

TABLE 31. ITEMS 1510 AND 1320.1330. &1340. NORMALLY RECOMMENDED PRE-RADIOThx TOOTH SOCKET HEALING TIMES VS. REPORTED ORN FREQUENCY

<table>
<thead>
<tr>
<th>RESPONDENT:</th>
<th>02/</th>
<th>04/</th>
<th>05/</th>
<th>01/</th>
<th>08/</th>
<th>03/</th>
<th>07/</th>
<th>10/</th>
<th>11/</th>
<th>12/</th>
<th>13/</th>
<th>15/</th>
<th>14/</th>
<th>09/</th>
<th>06/</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normally Recommended Healing Time (Days):</td>
<td>3</td>
<td>3</td>
<td>7</td>
<td>12</td>
<td>12</td>
<td>14</td>
<td>14</td>
<td>14</td>
<td>14</td>
<td>14</td>
<td>14</td>
<td>16</td>
<td>U</td>
<td>N/A</td>
<td></td>
</tr>
<tr>
<td>Reported z ORN Rate (%):</td>
<td>U</td>
<td>4</td>
<td>3</td>
<td>1</td>
<td>5</td>
<td>U</td>
<td>7</td>
<td>0.3</td>
<td>4</td>
<td>25</td>
<td>1</td>
<td>U</td>
<td>1</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Reported z' ORN Rate (%):</td>
<td>U</td>
<td>4</td>
<td>4</td>
<td>U</td>
<td>4</td>
<td>U</td>
<td>8</td>
<td>U</td>
<td>5</td>
<td>E</td>
<td>2</td>
<td>16</td>
<td>3</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Best available estimate (z &amp; z'):</td>
<td>U</td>
<td>4</td>
<td>3.5</td>
<td>1</td>
<td>4.5</td>
<td>U</td>
<td>7.5</td>
<td>0.3</td>
<td>4.5</td>
<td>25</td>
<td>1.5</td>
<td>16</td>
<td>2</td>
<td>1</td>
<td></td>
</tr>
</tbody>
</table>

4. MEAN ORN INCIDENCE RATES (For KEY, please see bottom of next page):
   \[ Z_{\text{mean}} = 3\%, \text{excluding 12/ outlier data.} \]
   \[ Z_{\text{mean}} = 4\%, \text{including 12/ outlier data.} \]
   \[ Z'_{\text{mean}} = 4\%, \text{excluding 12/ possibly invalid data, and 15/ outlier data.} \]
   \[ Z''_{\text{mean}} = 5\%, \text{excluding 12/ possibly-invalid data, but including 15/ outlier data.} \]

Potential Problems with these figures include the facts that
1. respondent 12/ reports approximately 60 cases of ORN per year, while only 15 cases of radiotherapy per year are reported. This suggests that the validities of 12/ incidence data are suspect. Might rates for ORN and radiotherapy be reversed?
2. the high incidences of ORN reported by respondents 03/ and 12/ (15 and 60, or 15 and 15 if respondent 12/ rates for ORN and radiotherapy are reversed) make these data outliers.
3. respondent 03/ reports neither related numbers of O-P squamous cell Ca patients nor radiotherapy patients.
4. the reported ORN incidence rate may be higher if Y or Y' data were available for respondent 03/.

5. Potential Problems with these figures include the facts that
   \[ Z_{\text{mean}} = 3\%, \text{excluding 12/ outlier data.} \]
   \[ Z_{\text{mean}} = 4\%, \text{including 12/ outlier data.} \]
   \[ Z'_{\text{mean}} = 4\%, \text{excluding 12/ possibly invalid data, and 15/ outlier data.} \]
   \[ Z''_{\text{mean}} = 5\%, \text{excluding 12/ possibly-invalid data, but including 15/ outlier data.} \]

(Rates are uncorrected for potential bias for the reasons outlined in the discussion section dealing with potential Survey bias.)
### TABLE 41. ITEM 1890 SERIES. FACTORS INDICATING EXTRACTION
(BY DECREASING AGREEMENT CONSENSUS - ONLY DATA OF ADEQUATE CONSENSUS REPORTED)

<table>
<thead>
<tr>
<th>ITEM</th>
<th>DESCRIPTION</th>
<th>ASSESSMENT</th>
<th>MEDIAN</th>
<th>Inter-Quartile Range</th>
<th>MEAN</th>
</tr>
</thead>
<tbody>
<tr>
<td>1940 f.</td>
<td>Oral hygiene status</td>
<td>AGREEMENT</td>
<td>6.3</td>
<td>0.3</td>
<td>6.2</td>
</tr>
<tr>
<td></td>
<td></td>
<td>CONFIDENCE</td>
<td>6.4</td>
<td>1.5</td>
<td>6.2</td>
</tr>
<tr>
<td>1890 a.</td>
<td>Traditional periodontal status</td>
<td>AGREEMENT</td>
<td>6.6</td>
<td>0.8 (25th %tile = 6.1)</td>
<td>6.6</td>
</tr>
<tr>
<td></td>
<td></td>
<td>CONFIDENCE</td>
<td>6.7</td>
<td>0.7 (25th %tile = 6.2)</td>
<td>6.7</td>
</tr>
<tr>
<td>1930 e.</td>
<td>Endodontic status</td>
<td>AGREEMENT</td>
<td>6.3</td>
<td>1.5</td>
<td>6.0</td>
</tr>
<tr>
<td></td>
<td></td>
<td>CONFIDENCE</td>
<td>6.4</td>
<td>1.5</td>
<td>6.1</td>
</tr>
<tr>
<td>1910 c.</td>
<td>Caries experience/anticipated rate</td>
<td>AGREEMENT</td>
<td>6.1</td>
<td>1.5</td>
<td>6.0</td>
</tr>
<tr>
<td></td>
<td></td>
<td>CONFIDENCE</td>
<td>6.3</td>
<td>1.3</td>
<td>6.3</td>
</tr>
<tr>
<td>1920 d.</td>
<td>Mechanical status of each tooth</td>
<td>AGREEMENT</td>
<td>6.0</td>
<td>1.6</td>
<td>5.5</td>
</tr>
<tr>
<td></td>
<td></td>
<td>CONFIDENCE</td>
<td>6.3</td>
<td>1.3</td>
<td>5.9</td>
</tr>
<tr>
<td>1960 h.</td>
<td>Anticipated vascular and cellular changes</td>
<td>AGREEMENT</td>
<td>6.3</td>
<td>1.8</td>
<td>5.9</td>
</tr>
<tr>
<td></td>
<td></td>
<td>CONFIDENCE</td>
<td>6.5</td>
<td>-</td>
<td>6.1</td>
</tr>
<tr>
<td>2060 q.</td>
<td>Patient's smoking status</td>
<td>AGREEMENT</td>
<td>4.5</td>
<td>2.9</td>
<td>4.2</td>
</tr>
<tr>
<td></td>
<td></td>
<td>CONFIDENCE</td>
<td>6.0</td>
<td>1.2</td>
<td>5.7</td>
</tr>
</tbody>
</table>

**KEY FOR TABLES 30 AND 31 ON LAST PAGE:**

INCIDENCE RATES Z AND Z' ARE DEFINED:

- **Z** = \( \frac{X}{Y} \) = Annual \# New Cases of Active ORN in clinic  
- **U** = Undefined  
- **Y** = Annual \# New Cases Oropharyngeal Squamous Cell Ca  
- **E** = Error (>100%)  
- **Z'** = \( \frac{X}{Y'} \) = Annual \# New Cases External & Combination RadioTx  
- **N/A** = Not Asked  
- **Y'** = "# New Cases External & Combination RadioTx For  

Note: Individual contributions of minimum recommended and normally recommended tooth extraction socket healing times prior to irradiation to high dose may be compared with individual respondents' reported ORN rates. [Table 29 last page; Fig. 5, 6 (Charts 1,2) in RESULTS p. 199]
### TABLE 43. Item3610 Scenario: Recommended Changes in Management  
\( n = 7 \) (categorizable responses)

<table>
<thead>
<tr>
<th>Frequency</th>
<th>Mean Rank</th>
<th>Product</th>
<th>Topic Number, Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>4 (2 ranked)</td>
<td>1.0</td>
<td>20.</td>
<td>583. Changes from standard scenario case in extraction criteria thresholds.</td>
</tr>
<tr>
<td>2</td>
<td>1.5</td>
<td>9.</td>
<td>582. Changes from standard scenario case in prescribed level of dental hygiene and other dental health routines (including, possibly, fluoride rinses.)</td>
</tr>
<tr>
<td>2 (1)</td>
<td>2</td>
<td>8.</td>
<td>588. Changes from standard scenario case in major surgical interventions, e.g. mandibulectomy, employed.</td>
</tr>
</tbody>
</table>

### TABLE 44. Item3640 Scenario: Recommended Changes in Management  
\( n = 6 \) (categorizable responses)

<table>
<thead>
<tr>
<th>Frequency</th>
<th>Mean Rank</th>
<th>Product</th>
<th>Topic Number, Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>5</td>
<td>1.4</td>
<td>23.</td>
<td>583. Changes from standard scenario case in extraction criteria thresholds.</td>
</tr>
<tr>
<td>3</td>
<td>1.3</td>
<td>14.</td>
<td>582. Changes from standard scenario case in prescribed level of dental hygiene and other dental health routines (including, possibly, fluoride rinses.)</td>
</tr>
</tbody>
</table>

### TABLE 45. Item3670 Scenario: Recommended Changes in Management  
\( n = 4 \) (categorizable responses)

<table>
<thead>
<tr>
<th>Frequency</th>
<th>Mean Rank</th>
<th>Product</th>
<th>Topic Number, Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>3 (2)</td>
<td>1.5</td>
<td>13.5</td>
<td>583. Changes from standard scenario case in extraction criteria thresholds.</td>
</tr>
</tbody>
</table>

### TABLE 46. Item3700 Scenario: Recommended Changes in Management  
\( n = 6 \) (categorizable responses)

<table>
<thead>
<tr>
<th>Frequency</th>
<th>Mean Rank</th>
<th>Product</th>
<th>Topic Number, Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>6 (5)</td>
<td>1.2</td>
<td>29.</td>
<td>583. Changes from standard scenario case in extraction criteria thresholds.</td>
</tr>
<tr>
<td>2</td>
<td>1.5</td>
<td>9.</td>
<td>582. Changes from standard scenario case in prescribed level of dental hygiene and other dental health routines (including, possibly, fluoride rinses.)</td>
</tr>
<tr>
<td>2</td>
<td>2.5</td>
<td>7.</td>
<td>589. Changes from standard scenario case in level of professional monitoring required</td>
</tr>
</tbody>
</table>

### TABLE 47. Item 3730 Part a. Recommended Changes in Management  
\( n = 9 \) (categorizable responses)

<table>
<thead>
<tr>
<th>Frequency</th>
<th>Mean Rank</th>
<th>Product</th>
<th>Topic Number, Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>4 (0)</td>
<td>1?</td>
<td>20.?</td>
<td>581. No changes from standard scenario case in clinical management.</td>
</tr>
<tr>
<td>4</td>
<td>1.75</td>
<td>17.</td>
<td>584. Changes from standard scenario case in prosthesis/es fabricated.</td>
</tr>
<tr>
<td>2</td>
<td>1.0</td>
<td>10.</td>
<td>582. Changes from standard scenario case in prescribed level of dental hygiene and other dental health routines (including, possibly, fluoride rinses.)</td>
</tr>
<tr>
<td>2</td>
<td>1.0</td>
<td>10.</td>
<td>587. Changes from standard scenario case in restorative dentistry employed.</td>
</tr>
<tr>
<td>2</td>
<td>2.0</td>
<td>8.</td>
<td>589. Changes from standard scenario case in level of professional monitoring required</td>
</tr>
</tbody>
</table>

*Note: Unlike other items in this section, Item 3730 was associated with quantitative ORN risk estimates of apparently adequate consensus-- Please table on the bottom of the next page.*
**TABLE 48. Item 3790 Scenario: Recommended Changes in Management**

- **n (categorizable responses) = 6.**

<table>
<thead>
<tr>
<th>Frequency</th>
<th>Mean Rank</th>
<th>Product</th>
<th>Topic Number, Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>2 (1)</td>
<td>1</td>
<td>10.</td>
<td>581. No changes from standard scenario case in clinical management.</td>
</tr>
<tr>
<td>2 (1)</td>
<td>2</td>
<td>8.</td>
<td>585. Changes from standard scenario case in antibacterial medication employed.</td>
</tr>
<tr>
<td>2</td>
<td>1</td>
<td>10, if collapsing accepted.</td>
<td>One 582. Changes from standard scenario in prescribed level of dental hygiene and other dental health routines (including, possibly, fluoride rinses.) collapsed with a related response from another respondent: One 589. Changes from standard scenario in level of professional monitoring required</td>
</tr>
</tbody>
</table>

**TABLE 49. Item 3760 Scenario: Recommended Changes in Management**

- **n (categorizable responses) = 6.**

<table>
<thead>
<tr>
<th>Frequency</th>
<th>Mean Rank</th>
<th>Product</th>
<th>Topic Number, Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>5 (2)</td>
<td>1.0</td>
<td>25.</td>
<td>581. No changes from standard scenario case in clinical management.</td>
</tr>
<tr>
<td>2 (1)</td>
<td>1</td>
<td>10. if collapsing accepted.</td>
<td>One 582. Changes from standard scenario in prescribed level of dental hygiene and other dental health routines (including, possibly, fluoride rinses.) collapsed with a related response from another respondent: One 589. Changes from standard scenario in level of professional monitoring required</td>
</tr>
</tbody>
</table>

**TABLE 50. Item 3820 Scenario: Recommended Changes in Management**

- **n (categorizable responses) = 7.**

<table>
<thead>
<tr>
<th>Frequency</th>
<th>Mean Rank</th>
<th>Product</th>
<th>Topic Number, Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>2 (0)</td>
<td>1?</td>
<td>10.?</td>
<td>581. No changes from standard scenario case in clinical management.</td>
</tr>
<tr>
<td>2 (1)</td>
<td>1</td>
<td>10.</td>
<td>583. Changes from standard scenario in extraction criteria thresholds.</td>
</tr>
<tr>
<td>2</td>
<td>1.5</td>
<td>9.</td>
<td>585. Changes from standard scenario in antibacterial medication employed.</td>
</tr>
<tr>
<td>2</td>
<td>1</td>
<td>10, if collapsing accepted.</td>
<td>One 582. Changes from standard scenario in prescribed level of dental hygiene and other dental health routines (including, possibly, fluoride rinses.) collapsed with a related response from another respondent: One 589. Changes from standard scenario in level of professional monitoring required</td>
</tr>
</tbody>
</table>

**TABLE 51. PERCENTAGE CHANGES IN OSTEORADIONECROSIS IF INTERVENTIONS WERE NOT MADE**

<table>
<thead>
<tr>
<th>Responses:</th>
<th>WERE NOT MADE</th>
<th>WERE MADE</th>
</tr>
</thead>
<tbody>
<tr>
<td>0,0,0,0; plus two unknown rises</td>
<td>0,0,0,0; plus one unknown fall</td>
<td></td>
</tr>
<tr>
<td>No.of Respondents:</td>
<td>6 (4)</td>
<td>5 (4)</td>
</tr>
<tr>
<td>MEDIAN = MEAN =</td>
<td>&gt; 0</td>
<td>&lt; 0</td>
</tr>
<tr>
<td>75th - 25th IQ Range</td>
<td>Presumably small.</td>
<td>Presumably small</td>
</tr>
<tr>
<td>TABLE 60. ITEMS 4160-4260: DATA AND CHARACTERISTICS OF DATA FOR PAIN AND FUNCTION DISTRIBUTION IN CATEGORIZED ORN</td>
<td></td>
<td></td>
</tr>
<tr>
<td>---------------------------------------------------------------</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ORN3(_b), #4160</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean</td>
<td>63.0</td>
<td>24.0</td>
</tr>
<tr>
<td>Median</td>
<td>60.2</td>
<td>30.0</td>
</tr>
<tr>
<td>Inter-Quartile Range</td>
<td>42.5</td>
<td>25.0</td>
</tr>
<tr>
<td>ORN3(_a), #4180</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean</td>
<td>30.0</td>
<td>19.0</td>
</tr>
<tr>
<td>Median</td>
<td>20.0</td>
<td>20.0</td>
</tr>
<tr>
<td>Inter-Quartile Range</td>
<td>45.0</td>
<td>12.5</td>
</tr>
<tr>
<td>ORN2, #4200</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean</td>
<td>15.8</td>
<td>19</td>
</tr>
<tr>
<td>Median</td>
<td>20.0</td>
<td>20.0</td>
</tr>
<tr>
<td>Inter-Quartile Range</td>
<td>20.5</td>
<td>22.5</td>
</tr>
<tr>
<td>ORN1(_b), #4220</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean</td>
<td>8.2</td>
<td>6.4</td>
</tr>
<tr>
<td>Median</td>
<td>5.0</td>
<td>5.0</td>
</tr>
<tr>
<td>Inter-Quartile Range</td>
<td>16.2</td>
<td>10.9</td>
</tr>
<tr>
<td>ORN1(_a), #4240</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean</td>
<td>3.8</td>
<td>8.8</td>
</tr>
<tr>
<td>Median</td>
<td>4.0</td>
<td>4.0</td>
</tr>
<tr>
<td>Inter-Quartile Range</td>
<td>5.6</td>
<td>14.3</td>
</tr>
<tr>
<td>ORN0, #4260</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean</td>
<td>1.4</td>
<td>1.8</td>
</tr>
<tr>
<td>Median</td>
<td>1.0</td>
<td>2.0</td>
</tr>
<tr>
<td>Inter-Quartile Range</td>
<td>Undef.</td>
<td>Undef.</td>
</tr>
<tr>
<td><strong>CONFIDENCE LEVELS</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(Individual submissions = 2, 5, 6, 6, &amp; 3, from Respondents 05, 08, 11, 12, &amp; 15)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>FOR ALL DATA</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(DATA TABULATED ABOVE.)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median, IQR, Mean:</td>
<td>5.0</td>
<td>3.0</td>
</tr>
<tr>
<td><strong>FOR DATA OF HIGHER CONFIDENCE (5 &amp; 6).</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(DATA TABULATED BELOW)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median, IQR, Mean:</td>
<td>5.7</td>
<td>-</td>
</tr>
</tbody>
</table>
**TABLE 60. ITEMS 4160-4260: DATA AND CHARACTERISTICS OF DATA FOR PAIN AND FUNCTION DISTRIBUTION IN CATEGORIZED ORN, cont.**

<table>
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<th>II. HIGH CONFIDENCE DATA*</th>
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<th>P1</th>
<th>P0</th>
<th>F4</th>
<th>F3</th>
<th>F2</th>
<th>F1</th>
<th>F0</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>ORN3b, #4160</strong></td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean</td>
<td>75.0</td>
<td>16.7</td>
<td>6.7</td>
<td>1.7</td>
<td>0</td>
<td>70.7</td>
<td>17.7</td>
<td>10.0</td>
<td>1.7</td>
<td>0</td>
</tr>
<tr>
<td>Median</td>
<td>80.0</td>
<td>16.7</td>
<td>6.7</td>
<td>1.7</td>
<td>0</td>
<td>80.0</td>
<td>10.0</td>
<td>10.0</td>
<td>1.7</td>
<td>0</td>
</tr>
<tr>
<td>Inter-Quartile Range</td>
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<td>Undef</td>
<td>Undef</td>
<td>Undef</td>
<td>Undef</td>
<td>49.0</td>
<td>20.3</td>
<td>15.0</td>
<td>Undef</td>
<td>Undef</td>
</tr>
<tr>
<td><strong>ORN3a, #4180</strong></td>
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<td></td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean</td>
<td>30.0</td>
<td>18.3</td>
<td>18.3</td>
<td>23.3</td>
<td>10.0</td>
<td>31.3</td>
<td>18.3</td>
<td>22.3</td>
<td>17.3</td>
<td>10.7</td>
</tr>
<tr>
<td>Median</td>
<td>15.0</td>
<td>20.0</td>
<td>18.3</td>
<td>20.0</td>
<td>10.0</td>
<td>15.0</td>
<td>20.0</td>
<td>27.0</td>
<td>25.0</td>
<td>5.0</td>
</tr>
<tr>
<td>Inter-Quartile Range</td>
<td>48.8</td>
<td>18.8</td>
<td>Undef</td>
<td>37.5</td>
<td>Undef</td>
<td>45.8</td>
<td>11.3</td>
<td>15.0</td>
<td>20.3</td>
<td>20.3</td>
</tr>
<tr>
<td><strong>ORN2, #4200</strong></td>
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<td></td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean</td>
<td>13.0</td>
<td>11.7</td>
<td>15.7</td>
<td>32.7</td>
<td>27.0</td>
<td>9.0</td>
<td>9.0</td>
<td>19.7</td>
<td>37.0</td>
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<tr>
<td>Median</td>
<td>6.0</td>
<td>12.0</td>
<td>20.0</td>
<td>28.0</td>
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<td>7.0</td>
<td>7.0</td>
<td>9.0</td>
<td>50.0</td>
<td>26.0</td>
</tr>
<tr>
<td>Inter-Quartile Range</td>
<td>20.3</td>
<td>12.8</td>
<td>14.3</td>
<td>22.5</td>
<td>22.5</td>
<td>15.0</td>
<td>15.0</td>
<td>2.25</td>
<td>30.8</td>
<td>37.5</td>
</tr>
<tr>
<td><strong>ORN1b, #4220</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<td></td>
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<td></td>
</tr>
<tr>
<td>Mean</td>
<td>8.3</td>
<td>5</td>
<td>18.3</td>
<td>11.7</td>
<td>56.7</td>
<td>24.3</td>
<td>14.3</td>
<td>12.7</td>
<td>16.7</td>
<td>32.0</td>
</tr>
<tr>
<td>Median</td>
<td>5.0</td>
<td>5.0</td>
<td>5.0</td>
<td>11.7</td>
<td>75.0</td>
<td>13.0</td>
<td>20.0</td>
<td>10.0</td>
<td>16.7</td>
<td>16.0</td>
</tr>
<tr>
<td>Inter-Quartile Range</td>
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<td>7.5</td>
<td>37.5</td>
<td>Undef</td>
<td>56.3</td>
<td>45.0</td>
<td>17.3</td>
<td>21.0</td>
<td>Undef</td>
<td>60.0</td>
</tr>
<tr>
<td><strong>ORN1a, #4240</strong></td>
<td></td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Mean</td>
<td>4.7</td>
<td>4.7</td>
<td>13.3</td>
<td>19.3</td>
<td>58.0</td>
<td>5.3</td>
<td>5.3</td>
<td>18.7</td>
<td>25.3</td>
<td>45.3</td>
</tr>
<tr>
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<td>4.0</td>
<td>4.0</td>
<td>10.0</td>
<td>20.0</td>
<td>54.0</td>
<td>6.0</td>
<td>6.0</td>
<td>11.0</td>
<td>35.0</td>
<td>41.0</td>
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<td>Inter-Quartile Range</td>
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<td>7.5</td>
<td>22.5</td>
<td>13.5</td>
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<td>71.3</td>
</tr>
<tr>
<td><strong>ORN0, #4260</strong></td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean</td>
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<td>1.3</td>
<td>4</td>
<td>12.3</td>
<td>81.7</td>
<td>2.0</td>
<td>2.0</td>
<td>9.0</td>
<td>17.0</td>
<td>70.0</td>
</tr>
<tr>
<td>Median</td>
<td>0.7</td>
<td>1.3</td>
<td>5.0</td>
<td>12.0</td>
<td>80.0</td>
<td>2.0</td>
<td>2.0</td>
<td>7.0</td>
<td>20.0</td>
<td>60.0</td>
</tr>
<tr>
<td>Inter-Quartile Range</td>
<td>Undef</td>
<td>Undef</td>
<td>5.3</td>
<td>3.8</td>
<td>11.3</td>
<td>Undef</td>
<td>Undef</td>
<td>15.0</td>
<td>15.8</td>
<td>30.0</td>
</tr>
</tbody>
</table>

* as explained at the bottom of the previous part of this table on the last page.
A COMPARISON OF DATA IN ITEMS 4040-4090 AND 4160-4260.

TABLE 61. # 4040-4090. RESPONDENT ASSOCIATIONS OF CATEGORIZED PAIN AND FUNCTION WITH CATEGORIZED ORN, AS PERCENTAGES

[= Item 4040-4090 data reinterpreted, with frequency in each ORN and Function/Pain Category scaled to total 100. (N.B.: 8 respondents cited 8 to 11 "P" or "F" per ORN Category.)]

<table>
<thead>
<tr>
<th>n = 8</th>
<th>P4</th>
<th>P3</th>
<th>P2</th>
<th>P1</th>
<th>P0</th>
<th>F4</th>
<th>F3</th>
<th>F2</th>
<th>F1</th>
<th>F0</th>
</tr>
</thead>
<tbody>
<tr>
<td>ORN3b</td>
<td>46</td>
<td>36</td>
<td>18</td>
<td>0</td>
<td>0</td>
<td>64</td>
<td>18</td>
<td>9</td>
<td>9</td>
<td>0</td>
</tr>
<tr>
<td>ORN3a</td>
<td>10</td>
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<td>50</td>
<td>10</td>
<td>0</td>
<td>9</td>
<td>54</td>
<td>28</td>
<td>9</td>
<td>0</td>
</tr>
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<td>ORN2</td>
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<td>9</td>
<td>36</td>
<td>46</td>
<td>0</td>
<td>9</td>
<td>18</td>
<td>55</td>
<td>18</td>
<td>0</td>
</tr>
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<td>ORN1b</td>
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<td>20</td>
<td>40</td>
<td>30</td>
<td>18</td>
<td>9</td>
<td>36.5</td>
<td>36.5</td>
<td>0</td>
</tr>
<tr>
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<td>10</td>
<td>60</td>
<td>30</td>
<td>0</td>
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<td>11</td>
<td>67</td>
<td>22</td>
</tr>
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<td>0</td>
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<td>0</td>
<td>0</td>
<td>11</td>
<td>89</td>
<td></td>
</tr>
</tbody>
</table>

TABLE 62. #4160-4260 PERCENTAGE DISTRIBUTION OF CATEGORIZED PAIN AND FUNCTION IN ORN CATEGORIES (5 RESPONDENTS)

[= ITEM 4160-4260 DATA REPEATED FOR COMPARISON WITH THE ABOVE TABLE]

<table>
<thead>
<tr>
<th>n = 5</th>
<th>P4</th>
<th>P3</th>
<th>P2</th>
<th>P1</th>
<th>P0</th>
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<th>F3</th>
<th>F2</th>
<th>F1</th>
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<td>8</td>
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<td>30</td>
<td>19</td>
<td>19</td>
<td>22</td>
<td>10</td>
<td>31</td>
<td>26</td>
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<td>9.5</td>
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<tr>
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<td>16</td>
<td>19</td>
<td>17.5</td>
<td>27.5</td>
<td>20.</td>
<td>13.5</td>
<td>13.5</td>
<td>24</td>
<td>30</td>
<td>19</td>
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<td>18.5</td>
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<td>47</td>
<td>18</td>
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<td>9</td>
<td>18</td>
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<td>19</td>
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<td>36</td>
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<td>2.2</td>
<td>2</td>
<td>8.4</td>
<td>13</td>
<td>74</td>
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TABLE 63. "MEANS" OF #4040-4090 AND #4160-4260 DATA PERCENTAGES

<table>
<thead>
<tr>
<th>P4</th>
<th>P3</th>
<th>P2</th>
<th>P1</th>
<th>P0</th>
<th>F4</th>
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<td>4.2</td>
<td>12.1</td>
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</table>

372
### RELIABILITY

#### TABLE 70. SUMMARY OF MEASURES OF ASSOCIATION AND DISPERSION, IN ITEMS ASSOCIATED WITH RELIABILITY CALCULATIONS.

<table>
<thead>
<tr>
<th>Item</th>
<th>Agreement Median</th>
<th>75 - 25 IQ</th>
<th>Confidence Median</th>
<th>75 - 25 IQ</th>
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<tbody>
<tr>
<td>1160</td>
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<td>2.1</td>
<td>6.1</td>
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</tr>
<tr>
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<td>3.2</td>
<td>6.2</td>
<td>1.8</td>
</tr>
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<td>5.3</td>
<td>2.6</td>
<td>6.0</td>
<td>1.6</td>
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<table>
<thead>
<tr>
<th>Item</th>
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<th>75 - 25 IQ</th>
<th>Confidence Median</th>
<th>75 - 25 IQ</th>
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<tbody>
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<td>1.6</td>
<td>6.4</td>
<td>1.1</td>
</tr>
</tbody>
</table>

#### TABLE 71. DATA PAIRS FOR RELIABILITY COMPARISONS.

(Unmatched sets in the table have been placed into subscript. These do not enter into reliability analysis.)

<table>
<thead>
<tr>
<th>Respondent</th>
<th>Agreement 1160</th>
<th>Agreement 3920</th>
<th>Confidence 1160</th>
<th>Confidence 3920</th>
<th>Agreement 1790</th>
<th>Agreement 1810</th>
<th>Confidence 1790</th>
<th>Confidence 1810</th>
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</thead>
<tbody>
<tr>
<td>1</td>
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<td>6</td>
<td>6</td>
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<td>7</td>
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</tr>
</tbody>
</table>

Kappa \(0.3\) including {7, 1}

Kappa \(0.4\) excluding {7, 1}
APPENDIX 2. LETTERS AND FORMS SENT TO RESPONDENTS

Form A-2

WHETHER OR NOT YOU PARTICIPATE IN MY STUDY, PLEASE COMPLETE THE FOLLOWING:

I, [NAME:], would consider the input of the following clinical experts in the prevention and minimization of osteoradionecrosis critical to achieving an adequate sampling of the range of expert informed opinion:

(N.B.: Fill in as few names, or as many, as you wish.)

Reimburse me for postage.

1. Name: .................................................................
   Title: ........................................................................
   Institution: ..................................................................
   City: ...........................................................................
   Specialty (e.g., Oral Medicine Specialist, Surgeon, Radiation Oncologist, Prosthodontist:)

2. Name: .................................................................
   Title: ........................................................................
   Institution: ..................................................................
   City: ...........................................................................
   Specialty (e.g., Oral Medicine Specialist, Surgeon, Radiation Oncologist, Prosthodontist:)

3. Name: .................................................................
   Title: ........................................................................
   Institution: ..................................................................
   City: ...........................................................................
   Specialty (e.g., Oral Medicine Specialist, Surgeon, Radiation Oncologist, Prosthodontist:)

.................................................................
APPENDIX 2. LETTERS AND FORMS SENT TO RESPONDENTS

4. Name: 
Title: 
Institution: 
City: 
Specialty (e.g., Oral Medicine Specialist, Surgeon, Radiation Oncologist, Prosthodontist:)

5. Name: 
Title: 
Institution: 
City: 
Specialty (e.g., Oral Medicine Specialist, Surgeon, Radiation Oncologist, Prosthodontist:)

..................
WHETHER OR NOT YOU WISH TO PARTICIPATE IN THE SURVEY, PLEASE COMPLETE THE FOLLOWING STATEMENT AND MAIL THE FORM TO ME:

I, ...................................., [name = optional] would consider the participation of the following clinical experts in the prevention of osteoradionecrosis important to this Delphi survey: (N.B.: Please fill in as few, or as many, as you wish.)

1. Name: .................................................................
   Title: .................................................................
   Institution: ..........................................................
   City: .................................................................
   Specialty (e.g., Oral Medicine Specialist, Surgeon, Radiation Oncologist, Prosthodontist:)
   .................................................................

2. Name: .................................................................
   Title: .................................................................
   Institution: ..........................................................
   City: .................................................................
   Specialty (e.g., Oral Medicine Specialist, Surgeon, Radiation Oncologist, Prosthodontist:)
   .................................................................

3. Name: .................................................................
   Title: .................................................................
   Institution: ..........................................................
   City: .................................................................
   Specialty (e.g., Oral Medicine Specialist, Surgeon, Radiation Oncologist, Prosthodontist:)
   .................................................................
A primary objective of this survey is to gather data to help solve the research question, "When should teeth in the high dose radiation volume be extracted in order to minimize osteoradionecrosis?" Toward this end, data from the literature will be augmented with information from this survey synthesizing your and other experts' clinical experience and perceptions. Data then will be abstracted into a framework for analysis, e.g., a decision tree.

An example of a simple decision tree is:

\[
\begin{align*}
\text{Average probability} & \quad \text{(UTILITY:)} \\
\text{of ORN occurrence,} & \quad \text{given "Yes,"} = a \\
\text{YES} & \quad \text{Average quality} \\
\text{-------------------------} & \quad \text{of life, given} \\
\text{"Yes,"} = b \\
\text{EXTRACT X TEETH?} & \\
\text{NO} & \quad \text{Average quality} \\
\text{-------------------------} & \quad \text{of life, given} \\
\text{Average probability} & \quad \text{"No,"} = d \\
\text{of ORN occurrence,} & \quad \text{given "No,"} = c
\end{align*}
\]

where "a" and "c" are ORN frequency variables, and "b" and "d" are utility (i.e., outcome) variables, and the average relative desirability for the choice "Yes" branch of the decision tree is "a" multiplied by "b," and for the choice "No" is "c" multiplied by "d."

In this illustration, the only example of a "decision node" is "Extract?" However, with multiple decision nodes, or with multi-attribute frequency or utility variables, the relative desirability of the two "branches" of the "decision tree" may reverse for certain values of the variables \(a, b, c,\) and \(d.\) (Sometimes \(a, b, c,\) and \(d\) themselves may be multi-attribute variables with their values determined in turn by the values of contributory variables.)

Sometimes a single decision can have multiple outcomes that are divorced from any future influence of the caregiver. For instance, the decision "Yes" might generate some chance of death, some chance of survival with unavoidable functional deficit, and some chance of survival with potential for complete prosthodontic rehabilitation. The choice "Yes", having multiple potential outcomes, then would be termed a "probability node." The relative desirabilities of the branches "Yes" and "No" could reverse if "Yes" and "No" generate different outcome probability distributions.
iii. OVERVIEW OF SURVEY CONTENTS:

SECTION A: OPEN-ENDED ITEMS  
(e.g., "List...")

I. Criteria for defining osteoradionecrosis (ORN).
   Criteria for deciding when and how to extract teeth. Characteristics of ORN lesions, etc.
   ....Page 5.

II. Technical and epidemiological factors that may influence your clinical perspectives. ....Page 14.

SECTION B: CLOSE-ENDED ITEMS  
(e.g., "Circle the number...")

I. Definition of osteoradionecrosis (ORN) .....Page 18.

II. Criteria for decisions to extract teeth in cases at risk for ORN. Effects on decision-making, and characteristics of, related factors and techniques.
   ....Page 19.

III. The effects on the prognosis for ORN of various factors.
   ....Page 37.

IV. " , Scenario-based.
   ....Page 44.

V. ORN outcomes: characteristics and distributions.
   ....Page 53.

iv. INTRODUCTORY NOTES:

1. **THIS SURVEY AND PROJECT WILL BE SEVERELY COMPROMISED IF EXCHANGE OF INFORMATION BETWEEN RESPONDENTS, OR BETWEEN PARTS A. AND B. OF THE SURVEY, CROSS-CONTAMINATES THE DATA. PLEASE NEVER DISCUSS THIS SURVEY WITH ANY OTHER POTENTIAL PARTICIPANTS UNTIL ALL ROUNDS ARE COMPLETED. PLEASE DO NOT REVISE YOUR SECTION A. STATEMENTS OF OPINION AFTER READING SUBSEQUENT SECTIONS. THANK YOU.**

2. **PLEASE ENSURE LEGIBILITY! THANK YOU.**

3. No inferences about the number or types of responses desired should be drawn from the number of lines provided for open-ended items.
4. For items with response lines that include a column on the left, e.g.

- first please list the indicated information in point form on separate lines, then
- RANK the importance of each point of information in the left column.
- Always use "1" to indicate the most important point.

NOTE - IT IS PERMISSIBLE TO RANK DIFFERENT LINES AS EQUAL IN IMPORTANCE, AND TO FORM GROUPS OF POINTS OF EQUAL IMPORTANCE. (Simply assign them the same "rank".)

5. No inferences should be drawn that suppositions included in items are correct. You must decide whether the assumption is valid or invalid, then decide either to
a. agree or disagree with the statement, or
b. explain or not explain,
as appropriate to the item, based on that decision.

6. MISCELLANEOUS NOTES ON SURVEY DESIGN:
Some survey questions are redundant. This is intentional and necessary.
References purposely have been omitted from this edition of the survey to avoid coloring the responses.
Most items will appear in one of a small variety of formats. This should facilitate the ease of completion of the survey.
Some items will include scenarios. Scenarios facilitate easy comparison of the effects on ORN of a variety of variables.
The second and third iterations of this survey will present statistical summaries of much of the data from this iteration, and may take one half as much time to complete as this iteration.

NOW, THE SURVEY! MANY THANKS FOR YOUR PARTICIPATION.
I EXPECT THAT YOU WILL FIND BOTH THE PROCESS AND THE RESULTS VERY INTERESTING. REMEMBER THAT YOU ARE WELCOME TO SUGGEST ADDITIONAL QUESTIONS OR MAKE OTHER SUGGESTIONS. (FOR FURTHER INFORMATION, PLEASE SEE TITLE PAGE.)
APPENDIX 3  DELPHI SURVEY

ROUND ONE  SECTION A.  PREDOMINANTLY OPEN-ENDED ITEMS.

A.I.  ORN.:  

1. My current criteria for defining ORN, listed in point form, are:

- 
- 
- 
- 

2. Very briefly, my description of the etiology/pathophysiology of ORN is:

- 
- 
- 
- 

3. My important criteria for diagnosing ORN are:

- 
- 
- 
- 

(Was importance ranked, 1 = most important?)

4. My important criteria for classifying the medical severity of an osteoradionecrotic lesion are:

- 
- 
- 
- 

(Was importance ranked, 1 = most important?)

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5. Characteristics and complications of ORN that I believe could affect a patient's quality of life are the following:

(Assert to view and rank the importance of factors from the perspective of the patient.)

---

6. I believe that the clinical presentation of osteoradionecrotic lesions typical of the maxilla differ from those of the mandible.

My feelings about the last statement are: [Circle a number:]

I DISAGREE 1 2 3 4 5 6 7 I AGREE

VERY STRONGLY I AM VERY My confidence in this answer is: VERY STRONGLY

UNCERTAIN 1 2 3 4 5 6 7 CERTAIN

The difference, if any, is:

---

7. I believe that osteoradionecrotic lesions in the maxilla have different effects on the quality of life than do osteoradionecrotic lesions in the mandible.

My feelings about the last statement are: [Circle a number:]

I DISAGREE 1 2 3 4 5 6 7 I AGREE

VERY STRONGLY I AM VERY My confidence in this answer is: VERY STRONGLY

UNCERTAIN 1 2 3 4 5 6 7 CERTAIN
The difference, if any, is:

8. I believe that the clinical presentation of osteoradionecrotic lesions typical of one part of the mandible differ from those typical of some other part(s) of the mandible.

My feelings about the last statement are: [Circle a number:]

I DISAGREE    1 2 3 4 5 6 7 I AGREE
VERY STRONGLY  I AM VERY 1 2 3 4 5 6 7 CERTAIN

The difference, if any, is:

9. I believe that osteoradionecrotic lesions typical of one part of the mandible have different effects on the quality of life than do osteoradionecrotic lesions typical of some other part(s) of the mandible.

My feelings about the last statement are: [Circle a number:]

I DISAGREE    1 2 3 4 5 6 7 I AGREE
VERY STRONGLY  I AM VERY 1 2 3 4 5 6 7 CERTAIN

The difference, if any, is:
10. My major criteria (indications) for extracting teeth in the future high dose radiation volume are:

<table>
<thead>
<tr>
<th>Importance Rank</th>
<th>Characteristic</th>
<th>Severity Impact</th>
</tr>
</thead>
<tbody>
<tr>
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</tr>
</tbody>
</table>

11.a. Case characteristics that I think increase the risk (i.e., expected frequency) of ORN are:

{N.B.: Examples might be specific types of oral/dental tissue pathology; anatomic/physiologic variation; systemic circulatory or metabolic pathology.}
Please use a separate sheet of paper if you need more space. (Was importance ranked, 1 = most important?)

b. [Theoretically, it may be possible that one condition predisposing ORN may produce ORNS all rather mild and self-limiting, while another may create ORNS that, proportionally, are much more severe or aggressive.]

Reviewing my list from the item part a. above, I recognize that certain of the factors listed predispose outcomes relatively more mild or severe than the average.

<table>
<thead>
<tr>
<th>My feelings about the last statement are:</th>
<th>Circle a number:</th>
</tr>
</thead>
<tbody>
<tr>
<td>I DISAGREE 1 2 3 4 5 6 7 I AGREE</td>
<td></td>
</tr>
<tr>
<td>VERY STRONGLY</td>
<td></td>
</tr>
<tr>
<td>I AM VERY MY CONFIDENCE IN THIS ANSWER IS:</td>
<td>VERY STRONGLY</td>
</tr>
<tr>
<td>UNCERTAIN 1 2 3 4 5 6 7 CERTAIN</td>
<td></td>
</tr>
</tbody>
</table>

c. If any factors listed in a. above influence the relative distribution of severity outcomes, please write in the right-hand "Severity" column a "+" when the factor tends to promote an unusually severe ORN, or a "-" when the factor tends to promote unusually mild ORN.
12. Forseeable dental, medical, or surgical cancer treatments in addition to radiotherapy that increase the likelihood that I would extract teeth prior to radiotherapy, as an ORN-prophylactic measure, are:

________________________________________________________________________________________

________________________________________________________________________________________

________________________________________________________________________________________

________________________________________________________________________________________

________________________________________________________________________________________

________________________________________________________________________________________

________________________________________________________________________________________

(Was importance ranked, 1 = most important?)

13. My decision to extract mandibular teeth during the pre-radiotherapy window is influenced by these aspects of the radiotherapy treatment plan:

________________________________________________________________________________________

________________________________________________________________________________________

________________________________________________________________________________________

________________________________________________________________________________________

________________________________________________________________________________________

________________________________________________________________________________________

________________________________________________________________________________________

________________________________________________________________________________________

________________________________________________________________________________________

________

(Was importance ranked, 1 = most important?)
14. Radiotherapeutic techniques and radiotherapy technical characteristics that I think will reduce the risk of ORN are:

(Was importance ranked, 1 = most important?)

15. I think that there are conditions under which a tooth with unchanged indications for extraction may be extracted in the high dose radiation volume after, rather than prior to, radiotherapy, with a lesser risk of ORN.

My feelings about the last statement are: [Circle a number:]

I DISAGREE 1 2 3 4 5 6 7 I AGREE

VERY STRONGLY I AM VERY MY confidence in this answer is: VERY STRONGLY I AM VERY

UNCERTAIN 1 2 3 4 5 6 7 CERTAIN

The rationale for my answer, and description of relevant conditions, if any, is the following:
16. **Dental extraction techniques/principles that I believe are important for minimizing ORN are:**

(Was importance ranked, 1 = most important?)

17. I find that the most clinically useful predictors of future oral hygiene performance are:

(Was importance ranked, 1 = most important?)

18. I find that the most clinically useful predictors of future compliance with recommended oral home care therapy (e.g., fluoride mouth trays) are:

(Was importance ranked, 1 = most important?)

19. **AN OPTIONAL ITEM** FOR PERSONS PARTICULARLY INTERESTED:

Background for OPTIONAL ITEM:

Dentists do not need to debate very often the relative desirabilities of placing, or not placing, a conservative restoration; thus, a dilemma usually is absent.

Clinical dilemmas occur when the relative merits of choosing among two courses of action are not clear. For instance, if one assumes that

a. extracting dentally diseased teeth prior to radiation therapy can decrease the incidence of ORN, and

b. ORN greatly impacts the quality of life of the
APPENDIX 3  DELPHI SURVEY

3. Some of these extracted teeth could have been salvaged in other circumstances and contributed to the quality of life of the patient, then one can state a primary clinical dilemma:

Can the extraction of indicated teeth prior to radiotherapy be justified if these extractions adversely impact the majority who would not develop ORN in any case, and if so, when?

[OPTIONAL ITEM, concluded:]
Other clinical dilemmas that I recognize as related to ORN (if any,) are:

(Was importance ranked, 1 = most important, and was the original, typewritten dilemma included in this ranking?)
A.II. TECHNICAL AND EPIDEMIOLOGICAL FACTORS THAT MAY BEAR ON MY PERSONAL EXPERIENCE AS AN OBSERVER/MANAGER OF ORN:

1.a. The nature of my practice is (oral surgery, prosthodontics, oral medicine, oncology, etc.):

b. I have practiced in this capacity _____ years.

c. My clinical degrees etc., and dates of graduation, are:

   Degree/etc.: ............ Year: ............
   Degree/etc.: ............ Year: ............
   Degree/etc.: ............ Year: ............

d. The cities where I have performed cancer-related practice during the past decade are:

   City: ......................... Years: ............
   City: ......................... Years: ............

2. The voltages and alternative sources of external beam radiation used in my clinic(s) over the past 10 years, and the proportion of total cases of oropharyngeal squamous cell carcinoma treated with each type, are:

   ............................................... ; ........ %
   ............................................... ; ........ %
   ............................................... ; ........ %

   [ N.B.: The next three questions request mean incidence numbers for the period 1992-1994. IF PRACTICAL, please refer to official oncology center statistics before providing the information, and indicate that the figures below have such references by placing a tick (✓) here:

   The figures below otherwise will be assumed to be approximate "best recollections." ]

3. The annual number of new cases of oropharyngeal squamous cell carcinoma treated in my oncology clinic(s) is _____.

4. The annual number of cases in my oncology clinic(s) receiving, for the first time, external beam (including
5. The annual mean number of new cases of active ORN seen in my oncology clinic(s) is ______.

6. The trend in the incidence of ORN in my clinic is:

"Background" for next few Items:

Certain perceptions of ORN may vary from one expert to another since one's experience may derive partly from factors not universally shared by others. Some instances of these factors may be:
- a clinic may have received a new, higher-voltage external beam radiation source 5 years sooner or later than the average;
- a clinic may or may not have instituted dental routines prophylactic for ORN by a certain year;
- a locale's experience of squamous cell carcinoma may be different than others or the average;
- a clinic's rate of ORN may be higher or lower than average.

7.a. Radiotherapeutic technical factors and clinical management routines that I think realistically could vary from one oncology clinic to another, thus altering clinicians' experience with ORN and potentially biasing perceptions of ORN effects and incidences, are:

7.b. Please rank the relative importances (1 = most important.)
8.a. **Major dental management practices** that I think *could* vary from one oncology clinic to another, thus altering clinicians' experience with ORN and potentially biasing perceptions of ORN effects and incidences, are:

__________________________
__________________________
__________________________
__________________________
__________________________
__________________________
__________________________
__________________________

8.b. Please rank the relative importances (1 = most important.)
8.c. Please circle the factors possibly personally applicable.

9.a. **Surgical management practices** that I think *could* vary from one oncology clinic to another, thus altering clinicians' experience with ORN and potentially biasing perceptions of ORN effects and incidences, are:

__________________________
__________________________
__________________________
__________________________
__________________________
__________________________
__________________________
__________________________
__________________________

9.b. Please rank the relative importances (1 = most important.)
9.c. Please circle the factors possibly personally applicable.
10. a. Clinical management practices not mentioned in 7., 8., 9., or 10. above, that I realistically think could vary from one oncology clinic to another, thus altering clinicians' experience with ORN and potentially biasing perceptions of ORN effects and incidences, are:

10. b. Please rank the relative importances (1 = most important.)

10. c. Please circle the factors possibly personally applicable.
ROUND ONE  SECTION B, PREDOMINANTLY CLOSE-ENDED ITEMS.

I. DEFINITIONS:

1. I think that ORN is better defined as:
   (Circle a. or b., please.)
   a. "an exposure of nonviable irradiated bone, which fails to heal without intervention."
   OR
   b. "an exposure of nonviable irradiated bone, which fails to heal without intervention, for 'X' time,"

   where 'X', if adopted as a routine standard for most clinical studies, should be:
   (Circle one, please.)
   a. any duration (thus, time of exposure is irrelevant.)
   b. 1 month or longer
   c. 2 months "
   d. 3 months "
   e. 4 months "
   f. 6 months "
   g. 9 months "
   h. 12 months "
   i. OTHER (Please state:)

   I AM VERY Uncertain My confidence in this answer is: I AM VERY
   VERY STRONGLY
   CERTAIN
   (Please circle a Number)

   (Note: References are omitted from this survey edition.)

2. I think that the adjective "nonviable" (as in "nonviable irradiated bone") should not be part of a definition of osteoradionecrosis, since the viability of exposed bone would be difficult to determine clinically.

   My feelings about the last statement are: (Circle a number:)
   I DISAGREE 1 2 3 4 5 6 7 I AGREE
   VERY STRONGLY
   I AM VERY Uncertain My confidence in this answer is: I AM VERY
   VERY STRONGLY
   CERTAIN
   (Note: References are omitted from this survey edition.)

3. I think that the phrase "in the absence of tumor" should an integral part of a definition for osteoradionecrosis.

   My feelings about the last statement are: (Circle a number:)
   I DISAGREE 1 2 3 4 5 6 7 I AGREE
   VERY STRONGLY
   I AM VERY Uncertain My confidence in this answer is: I AM VERY
   VERY STRONGLY
   CERTAIN
   (Note: References are omitted from this survey edition.)

(403)
II. CRITERIA FOR DECISION TO EXTRACT: EFFECTS OF TREATMENT.

1. Other things being equal, if the risk of ORN from non-dental causes increases, I will be more likely to recommend extraction of teeth.

   My feelings about the last statement are: [Circle a number:]
   
   I DISAGREE 1 2 3 4 5 6 7 I AGREE
   VERY STRONGLY — — — — — — — — VERY STRONGLY
   I AM VERY My confidence in this answer is: I AM VERY
   UNCERTAIN 1 2 3 4 5 6 7 CERTAIN

2. Other things being equal, if the risk of ORN from dental causes increases, I will be more likely to extract the teeth involved.

   My feelings about the last statement are: [Circle a number:]
   
   I DISAGREE 1 2 3 4 5 6 7 I AGREE
   VERY STRONGLY — — — — — — — — VERY STRONGLY
   I AM VERY My confidence in this answer is: I AM VERY
   UNCERTAIN 1 2 3 4 5 6 7 CERTAIN

3. I think that patients with teeth can, under some circumstances, be expected to experience a lower frequency of ORN than chronically edentulous patients.

   My feelings about the last statement are: [Circle a number:]
   
   I DISAGREE 1 2 3 4 5 6 7 I AGREE
   VERY STRONGLY — — — — — — — — VERY STRONGLY
   I AM VERY My confidence in this answer is: I AM VERY
   UNCERTAIN 1 2 3 4 5 6 7 CERTAIN

4. I favor the extraction of all mandibular teeth in the high dose radiation volume.

   My feelings about the last statement are: [Circle a number:]
   
   I DISAGREE 1 2 3 4 5 6 7 I AGREE
   VERY STRONGLY — — — — — — — — VERY STRONGLY
   I AM VERY My confidence in this answer is: I AM VERY
   UNCERTAIN 1 2 3 4 5 6 7 CERTAIN

5. The following statements closely reflect my personal treatment philosophies for patients soon to receive radiotherapy involving the mandible:
   (Please circle the letters of all relevant statements:)
   
   a. Extract all teeth in the mouth.
   b. Extract all mandibular teeth.
   c. Extract all teeth in the high dose radiation volume.
d. Extract all mandibular teeth in the high dose radiation volume.
e. Extract all mandibular teeth in the high dose radiation volume that have an infection of periodontal origin.
f. Extract all mandibular teeth in the high dose radiation volume that have a history of severe periodontal disease.
g. Extract all mandibular teeth in the high dose radiation volume that have a history of moderate periodontal disease.
h. Extract all mandibular teeth in the high dose radiation volume that have a history of mild periodontal disease.
i. Extract all mandibular teeth in the high dose radiation volume that have an infection of endodontic origin.
j. Extract all mandibular teeth in the high dose radiation volume that have a periapical lesion.
k. Extract all mandibular teeth in the high dose radiation volume that have a history of endodontic treatment (even if apparently successful, i.e. asymptomatic and without apparent residual periapical lesion.)
l. Consider retaining a periodontally-involved tooth particularly important for prosthodontic rehabilitation, that otherwise might be extracted.
m. Consider retaining an endodontically-involved tooth particularly important for prosthodontic rehabilitation, that otherwise might be extracted.
n. [OPTIONAL] Other (Please explain:)

—

o. [OPTIONAL] Other (Please explain:)

—

6. Assuming that a patient, an otherwise healthy 60 year old male requires mandibular tooth extractions in a future high dose radiation volume, the number of post-extraction days prior to radiotherapy that:

a. I would recommend is:

PLEASE CIRCLE ONE:
1 2 3 4 5 6 7 8 9 10 12 14 16 18 20 22 24 26 days.

I AM VERY My confidence in this answer is: I AM VERY 
UNCERTAIN 1 2 3 4 5 6 7 CERTAIN
b. I would consider the absolute minimum is:  

1520  

PLEASE CIRCLE ONE:  

1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 days.  

I AM VERY My confidence in this answer is: I AM VERY  

UNCERTAIN 1 2 3 4 5 6 7 CERTAIN  

(Please circle a Number)  

PLEASE NOTE: UNLESS OTHERWISE STATED, ALL "TEETH" MENTIONED IN SUBSEQUENT ITEMS OF THIS SECTION ARE IN THE HIGH DOSE RADIATION VOLUME.  

7. I think that extracting certain types of dentally-  

diseased teeth prior to radiotherapy can decrease the expected incidence of ORN, compared to no extraction.  

My feelings about the last statement are: [Circle a number:]  

I DISAGREE 1 2 3 4 5 6 7 I AGREE  

VERY STRONGLY ———— Very STRONGLY  

I AM VERY My confidence in this answer is: I AM VERY  

UNCERTAIN 1 2 3 4 5 6 7 CERTAIN  

(Please circle a Number)  

8. I think that extracting certain types of dentally-  

diseased teeth after radiotherapy can decrease the expected incidence of ORN, compared to no extraction.  

My feelings about the last statement are: [Circle a number:]  

I DISAGREE 1 2 3 4 5 6 7 I AGREE  

VERY STRONGLY ———— Very STRONGLY  

I AM VERY My confidence in this answer is: I AM VERY  

UNCERTAIN 1 2 3 4 5 6 7 CERTAIN  

(Please circle a Number)  

9. Assuming that extraction sites are allowed "adequate"  

time for healing prior to radiotherapy, if I state,  

"ORN occurs 'X' times as frequently when teeth are extracted after radiotherapy, rather than before, other things being equal," then 'X' =:  

Please circle one:  

0.4 0.5 0.6 0.7 0.85 1.0 1.2 1.4 1.7 2.0 2.4 2.8  

or  

I AM VERY My confidence in this answer is: I AM VERY  

UNCERTAIN 1 2 3 4 5 6 7 CERTAIN  

(Please circle a Number)
10. To reduce the risk of ORN following the extraction of a tooth, I consider that it is more important to achieve primary soft-tissue closure (even if this requires very aggressive osteoplasty,) than it is important to minimize osseous trauma.

My feelings about the last statement are: [Circle a number:]

I DISAGREE 1 2 3 4 5 6 7 I AGREE
VERY STRONGLY
I AM VERY My confidence in this answer is: VERY STRONGLY
UNCERTAIN 1 2 3 4 5 6 7 CERTAIN

11. To reduce the risk of ORN following the extraction of a tooth, I believe it important to place an intra-alveolar dressing.

My feelings about the last statement are: [Circle a number:]

I DISAGREE 1 2 3 4 5 6 7 I AGREE
VERY STRONGLY
I AM VERY My confidence in this answer is: VERY STRONGLY
UNCERTAIN 1 2 3 4 5 6 7 CERTAIN

12. To reduce the risk of ORN following the extraction of a tooth, I believe it important to place an intra-alveolar dressing with topical antibiotic.

My feelings about the last statement are: [Circle a number:]

I DISAGREE 1 2 3 4 5 6 7 I AGREE
VERY STRONGLY
I AM VERY My confidence in this answer is: VERY STRONGLY
UNCERTAIN 1 2 3 4 5 6 7 CERTAIN

13. To reduce the risk for ORN following the extraction of a tooth, I believe it important to provide antibiotic coverage prior to, and during, the extraction.

My feelings about the last statement are: [Circle a number:]

I DISAGREE 1 2 3 4 5 6 7 I AGREE
VERY STRONGLY
I AM VERY My confidence in this answer is: VERY STRONGLY
UNCERTAIN 1 2 3 4 5 6 7 CERTAIN

14. To reduce the risk for ORN following the extraction of a tooth, I believe it important to provide chronic antibiotic coverage to patients at risk for ORN.

My feelings about the last statement are: [Circle a number:]

I DISAGREE 1 2 3 4 5 6 7 I AGREE
VERY STRONGLY
I AM VERY My confidence in this answer is: VERY STRONGLY
UNCERTAIN 1 2 3 4 5 6 7 CERTAIN
15. I believe that hermetic (air-tight) soft-tissue closure following the extraction of a tooth is required to minimize the risk of ORN.

My feelings about the last statement are: [Circle a number:]

I DISAGREE 1 2 3 4 5 6 7 I AGREE
VERY STRONGLY 1 2 3 4 5 6 7 I AM VERY
I AM VERY My confidence in this answer is: I AM VERY STRONGLY
UNCERTAIN 1 2 3 4 5 6 7 CERTAIN

16. I believe that the risk for ORN could be reduced by requiring patients to undergo naso-gastric feeding while a tooth extraction site heals.

My feelings about the last statement are: [Circle a number:]

I DISAGREE 1 2 3 4 5 6 7 I AGREE
VERY STRONGLY 1 2 3 4 5 6 7 I AM VERY
I AM VERY My confidence in this answer is: I AM VERY STRONGLY
UNCERTAIN 1 2 3 4 5 6 7 CERTAIN

17. I think that endodontic treatment of a tooth carries with it a significant adverse impact on the risk (expected frequency) for ORN.

My feelings about the last statement are: [Circle a number:]

I DISAGREE 1 2 3 4 5 6 7 I AGREE
VERY STRONGLY 1 2 3 4 5 6 7 I AM VERY
I AM VERY My confidence in this answer is: I AM VERY STRONGLY
UNCERTAIN 1 2 3 4 5 6 7 CERTAIN

18. I think that endodontically treating selected teeth prior to radiotherapy can decrease the expected future incidence of ORN, compared to no treatment.

My feelings about the last statement are: [Circle a number:]

I DISAGREE 1 2 3 4 5 6 7 I AGREE
VERY STRONGLY 1 2 3 4 5 6 7 I AM VERY
I AM VERY My confidence in this answer is: I AM VERY STRONGLY
UNCERTAIN 1 2 3 4 5 6 7 CERTAIN

19. I think that endodontically treating selected teeth after radiotherapy can decrease the expected future incidence of ORN, compared to no treatment.

My feelings about the last statement are: [Circle a number:]

I DISAGREE 1 2 3 4 5 6 7 I AGREE
VERY STRONGLY 1 2 3 4 5 6 7 I AM VERY
I AM VERY My confidence in this answer is: I AM VERY STRONGLY
UNCERTAIN 1 2 3 4 5 6 7 CERTAIN
20. Assuming that endodontic treatment sites are allowed "adequate" time for healing prior to radiotherapy, if I state, "ORN occurs 'X' times as frequently when teeth are treated endodontically after radiotherapy, rather than before, other things being equal," then 'X' =:

Please circle one:
0.4 0.5 0.6 0.7 0.85 1.0 1.2 1.4 1.7 2.0 2.4 2.8

I AM VERY My confidence in this answer is: I AM VERY UNCERTAIN 1 2 3 4 5 6 7 CERTAIN (Please circle a Number)

21. I think that ORN will occur less frequently if a periapically involved but otherwise sound tooth is treated endodontically rather than extracted prior to radiotherapy.

My feelings about the last statement are: [Circle a number:]
I DISAGREE 1 2 3 4 5 6 7 I AGREE
VERY STRONGLY I AM VERY My confidence in this answer is: I AM VERY UNCERTAIN 1 2 3 4 5 6 7 CERTAIN

22. Assuming that treatment sites are allowed "adequate" time for healing prior to radiotherapy, if I state, "ORN occurs 'X' times as frequently when teeth with periapical pathology are treated endodontically before radiotherapy, rather than extracted," then 'X' =:

Please circle one:
0.4 0.5 0.6 0.7 0.85 1.0 1.2 1.4 1.7 2.0 2.4 2.8

I AM VERY My confidence in this answer is: I AM VERY UNCERTAIN 1 2 3 4 5 6 7 CERTAIN (Please circle a Number)

23.a. I consider all of the following factors postulated to affect dental extraction treatment planning to be largely under my control, in the pre-radiotherapy time "window:"
1. the timing of extractions,
2. dental use of antibiotics,
3. the endodontic/caries/& restorative status of teeth (in the sense that most pathology can be rectified, unless the tooth is unrestorable)
4. the dental treatment plan (including the timing and type of dental prosthesis and liners,) and
5. the dental surgical technique.

My feelings about the last statement are: [Circle a number:]
I DISAGREE 1 2 3 4 5 6 7 I AGREE
VERY STRONGLY I AM VERY My confidence in this answer is: I AM VERY UNCERTAIN 1 2 3 4 5 6 7 CERTAIN
b. If you disagree with any of the factors above, please circle the number of the factor. Feel free to explain further, or suggest other factors:

________________________________________________________________________

________________________________________________________________________

________________________________________________________________________

________________________________________________________________________

24.a. I consider the following factors postulated to affect the prognosis for the severity of ORN, and thus my tooth extraction treatment planning, to be partially under my control:

1. the overall balance of the bite, and individual occlusal interferences in the bite
2. the effectiveness of dental procedures
3. slightly, the tumor control surgical technique, in the sense that my emphasis to the surgeon of the importance of certain oral structures to prosthodontic rehabilitation, may influence his surgery.

My feelings about the last statement are: [Circle a number:]

I DISAGREE 1 2 3 4 5 6 7 I AGREE
VERY STRONGLY _______ _______ _______ _______ _______ _______ VERY STRONGLY
I AM VERY My confidence in this answer is: I AM VERY
UNCERTAIN 1 2 3 4 5 6 7 CERTAIN

b. If you disagree with any of the factors above, please circle the number of the factor. Feel free to explain further, or suggest other factors:

________________________________________________________________________

________________________________________________________________________

________________________________________________________________________

25.a. I consider all of the following factors postulated to affect dental extraction treatment planning to be beyond my control, at least in the pre-radiotherapy time "window:"

1. the prognosis for patient survival,
2. idiopathic factors,
3. the prognosis for salivary function,
4. the pre-irradiation vitality and healing capacity of the local tissues,
5. the post-irradiation vitality and healing capacity of the local tissues,
6. the circulatory and metabolic status of the
patient,
7. the periodontal status of the patient,
8. the non-restorability of the tooth due to structural loss (e.g., due to caries),
9. the presence of Black Class II restorations near the bone,
10. parafunctional habits, if any (e.g. bruxism and clenching),
11. the patient's psychology,
12. age,
13. smoking status,
14. the urgency of radiotherapy, and
15. the radiotherapy treatment plan.
16. the factors listed the next item suggested to be under the control of the patient.

My feelings about the last statement are: [Circle a number:]
I DISAGREE 1 2 3 4 5 6 7 I AGREE
VERY STRONGLY
I AM VERY My confidence in this answer is: I AM VERY STRONGLY
UNCERTAIN 1 2 3 4 5 6 7 CERTAIN

b. If you disagree with any of the factors above, please circle the number of the factor.
Feel free to explain further, or suggest other factors:

26.a. I consider the following factors postulated to affect the caries rate, and thus the prognosis for ORN and my tooth extraction treatment planning, to be for the most part under the control of the patient, rather than me:
1. diet,
2. oral hygiene status; prognosis for same in the future, and
3. future compliance with recommended home care and therapy.

My feelings about the last statement are: [Circle a number:]
I DISAGREE 1 2 3 4 5 6 7 I AGREE
VERY STRONGLY
I AM VERY My confidence in this answer is: I AM VERY STRONGLY
UNCERTAIN 1 2 3 4 5 6 7 CERTAIN

b. If you disagree with any of the factors above, please circle the number of the factor.
Feel free to explain further or suggest other factors:
27. Infections of dental origin (whether of endodontic or periodontal origin) affect my treatment planning for ORN-prophylactic tooth extraction.

My feelings about the last statement are: [Circle a number:]

I DISAGREE 1 2 3 4 5 6 7 I AGREE
VERY STRONGLY   
I AM VERY My confidence in this answer is: I AM VERY
UNCERTAIN 1 2 3 4 5 6 7 CERTAIN

28. I can assess infections of dental origin (whether endodontic or periodontal) in a quantitative fashion.

My feelings about the last statement are: [Circle a number:]

I DISAGREE 1 2 3 4 5 6 7 I AGREE
VERY STRONGLY   
I AM VERY My confidence in this answer is: I AM VERY
UNCERTAIN 1 2 3 4 5 6 7 CERTAIN

29. I need to consider periodontal pockets, furcation classes, mobility, horizontal and vertical bone loss, etc. before establishing a treatment plan for ORN-prophylactic tooth extraction.

My feelings about the last statement are: [Circle a number:]

I DISAGREE 1 2 3 4 5 6 7 I AGREE
VERY STRONGLY   
I AM VERY My confidence in this answer is: I AM VERY
UNCERTAIN 1 2 3 4 5 6 7 CERTAIN

30. I can assess periodontal pockets, furcation classes, mobility, horizontal and vertical bone loss, etc., in a quantitative fashion.

My feelings about the last statement are: [Circle a number:]

I DISAGREE 1 2 3 4 5 6 7 I AGREE
VERY STRONGLY   
I AM VERY My confidence in this answer is: I AM VERY
UNCERTAIN 1 2 3 4 5 6 7 CERTAIN
31. I need to estimate periodontal disease activity and potential for progression through surrogates that I trust (possible examples: bleeding on probing, microbiological assays, chemical tests, etc.) before I establish a treatment plan for ORN-prophylactic tooth extraction.

My feelings about the last statement are: [Circle a number:]

I DISAGREE 1 2 3 4 5 6 7 I AGREE
 VERY STRONGLY
 I AM VERY My confidence in this answer is: I AM VERY
 UNCERTAIN 1 2 3 4 5 6 7 CERTAIN

32. I can assess periodontal pockets, furcation classes, mobility, horizontal and vertical bone loss, etc., in a quantitative fashion.

My feelings about the last statement are: [Circle a number:]

I DISAGREE 1 2 3 4 5 6 7 I AGREE
 VERY STRONGLY
 I AM VERY My confidence in this answer is: I AM VERY
 UNCERTAIN 1 2 3 4 5 6 7 CERTAIN

33. I need to consider the presence/absence/type of periapical radiolucency and endodontic symptoms/clinical history before establishing a treatment plan for ORN-prophylactic tooth extraction.

My feelings about the last statement are: [Circle a number:]

I DISAGREE 1 2 3 4 5 6 7 I AGREE
 VERY STRONGLY
 I AM VERY My confidence in this answer is: I AM VERY
 UNCERTAIN 1 2 3 4 5 6 7 CERTAIN

34. I can assess the presence/absence/type of periapical radiolucency and endodontic symptoms/clinical history, in a quantitative fashion.

My feelings about the last statement are: [Circle a number:]

I DISAGREE 1 2 3 4 5 6 7 I AGREE
 VERY STRONGLY
 I AM VERY My confidence in this answer is: I AM VERY
 UNCERTAIN 1 2 3 4 5 6 7 CERTAIN
35. I need to assess the presence/absence/type of unbalanced bite, occlusal interference, parafunctional habits e.g. bruxism and clenching, etc. (i.e. subdivisions of the factor, "Dental Occlusion,"
) before establishing a treatment plan for ORN-prophylactic tooth extraction.

My feelings about the last statement are: [Circle a number:]

I DISAGREE 1 2 3 4 5 6 7 I AGREE

VERY STRONGLY — — — — — — — — — VERY STRONGLY

I AM VERY My confidence in this answer is: I AM VERY

UNCERTAIN 1 2 3 4 5 6 7 CERTAIN

36. I can assess unbalanced bite, occlusal interference, parafunctional habits (e.g. bruxism and clenching, etc.,) in a quantitative fashion.

My feelings about the last statement are: [Circle a number:]

I DISAGREE 1 2 3 4 5 6 7 I AGREE

VERY STRONGLY — — — — — — — — — VERY STRONGLY

I AM VERY My confidence in this answer is: I AM VERY

UNCERTAIN 1 2 3 4 5 6 7 CERTAIN

37. I need to consider the prognosis for patient compliance with recommended home care therapy and oral hygiene before establishing a treatment plan for ORN-prophylactic tooth extraction.

My feelings about the last statement are: [Circle a number:]

I DISAGREE 1 2 3 4 5 6 7 I AGREE

VERY STRONGLY — — — — — — — — — VERY STRONGLY

I AM VERY My confidence in this answer is: I AM VERY

UNCERTAIN 1 2 3 4 5 6 7 CERTAIN

38. I need to consider the prognosis for patient attendance, and compliance with, recommended chair-side dental professional services, before establishing a treatment plan for ORN-prophylactic tooth extraction.

My feelings about the last statement are: [Circle a number:]

I DISAGREE 1 2 3 4 5 6 7 I AGREE

VERY STRONGLY — — — — — — — — — VERY STRONGLY

I AM VERY My confidence in this answer is: I AM VERY

UNCERTAIN 1 2 3 4 5 6 7 CERTAIN

================================================================
39. My decision whether to extract teeth depends exclusively on my assessment of the anticipated level of trauma (from all sources) to be received by the tissue in the high-dose radiation volume, in relation to the anticipated healing capacity and resistance to insult of tissue in high dose volume.

My feelings about the last statement are: [Circle a number:]

I DISAGREE 1 2 3 4 5 6 7 I AGREE
VERY STRONGLY - - - - - - - VERY STRONGLY
I AM VERY My confidence in this answer is: I AM VERY
UNCERTAIN 1 2 3 4 5 6 7 CERTAIN

EXPLANATION: [OPTIONAL !]


PLEASE NOTE THAT THE SCALE USED TO THIS POINT --

"My feelings about the last statement are: [Circle a number:]

I DISAGREE 1 2 3 4 5 6 7 I AGREE
VERY STRONGLY - - - - - - - VERY STRONGLY
I AM VERY My confidence in this answer is: I AM VERY
UNCERTAIN 1 2 3 4 5 6 7 CERTAIN"

WILL BE REPLACED WITH A "MINIATURE VERSION" IN THE NEXT TWO ITEMS. THE MINIATURE VERSION

" I DISAGREE 1 2 3 4 5 6 7 I AGREE
AM UNCERTAIN 1 2 3 4 5 6 7 AM CERTAIN"

SHOULD BE TREATED IDENTICALLY -- PLEASE recognize that "1" still indicates very strong agreement or great uncertainty, and "7" very strong agreement or certainty. THANKS.

For the remaining two items in this section, please consider the validity of the "root" in relation to the series of factors that complete the statement(s):
40. **MY DECISION WHETHER TO EXTRACT TEETH DEPENDS STRONGLY ON MY ASSESSMENT OF:**

a. **the "passive" periodontal status** (e.g., periodontal pocket depths, furcation involvements, etc.) of teeth in the high dose radiation volume.

<table>
<thead>
<tr>
<th>DISAGREE 1 2 3 4 5 6 7</th>
<th>AGREE 1 2 3 4 5 6 7</th>
</tr>
</thead>
<tbody>
<tr>
<td>AM UNCERTAIN 1 2 3 4 5 6 7</td>
<td>AM CERTAIN</td>
</tr>
</tbody>
</table>

b. **my estimation of periodontal disease activity** through such surrogates as bleeding on probing, microbiological assays, chemical tests, etc.

<table>
<thead>
<tr>
<th>DISAGREE 1 2 3 4 5 6 7</th>
<th>AGREE 1 2 3 4 5 6 7</th>
</tr>
</thead>
<tbody>
<tr>
<td>AM UNCERTAIN 1 2 3 4 5 6 7</td>
<td>AM CERTAIN</td>
</tr>
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c. **the dentition's recent caries experience /expected caries rate.**

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d. **the mechanical integrity restorative status** of each tooth in the high-dose radiation volume.

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e. **the endodontic status** of each tooth in the high-dose radiation volume.

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f. **the oral hygiene status** of the dentition, independent of the caries rate.

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- the dental occlusion in all manners, including parafunctional habits.
  
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- anticipated level of trauma from therapeutic surgery.
  
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- the salivary or xerostomia status of the patient.
  
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- local tissue characteristics* other than k. & l.
  
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  * -- Please specify these tissue characteristics:

- the systemic metabolic state [NOT circulatory status]
  
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40. MY DECISION WHETHER TO EXTRACT TEETH DEPENDS STRONGLY ON MY ASSESSMENT OF:

o. - the patient's age
2040
I DISAGREE 1 2 3 4 5 6 7 I AGREE
AM UNCERTAIN 1 2 3 4 5 6 7 I AGREE

p. - the patient's diet (excluding effects on caries rate)
2050
I DISAGREE 1 2 3 4 5 6 7 I AGREE
AM UNCERTAIN 1 2 3 4 5 6 7 I AGREE

q. - the patient's smoking status.
2060
I DISAGREE 1 2 3 4 5 6 7 I AGREE
AM UNCERTAIN 1 2 3 4 5 6 7 I AGREE

r. - idiopathic factors
2070
I DISAGREE 1 2 3 4 5 6 7 I AGREE
AM UNCERTAIN 1 2 3 4 5 6 7 I AGREE

s. - the patient's prognosis for survival
2080
I DISAGREE 1 2 3 4 5 6 7 I AGREE
AM UNCERTAIN 1 2 3 4 5 6 7 I AGREE

[OPTIONAL: BLANKS FOR YOUR POTENTIAL SUGGESTIONS. TRY TO ENSURE, HOWEVER, THAT THE FACTORS ARE INDEPENDENT, RATHER THAN CONTRIBUTORY, TO THE FACTORS LISTED ABOVE.]

t, u

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I DISAGREE 1 2 3 4 5 6 7 I AGREE
AM UNCERTAIN 1 2 3 4 5 6 7 I AGREE

u.

I DISAGREE 1 2 3 4 5 6 7 I AGREE
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Although distinctions may be arbitrary sometimes, indications for ORN-prophylactic tooth extraction might be divided into two classes:

- **1. Classic Indication:** ideally, an absolute and very sharply demarcated indication, sufficient unto itself, for extraction; in practice, using as an example a "black/white decision," an indication with only a narrow 'gray' area in which other variables need to be considered before deciding whether to extract.

- **2. Modifying Indication Factor:** an indication for extraction which contributes, in combination with one or more other factors considered at the same time, to a decision whether to extract.

41. **THIS FACTOR, WHEN PATHOLOGIC, IS USUALLY A CLASSIC INDICATION, RATHER THAN A MODIFYING INDICATION FACTOR, IN THE DECISION TO EXTRACT:**

---

**a.** the "passive" periodontal status (e.g., periodontal pocket depths, furcation involvements, etc.) of teeth in the high dose radiation volume.

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**b.** my estimation of periodontal disease activity through such surrogates as bleeding on probing, microbiological assays, chemical tests, etc.

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**c.** the dentition's recent caries experience /expected caries rate.

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**d.** the mechanical integrity restorative status of each tooth in the high-dose radiation volume.

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**e.** the endodontic status of each tooth in the high-dose radiation volume.

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41. **THIS FACTOR, WHEN PATHOLOGIC, IS USUALLY A CLASSIC INDICATION, RATHER THAN A MODIFYING INDICATION FACTOR, IN THE DECISION TO EXTRACT:**

f. - the oral hygiene status of the dentition, independent of the caries rate.

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g. - the dental occlusion in all manners, including parafunctional habits.

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h. - anticipated vascular and cellular changes induced by high dose therapeutic irradiation.

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i. - anticipated level of trauma from therapeutic surgery.

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j. - the salivary or xerostomia status of the patient.

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k. - the anticipated oxygen perfusion to the high-dose radiation volume.

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l. - the anticipated delicacy/friability of the local oral mucosa, in combination with local supra-osseous tissue contours

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m. - local tissue characteristics* other than k. & l.

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* -- Please specify these tissue characteristics:
41. **THIS FACTOR, WHEN PATHOLOGIC, IS USUALLY A CLASSIC INDICATION, RATHER THAN A MODIFYING INDICATION FACTOR, IN THE DECISION TO EXTRACT:**

n. - the systemic metabolic state (e.g., acidotic, diabetic, etc.; **NOT circulatory status**)

o. - the patient's age

p. - the patient's diet (excluding effects on caries rate)

q. - the patient's smoking status.

r,s. [OPTIONAL: BLANKS FOR YOUR POTENTIAL SUGGESTIONS. TRY TO ENSURE, HOWEVER, THAT THE FACTORS ARE INDEPENDENT, RATHER THAN CONTRIBUTORY, TO THE FACTORS LISTED ABOVE.]

r.

s.

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3030

3040
III. PROGNOSTIC FACTORS: THEORY, ETC.

1. I think that the percentage of osteonecrosis of the mandible in head and neck cancer patients that occurs without irradiation as one etiologic factor is: %.

I would estimate "95% confidence limits" for this, i.e. a range of values 95% certain to include the true percentage, as:

_______ to _______ %

2. I think that the percentage of ORN accounted for by idiopathic factors (i.e., factors not now definable) is _______ %. "95% confidence limits" = _______ to _______ %

3. I think that the maximum percentage of ORN that theoretically could be accounted for by dental health factors (e.g., given a hypothetical scenario in which teeth terribly dentally diseased are not extracted at all) is _______ %.

4. Assuming severely diminished saliva levels and a moderately-low pre-radiotherapy recent caries rate, by what percentage would the expected frequency of ORN be reduced through post-radiation home care (artificial saliva, fluoride rinses, increased oral hygiene, etc.),
   a. assuming ideal patient compliance?  b. assuming very poor patient compliance?
   ORN will decrease _____ %  ORN will decrease _____ %

5. Assuming moderately diminished saliva levels and a moderately-low pre-radiotherapy recent caries rate, by what percentage would the expected frequency of ORN be reduced through post-radiation home care,
   a. assuming ideal patient compliance?  b. assuming very poor patient compliance?
   ORN will decrease _____ %  ORN will decrease _____ %

6. Assuming mildly diminished saliva levels and a recent moderately-low pre-radiotherapy recent caries rate, by what percentage would the expected frequency of ORN be reduced through post-radiation home care,
   a. assuming ideal patient compliance?  b. assuming very poor patient compliance?
   ORN will decrease _____ %  ORN will decrease _____ %

422
7. I think that the dentist is able to predict a patient's future compliance with recommended home care therapy. My feelings about the last statement are: [Circle a number:]

I DISAGREE 1 2 3 4 5 6 7 I AGREE

VERY STRONGLY My confidence in this answer is: VERY STRONGLY

UNCERTAIN 1 2 3 4 5 6 7 CERTAIN

8. I think that the plaque index is a useful predictor of future oral hygiene:

My feelings about the last statement are: [Circle a number:]

I DISAGREE 1 2 3 4 5 6 7 I AGREE

VERY STRONGLY My confidence in this answer is: VERY STRONGLY

UNCERTAIN 1 2 3 4 5 6 7 CERTAIN

9. Please rank the relative importance of these factors in relation to the prognosis for ORN occurrence, "1" being the most important:

_____ - the overall dosage
_____ - the time dose factor
_____ - the radiation intensity
_____ - the radiation timing

My confidence in this answer is: I AM VERY

UNCERTAIN 1 2 3 4 5 6 7 CERTAIN

10. I believe that patients receiving interstitial radiation in addition to external radiation will experience a higher frequency of ORN than patients receiving that same external radiation alone.

My feelings about the last statement are: [Circle a number:]

I DISAGREE 1 2 3 4 5 6 7 I AGREE

VERY STRONGLY My confidence in this answer is: VERY STRONGLY

UNCERTAIN 1 2 3 4 5 6 7 CERTAIN

11.a. Please circle the number identifier (e.g., "1.") of the factors listed below that are both practically assessable (at the very least, qualitatively) and prognostic for ORN frequency:

1. the anticipated blood supply, or oxygen perfusion of, the high-dose irradiated mandibular volume

2. the systemic metabolic state (e.g., acidic, diabetic, etc.; NOT circulatory status)
APPENDIX 3  DELPHI SURVEY

3. the patient's age
4. the patient's diet (excluding effects on caries rate)
5. the patient's smoking status
6. the friability of the oral mucosa in the local area, in combination with local supra-osseous tissue contours
7. the oral hygiene status of the dentition
8. the dentition's recent caries experience/rate
9. the salivation or xerostomia status of the patient
10. the periodontal status of teeth in the high dose volume
11. the endodontic status of each tooth in high-dose radiation volume
12. the restorative status of each tooth in the high-dose radiation volume
13. the dental occlusion in all manners, including parafunctional habits
14. Idiopathic Factors
15. Radiation trauma in relation to healing potential
16. Surgical trauma in relation to healing potential
17. The patient's prognosis for survival

I AM VERY UNCERTAIN 1 2 3 4 5 6 7 CERTAIN

b. Please write an asterisk (*) to the left of the listed factors that you regard as significant prognosticators for ORN frequency, but which are not routinely assessable.

12. I think that the risk of ORN is dependent exclusively on the anticipated level of trauma (from all sources) to be received by the tissue in the high-dose radiation volume, in relation to the anticipated healing capacity and resistance to insult of the tissue in high dose volume.

My feelings about the last statement are: [Circle a number:]

I DISAGREE 1 2 3 4 5 6 7 I AGREE
VERY STRONGLY 1 2 3 4 5 6 7 I AM VERY
I AM VERY 1 2 3 4 5 6 7 I AM VERY
UNCERTAIN 1 2 3 4 5 6 7 CERTAIN

EXPLANATION: [ OPTIONAL ! ]
13. This factor, when undesirable, can strongly increase the risk for ORN:

a. - the "passive" periodontal status (e.g., periodontal pocket depths, furcation involvements, etc.) of teeth in the high dose radiation volume.

   I DISAGREE 1 2 3 4 5 6 7 I AGREE
   AM UNCERTAIN 1 2 3 4 5 6 7 AM CERTAIN

b. - the periodontal disease activity level as estimated through surrogates such as bleeding on probing, microbiological assays, chemical tests, etc.

   I DISAGREE 1 2 3 4 5 6 7 I AGREE
   AM UNCERTAIN 1 2 3 4 5 6 7 AM CERTAIN

c. - the dentition's recent caries experience /expected caries rate.

   I DISAGREE 1 2 3 4 5 6 7 I AGREE
   AM UNCERTAIN 1 2 3 4 5 6 7 AM CERTAIN

d. - the mechanical soundness of each tooth in the high-dose radiation volume.

   I DISAGREE 1 2 3 4 5 6 7 I AGREE
   AM UNCERTAIN 1 2 3 4 5 6 7 AM CERTAIN

e. - the endodontic status of each tooth in the high-dose radiation volume.

   I DISAGREE 1 2 3 4 5 6 7 I AGREE
   AM UNCERTAIN 1 2 3 4 5 6 7 AM CERTAIN

f. - the oral hygiene status of the dentition, independent of the caries rate.

   I DISAGREE 1 2 3 4 5 6 7 I AGREE
   AM UNCERTAIN 1 2 3 4 5 6 7 AM CERTAIN

g. - the dental occlusion in all manners, including parafunctional habits.

   I DISAGREE 1 2 3 4 5 6 7 I AGREE
   AM UNCERTAIN 1 2 3 4 5 6 7 AM CERTAIN

h. - anticipated vascular and cellular changes induced by high dose therapeutic irradiation.

   I DISAGREE 1 2 3 4 5 6 7 I AGREE
   AM UNCERTAIN 1 2 3 4 5 6 7 AM CERTAIN
13. This factor, when undesirable, can strongly increase the risk for ORN:

i. - anticipated level of trauma from therapeutic surgery.

I DISAGREE 1 2 3 4 5 6 7 I AGREE
AM UNCERTAIN 1 2 3 4 5 6 7 AM CERTAIN

j. - the salivary or xerostomia status of the patient.

I DISAGREE 1 2 3 4 5 6 7 I AGREE
AM UNCERTAIN 1 2 3 4 5 6 7 AM CERTAIN

k. - the anticipated oxygen perfusion to the high-dose radiation volume.

I DISAGREE 1 2 3 4 5 6 7 I AGREE
AM UNCERTAIN 1 2 3 4 5 6 7 AM CERTAIN

l. - the anticipated delicacy/friability of the local oral mucosa, in combination with local supra-osseous tissue contours

I DISAGREE 1 2 3 4 5 6 7 I AGREE
AM UNCERTAIN 1 2 3 4 5 6 7 AM CERTAIN

m. - local tissue characteristics* other than k. & l.

I DISAGREE 1 2 3 4 5 6 7 I AGREE
AM UNCERTAIN 1 2 3 4 5 6 7 AM CERTAIN

* Please specify these tissue characteristics:

n. - the systemic metabolic state [NOT circulatory status]

I DISAGREE 1 2 3 4 5 6 7 I AGREE
AM UNCERTAIN 1 2 3 4 5 6 7 AM CERTAIN

o. - the patient's age

I DISAGREE 1 2 3 4 5 6 7 I AGREE
AM UNCERTAIN 1 2 3 4 5 6 7 AM CERTAIN

p. - the patient's diet (excluding effects on caries rate)

I DISAGREE 1 2 3 4 5 6 7 I AGREE
AM UNCERTAIN 1 2 3 4 5 6 7 AM CERTAIN

q. - the patient's smoking status.

I DISAGREE 1 2 3 4 5 6 7 I AGREE
AM UNCERTAIN 1 2 3 4 5 6 7 AM CERTAIN
13. This factor, when undesirable, can strongly increase the risk for ORN:

\[
\begin{array}{cccccccc}
& 1 & 2 & 3 & 4 & 5 & 6 & 7 & 8 \\
r & & & & & & & & \\
s & & & & & & & & \\
\end{array}
\]

(Optional: Blanks for your potential suggestions. Try to ensure, however, that the factors are independent, rather than contributory, to the factors listed above.)

I DISAGREE
I AGREE
AM CERTAIN

I AM VERY
My confidence in this answer is: I AM VERY
UNCERTAIN
AM CERTAIN

14. Please rank the relative importances (1 = the most important) of factors a. through e., (infections of equal purulence, post-radiotherapy) in relation to a prediction of ORN risk:

- a. chronic periodontal infection
- b. acute periodontal infection
- c. chronic endodontic infection draining periodontally
- d. endodontic infection draining through buccal bone
- e. acute periapical abscess subsequent to radiotherapy.

I AM VERY
My confidence in this answer is: I AM VERY
UNCERTAIN
AM CERTAIN

15.a. Please rank along the left column the relative importances (1 = the most important) of factors a. through j., in relation to a prediction of ORN risk:

- a. tooth unopposed occlusion
- b. tooth traumatic occlusion
- c. tooth root proximity
- d. periodontal pocket depth
- e. tooth periodontal infection
- f. tooth furcation classification
- g. tooth mobility
- h. tooth horizontal bone loss
- i. tooth vertical bone loss
- j. bleeding on probing
I AM VERY UNCERTAIN

b. Now, assume that tests k. and l. are available. Please rank along the right column the relative importances (1 = the most important) of factors a. through l., in relation to a prediction of ORN risk.

k. pathologic periodontal flora (e.g., motile Gram neg./spirochaetes) .......... |__

l. chemical test suggestive of periodontal disease activity (e.g., collagenase, hydroxyproline, cyclic AMP, Interleukin 1) ........... |__

I AM VERY UNCERTAIN

16. Please rank along the left column the relative importances (1 = the most important) of factors a. through d., in relation to a prediction of ORN risk:

<table>
<thead>
<tr>
<th></th>
<th>a. bruxism</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>b. clenching</td>
</tr>
<tr>
<td></td>
<td>c. generalized non-working occlusal interferences</td>
</tr>
<tr>
<td></td>
<td>d. general trend for bite pressure to be concentrated in one area of the jaw.</td>
</tr>
</tbody>
</table>

I AM VERY UNCERTAIN

17. I would regard the extraction of a retained tooth root that is exposed, asymptomatic, and out of occlusion to be less risky for ORN than leaving the root in place.

My feelings about the last statement are: [Circle a number:]

I DISAGREE | 1 2 3 4 5 6 7 I AGREE

VERY STRONGLY | ------ ------ ------ ------ ------ --------

I AM VERY UNCERTAIN | 1 2 3 4 5 6 7 CERTAIN

18. I would regard the extraction of an otherwise healthy tooth with a Class II restoration margin very near the interproximal bone to be less risky for ORN than leaving the tooth in place.

My feelings about the last statement are: [Circle a number:]

I DISAGREE | 1 2 3 4 5 6 7 I AGREE

VERY STRONGLY | ------ ------ ------ ------ ------ --------

I AM VERY UNCERTAIN | 1 2 3 4 5 6 7 CERTAIN
19. I would regard the post-radiotherapeutic use of an old 3500 denture to be preferable to the fabrication and use of a new denture, since the old denture would be better tolerated and ultimately less risk for ORN.

My feelings about the last statement are: [Circle a number:]

I DISAGREE 1 2 3 4 5 6 7 I AGREE

VERYSIMPLY — — — I AM VERY My confidence in this answer is: I AM VERY

UNCERTAIN 1 2 3 4 5 6 7 CERTAIN

IV. SCENARIO-RELATED INFORMATION.

"STANDARD REFERENCE SCENARIO PATIENT:"

- Male
- 60 years old
- Physically moderately fit for his age
- No history of previous major medical illness, or major surgery
- Normal salivary flow and gland health
- Intact 32-tooth dentition, 30 teeth erupted, lower two 3rd molars slightly impacted with slight soft-tissue opercular coverage, no significant history of pericoronitis
- No present caries; no anterior teeth restored; non-extensive Class II and buccal amalgam restorations in all first and second premolars and first and second molars. No endodontic problems.
- Has moderate supragingival plaque and calculus and mild sub-gingival calculus everywhere; mild periodontitis of all teeth
- Angle Class I occlusion, minor crowding and minor occlusal anterior and posterior interferences.
- Visits a dentist every two years, usually getting his teeth cleaned.
- Last restoration was six months ago.
- Moderately low caries rate.
- Is a moderately heavy drinker, smoked cigarettes until 15 years ago
- Is expected to comply moderately well with recommended home care therapy.
- Has a T2MoNo squamous cell carcinoma of the lingual attached gingiva of the lower left second molar.
- Oncologist's treatment plan calls for no surgery, but external beam megavoltage radiation, dose 200 cGrays per fraction once per day, 30 fractions over 5 weeks, for a total of 6000 cGray.
1.a. Given the "Standard Reference Scenario," above (with a
T2M0N0 squamous cell carcinoma on the lingual attached
gingiva of the lower left second molar,) I would
estimate the mean risk (expected absolute frequency of
ORN) to be, for

i. my oncology center:
   (which will
   remain anonymous:)

   ORN FREQUENCY = ______ %

ii. all oncology centers
   ( = in Australia, Canada,
   Europe, and U.S., for the
   purposes of this survey:)

   ORN FREQUENCY = ______ %

I would estimate 95% confidence limits, i.e. a range of
values 95% certain to include the true ORN rate, other
things being equal, to be, for

i. my oncology center
   (which will
   remain anonymous:)

   ORN FREQUENCY = ______ % to ______ %

ii. all oncology centers
   ( = in Australia, Canada,
   Europe, and U.S., for the
   purposes of this survey:)

   ORN FREQUENCY = ______ % to ______ %

Given a scenario similar to the above ("Standard
Reference Scenario") except for the location of the
cancerous lesion, I would estimate the risk for ORN to be:

b. for a lesion on PALATAL ALVEOLAR GINGIVA ADJACENT TO
   THE UPPER LEFT SECOND MOLAR:

   Frequency = ______ %
   Please Circle one: ; for My Center; ; for ALL centers;

2. Compared to the "Standard Reference Scenario" in which
the lesion was a T2M0NO lesion on the lingual attached
gingiva of the L.L. 2nd molar, for an otherwise similar
Scenario in which the lesion is T3M0N1 (presumably
requiring radical neck dissection and quite possibly
necessitating other management changes) --
a. I would anticipate these changes in the dental management of the case:

(Note: For the purposes of this question only, the term "dental" should be taken to include all clinical activities that directly affect the teeth, even surgical interventions such as the radical mandibulectomy.)

[Please rank their relative impact for prevention of ORN, (1 = most important.)]

b. I would expect the frequency of ORN to

Please Circle One: Rise or Fall Please Specify: by ___ %

relative to the "Standard Reference Scenario," if these suggested dental management changes were NOT made,

while I would expect the frequency of ORN to

Please Circle One: Rise or Fall Please Specify: by ___ %

if the suggested management changes were made.

3. Considering a variation of the "Standard Reference Scenario" (T1M0N0) in which some teeth in the high dose radiation volume have progressive periodontal disease:

i. one molar will develop 5 mm. periodontal pockets and one 6mm. pocket with a Class II furcation involvement.

ii. 2 other teeth will progress from 4 mm. pockets to 5 mm. pockets.

iii. The remaining teeth will have pockets stable at 4 mm.

a. I would anticipate these changes in the dental management of the case, relative to that for the "Standard Reference Scenario":

431
[Please rank their relative impact for prevention of ORN, \((1 = \text{most important})\)]

b. I would expect the frequency of ORN to

Please Circle One: Rise or Fall Please Specify: by \(\_\_\_\_\_\_\%\), relative to the "Standard Reference Scenario," if these suggested dental management changes were NOT made, while I would expect the frequency of ORN to

Please Circle One: Rise or Fall Please Specify: by \(\_\_\_\_\_\_\%\) if the suggested management changes were made.

4. Considering a variation of our "Standard Reference Scenario" in which the periodontal status is relatively stable, and in which "physiologic atrophy" of the gingiva has prevented progression of pocket depth beyond 4mm., but in which generalized 2 1/2 mm. horizontal bone loss of both the mandible and the maxilla has resulted in generalized Class I molar furcation involvements —

a. I would anticipate these changes in the dental management of the case, relative to that for the "Standard Reference Scenario":

---
APPENDIX 3  DELPHI SURVEY

b. I would expect the frequency of ORN to
   Please
   Circle One: Rise or Fall
   Specify: by ___ %,
relative to the "Standard Reference Scenario," if these suggested dental management changes were NOT made, while I would expect the frequency of ORN to
   Please
   Circle One: Rise or Fall
   Specify: by ___ %
if the suggested management changes were made.

5. Considering a variation of the "Standard Reference Scenario" in which the patient does not have much periodontal disease but is expected to be only poorly compliant with recommended home care therapy (e.g. fluoride and artificial saliva rinses) --

   a. I would anticipate these changes in the dental management of the case, relative to that for the "Standard Reference Scenario":

   [Please rank their relative impact for prevention of ORN, (1 = most important.)]

b. I would expect the frequency of ORN to
   Please
   Circle One: Rise or Fall
   Specify: by ___ %,
relative to the "Standard Reference Scenario," if these suggested dental management changes were NOT made,
while I would expect the frequency of ORN to rise or fall by ______ % if the suggested management changes were made.

6. Considering a variation of the Standard Reference Scenario in which the patient does not have much periodontal disease but is a severe bruxer and already has worn through the occlusal enamel of most teeth —

a. I would anticipate these changes in the dental management of the case, relative to that for the "Standard Reference Scenario":

[Please rank their relative impact for prevention of ORN, (1 = most important.)]

b. I would expect the frequency of ORN to rise or fall by ______ %, relative to the "Standard Reference Scenario," if these suggested dental management changes were NOT made, while I would expect the frequency of ORN to rise or fall by ______ % if the suggested management changes were made.

7. Considering a variation of the "Standard Reference Scenario" in which the patient has pre-existing salivary gland dysfunction that, even before radiotherapy, reduces by half the flow of saliva from all glands —
a. I would anticipate these changes in the dental management of the case, relative to that for the "Standard Reference Scenario":

_________________________________________________________________________

_________________________________________________________________________

_________________________________________________________________________

_________________________________________________________________________

_________________________________________________________________________

_________________________________________________________________________

_________________________________________________________________________

_________________________________________________________________________

[Please rank their relative impact for prevention of ORN, (1 = most important.)]

b. I would expect the frequency of ORN to
Please Circle One: Rise or Fall Specify: by ___ %, relative to the "Standard Reference Scenario," if these suggested dental management changes were NOT made, while I would expect the frequency of ORN to
Please Circle One: Rise or Fall Specify: by ___ % if the suggested management changes were made.

8. Considering a variation of the "Standard Reference Scenario" in which the patient has an infection draining through the periodontium that has indicated extraction of this affected mandibular molar in the future high-dose radiation volume, and assuming that good closure of the surgical flaps and smooth tissue contours are achieved without severe osteoplasty --

a. I would anticipate these changes in the dental management of the case, relative to that for the "Standard Reference Scenario":

_________________________________________________________________________

_________________________________________________________________________

_________________________________________________________________________

_________________________________________________________________________

_________________________________________________________________________

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_________________________________________________________________________

_________________________________________________________________________
[Please rank their relative impact for prevention of ORN, (1 = most important.)]

b. I would expect the frequency of ORN to relative to the "Standard Reference Scenario," if these suggested dental management changes were NOT made, while I would expect the frequency of ORN to if the suggested management changes were made.

9. Considering a variation of the "Standard Reference Scenario" in which the patient has an infection draining through the buccal bone that has indicated extraction of this affected mandibular molar in the future high-dose radiation volume, and assuming that good closure of the surgical flaps and smooth tissue contours are achieved without severe osteoplasty --

a. I would anticipate these changes in the dental management of the case, relative to that for the "Standard Reference Scenario":

[Please rank their relative impact for prevention of ORN, (1 = most important.)]

b. I would expect the frequency of ORN to
relative to the "Standard Reference Scenario," if these suggested dental management changes were NOT made, while I would expect the frequency of ORN to

Please Circle One: Rise or Fall

Please Specify: by ____ %

if the suggested management changes were made.

10.a. In Item 1.a., 95% confidence limits were estimated for the risk of ORN in the "Standard Reference Scenario". If any of the other scenarios would entail confidence limits that are substantially greater or less (proportionate to the risk,) then please explain:


b. Please review for accuracy your Item 1.a. estimates for 95% confidence limits for the expected frequency of ORN.

11. Assuming that the patient in the "Standard Reference Scenario" developed rampant, uncontrollable post-irradiation caries — I would estimate that the risk (expected frequency) for ORN, relative to the "Standard Reference Scenario," would, if these teeth were not extracted, Please Circle One: Rise or Fall

Please Specify: by ____ %.

I would estimate 95% confidence limits for the latter change to be

______ % to ______ %.

12. Assuming that a patient otherwise like that in the "Standard Reference Scenario" had severe periodontal disease of all teeth in the high dose radiation volume — I would estimate that the risk (expected frequency) for ORN, relative to the "Standard Reference Scenario," would, if these teeth were not extracted, Please Circle One: Rise or Fall

Please Specify: by ____ %.
APPENDIX 3 DELPHI SURVEY

I would estimate 95% confidence limits for the latter change to be

______ % to ______ % .

13. Assuming that a patient otherwise like that in the "Standard Reference Scenario" had infections of endodontic origin of all teeth in the high dose radiation volume, --

I would estimate that the risk (expected frequency) for ORN, relative to the "Standard Reference Scenario," would, if these teeth were not extracted,

Please Circle One: Rise or Fall Specify: by ______ % .

I would estimate 95% confidence limits for the latter change to be

______ % to ______ % .

V. OUTCOMES.

Background: ORN lesions can be classified. [The scheme below is directly adapted from one published in the literature, but will not be attributed in this edition of the survey.]

ORN 0 = No History of ORN
ORN 1 = Resolved ORN
   1a = No history of pathological fracture
   1b = History of pathologic fracture, since resolved
ORN 2 = Chronic, Non-progressive, Localized ORN
   (No pathologic fracture or anticipation of same)
ORN 3 = Active, Progressive, ORN
   3a = No pathologic fracture
   3b = Pathologic fracture.

1. Other things being equal, whether the risk of ORN is 0.1% or 30%, I believe that ORN will distribute in similar hypothetical proportions into the severity classifications just outlined.

My feelings about the last statement are: [Circle a number:]

I DISAGREE 1 2 3 4 5* 6* 7* I AGREE
VERY STRONGLY
I AM VERY
My confidence in this answer is: I AM VERY
UNCERTAIN 1 2 3 4 5 6 7 CERTAIN
2. [* -- NOTE: IF ITEM 1, RESULTED IN AGREEMENT LEVELS 5, 6, OR 7, THEN THIS ITEM MAY BE OMITTED.*]

a. The possible prognostic factors, and/or anatomic locations that would NOT ONLY change the occurrence of ORN, but skew a hypothetical distribution of ORN severity outcomes (i.e., ORN 0, ORN 1a, ORN 1b, ORN 2, ORN 3a, ORN 3b, above) one way or the other, are:

<table>
<thead>
<tr>
<th>Importance:</th>
<th>FACTOR:</th>
<th>Impact, +or-, on Freq.:</th>
<th>Svnty:</th>
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</tbody>
</table>

b. [INSTRUCTION: At the right, please place in each of two columns a "+" if the factor would increase the frequency or severity of ORN, respectively, and a "-" if it would decrease the frequency or severity of expected ORN outcomes....

c. To the left, please assign an arbitrary importance rating of "10" to the factor skewing the distribution the most powerfully, then rate the other factors proportionally to this.

******************************************************************************
BACKGROUND FOR LAST ITEMS:

Please consider a complementary scheme (by the author of this survey) for classifying ORN outcomes. [Although this scheme suffers from unclear end-points, it may serve as an introductory ordinal classification:]

P4 = Generally or frequently Excruciating Pain
P3 = Generally or frequently Severe Pain
P2 = Generally or frequently Moderate Pain
P1 = Generally or frequently Mild Pain
P0 = Generally No Pain

F4 = Function of jaws severely impaired (either anatomically, physiologically, or due to pain;) Use of dentition or dental prosthesis either ineffective or impractical.
F3 = Function of jaws mildly or moderately impaired (either anatomically, physiologically, or due to pain;) Use of dentition or dental prosthesis either ineffective or impractical.
F2 = Jaws functional but severely compromised function of dentition or dental prosthesis.
F1 = Jaws and dentition or dental prosthesis all functioning with at least a moderate degree of utility.
F0 = Jaws and dentition or dental prosthesis all functioning well.

[NOTE: CORRELATION OF ORN OUTCOMES WITH QUALITY OF LIFE IS BEYOND THE SCOPE OF THIS STUDY. NEVERTHELESS, THE ANSWERS TO THE NEXT THREE QUESTIONS WILL BE HELPFUL TO THE STUDY.]

3. I agree that the P4—>P0 scale would associate positively with quality of life.

My feelings about the last statement are: [Circle a number:]

I DISAGREE 1 2 3 4 5 6 7 I AGREE
VERY STRONGLY
I AM VERY My confidence in this answer is: I AM VERY
UNCERTAIN 1 2 3 4 5 6 7 CERTAIN

4. I agree that the F4—>F0 scale would associate positively with quality of life.

My feelings about the last statement are: [Circle a number:]

I DISAGREE 1 2 3 4 5 6 7 I AGREE
VERY STRONGLY
I AM VERY My confidence in this answer is: I AM VERY
UNCERTAIN 1 2 3 4 5 6 7 CERTAIN
5. I think that a future quality of life scale would be incomplete were it not to include this factor/these factors along with the F4→F0 and P4→P0 scales just mentioned:

FURTHER BACKGROUND FOR LAST ITEMS:

Although patients may be evaluated in cross-sectional surveys, such evaluation would not uniformly supply information about END-states, since the clinical course of some patients would still be in progress and some of the "outcome states" evaluated in such a study would still be in a state of transition. The items below request NOT the information that would be derived from a "cross-sectional" survey, but from evaluations of all patients in equivalent "mature" states of their clinical course.

6. Patients with a history of ORN or at risk for ORN (at a mature stage of their post-radiotherapy clinical course, in Australia, Canada, Europe, and the U.S.A.) would have the following distribution of ORN severities:

a. ORN 0, No History of ORN:
   PROPORTION OF ALL CASES = _____ %.

b. ORN 1, Resolved ORN, =
   1a = No history of pathological fracture:
   PROPORTION OF ALL CASES = _____ %.
   † 1b = History of pathological fracture, since resolved:
   PROPORTION OF ALL CASES = _____ %.

c. ORN 2, Chronic, Non-progressive, Localized ORN
   (No pathologic fracture or anticipation of same:)
   PROPORTION OF ALL CASES = _____ %.

d. ORN 3 = Active, Progressive, ORN, =
   3a = No pathologic fracture:
   PROPORTION OF ALL CASES = _____ %.
   † 3b = Pathologic fracture:
   PROPORTION OF ALL CASES = _____ %.

100 %

==========
The function and pain classifications that *often are* associated with each ORN class are:

(Please circle the pain and function classifications appropriate to each ORN classification:)

<table>
<thead>
<tr>
<th>ORN Class:</th>
<th>Pain and Function Classifications:</th>
</tr>
</thead>
<tbody>
<tr>
<td>ORN 3b:</td>
<td>P4  P3  P2  P1  P0  F4  F3  F2  F1  F0</td>
</tr>
<tr>
<td>ORN 3a:</td>
<td>P4  P3  P2  P1  P0  F4  F3  F2  F1  F0</td>
</tr>
<tr>
<td>ORN 2:</td>
<td>P4  P3  P2  P1  P0  F4  F3  F2  F1  F0</td>
</tr>
<tr>
<td>ORN 1b:</td>
<td>P4  P3  P2  P1  P0  F4  F3  F2  F1  F0</td>
</tr>
<tr>
<td>ORN 1a:</td>
<td>P4  P3  P2  P1  P0  F4  F3  F2  F1  F0</td>
</tr>
<tr>
<td>ORN 0:</td>
<td>P4  P3  P2  P1  P0  F4  F3  F2  F1  F0</td>
</tr>
</tbody>
</table>

A graph illustrating purely hypothetical distribution of pain and function for a certain ORN classification is presented below. For each graph note that the percentages associated with P4, P3, P2, P1, and P0 add up to 100%, and that the percentages associated with F4, F3, F2, F1, and F0 add up to 100%.

<table>
<thead>
<tr>
<th>Proportion (%)</th>
<th>Pain Category</th>
<th>Function Category</th>
</tr>
</thead>
<tbody>
<tr>
<td>60%</td>
<td>40%</td>
<td>0%</td>
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<tr>
<td>40%</td>
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<tr>
<td>20%</td>
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<tr>
<td>0%</td>
<td>P4  P3  P2  P1  P0  F4  F3  F2  F1  F0</td>
<td></td>
</tr>
</tbody>
</table>
Given an opportunity to determine the final Pain and Function correlations for patients in the various ORN severity categories, I would anticipate finding pain and function outcomes in these proportions:

### a. for patients classed ORN CLASS 3b (Active, progressive ORN with pathologic bone fracture:)

<table>
<thead>
<tr>
<th>Proportion (Percentage) of Total in Pain or Function Category</th>
<th>P4</th>
<th>P3</th>
<th>P2</th>
<th>P1</th>
<th>P0</th>
<th>F4</th>
<th>F3</th>
<th>F2</th>
<th>F1</th>
<th>F0</th>
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</tbody>
</table>

I AM VERY UNCERTAIN 1 2 3 4 5 6 7 CERTAIN

### b. for patients classed ORN CLASS 3a (Active, progressive ORN without pathologic fracture:)

<table>
<thead>
<tr>
<th>Proportion (Percentage) of Total in Pain or Function Category</th>
<th>P4</th>
<th>P3</th>
<th>P2</th>
<th>P1</th>
<th>P0</th>
<th>F4</th>
<th>F3</th>
<th>F2</th>
<th>F1</th>
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<tbody>
<tr>
<td>% 100-</td>
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</tbody>
</table>

I AM VERY UNCERTAIN 1 2 3 4 5 6 7 CERTAIN
### APPENDIX 3 DELPHI SURVEY

#### for patients classed ORN CLASS 2 (Chronic, Local, Non-progressive ORN:)

<table>
<thead>
<tr>
<th>% 100</th>
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<th>P1</th>
<th>P2</th>
<th>P3</th>
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<tr>
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<td>(Percentage)</td>
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<tr>
<td>of Total in</td>
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<tr>
<td>Pain or Function</td>
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</table>

I AM VERY My confidence in this answer is: I AM VERY UNCERTAIN 1 2 3 4 5 6 7 CERTAIN

#### for patients classed ORN CLASS 1b (History of ORN with fracture, all since resolved:)

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<th>F2</th>
<th>F3</th>
<th>F4</th>
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<tbody>
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<tr>
<td>(Percentage)</td>
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</tbody>
</table>

I AM VERY My confidence in this answer is: I AM VERY UNCERTAIN 1 2 3 4 5 6 7 CERTAIN
e. for patients classed ORN CLASS 1a (History of ORN without fracture, since resolved:)

<table>
<thead>
<tr>
<th>Proportion</th>
<th>% 100-</th>
<th>80-</th>
<th>60-</th>
<th>40-</th>
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<td>of Total in</td>
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<td>F2</td>
<td>F1</td>
<td>F0</td>
</tr>
</tbody>
</table>

I AM VERY My confidence in this answer is: I AM VERY UNCERTAIN

f. for patients classed ORN CLASS 0 (i.e., no history of ORN, although at risk for ORN:)

<table>
<thead>
<tr>
<th>Proportion</th>
<th>% 100-</th>
<th>80-</th>
<th>60-</th>
<th>40-</th>
<th>20-</th>
<th>0-</th>
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<tbody>
<tr>
<td>(Percentage)</td>
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<td>of Total in</td>
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<td>F3</td>
<td>F2</td>
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<td>F0</td>
</tr>
</tbody>
</table>

I AM VERY My confidence in this answer is: I AM VERY UNCERTAIN

Thank you very much for your participation in the first iteration of this survey and completion of all questions. The next iteration will, to some extent, simply summarize the results of this iteration, and may take one half as much time.

Feel free to contact me with suggestions. — C.K.C.
APPENDIX 4. RESPONSES OF LOW DATA QUALITY.

(DETAILS, COMPLEMENTING FINAL RESULTS SUBSECTION OF SAME NAME.)

1. Direct Assessment of ORN Risk Factors, c. Endodontics In Greater Detail

Items 1680 and 1660 dealing with the risk for ORN of teeth treated before or after therapeutic radiation relative to similarly-timed extractions, were associated with inadequate confidence and/or consensus.

The low consensus in responses to Items 1600, 1610, and 3480 implied inadequate data quality. These items considered the desirability as ORN prophylactic measures of:

- the desirability of chronic antibiotic coverage to patients at risk
- hermetic (air-tight) soft-tissue closure following the extraction of a tooth, and
- the extraction of a retained tooth root that is exposed, asymptomatic, and out of occlusion.

2. Indirect Assessment of ORN "Risk Factors" a. Perceived Relevance to ORN-Prophylactic Treatment Planning.

Responses to Item 1800, "I need to estimate periodontal disease activity and potential for progression through surrogates that I trust (possible examples: bleeding on probing, microbiological assays, chemical tests, etc.), before I establish a treatment plan for ORN-prophylactic tooth extraction," were of low data quality due to low consensus.

2. Indirect Assessment of ORN "Risk Factors" b. Factor Practicality for Decision Analysis, e.g. Quantifiability.

Low consensus is associated with the responses to items 1850 and 1775 questioning whether respondents can assess in a quantitative fashion

- unbalanced bite, occlusal interference, [and] parafunctional habits (e.g. bruxism and clenching, etc.,)
- infections of dental origin (whether endodontic or periodontal).


Item 1710 responses were associated with low consensus. Item 1710. was, "I consider the following factors postulated to affect the prognosis for the severity of ORN, and thus my tooth extraction treatment planning, to be partially under my control:

1. the overall balance of the bite, and individual occlusal interferences in the bite
2. the effectiveness of dental procedures
3. slightly, the tumor control surgical technique, in the sense that my emphasis to the surgeon of the importance of certain oral structures to prosthodontic rehabilitation, may influence his surgery."

3. Factors affecting Decisions to Extract Teeth in Sites Irradiated to High Dose a. General

"1880. My decision whether to extract teeth depends exclusively on my assessment of the anticipated level of trauma (from all sources) to be received by the tissue in the high-dose radiation volume, in relation to the anticipated healing capacity and resistance to insult of tissue in high dose volume." The quality of responses to this item are inadequate due to the very low consensus.

Items for which consensus was adequate in the 1890+ series ("My decision to extract depends strongly on"), but not in the 3240+ series ("This factor, when undesirable, can strongly increase the risk for ORN"), were:

- my estimation of periodontal disease activity through such surrogates as bleeding on probing, microbiological assays, chemical tests, etc. (Consensus = 3.0 = marginal in the analogous Item 3250)

1900 k. - the anticipated oxygen perfusion to the high-dose radiation volume.

1990 DISAGREE 1 2 3 4 5 6 7 I AGREE

2070 r. - idiopathic factors

2030 n.-the systemic metabolic state [NOT circulatory status]

1950 g. - the dental occlusion in all manners, including parafunctional habits.

1900 DISAGREE 1 2 3 4 5 6 7 I AGREE
1970. i. - anticipated level of trauma from therapeutic surgery.

I DISAGREE 1 2 3 4 5 ↓6 7 I AGREE

Consensus also was inadequate in some of the Items 2110-3030, "This factor, when pathologic, is usually a classic indication, rather than a modifying indication factor, in the decision to extract." Items for which consensus was inadequate were:

<table>
<thead>
<tr>
<th>TABLE. ITEMS 2110-3030 SUITABILITY OF FACTORS AS CLASSIC INDICATIONS FOR EXTRACTION: RESPONSES OF INADEQUATE CONSENSUS AGREEMENT</th>
</tr>
</thead>
<tbody>
<tr>
<td>AGREEMENT LEVEL:</td>
</tr>
<tr>
<td>FACTOR:</td>
</tr>
<tr>
<td>INTER-QUARTILE RANGE:</td>
</tr>
<tr>
<td>CONFIDENCE LEVEL:</td>
</tr>
<tr>
<td>HIGH MOD. MARG.</td>
</tr>
<tr>
<td>5.4 Recent Caries Experience/ Expected Caries Rate</td>
</tr>
<tr>
<td>5.3 Oral Hygiene Status, independent of caries rate</td>
</tr>
<tr>
<td>5.2 Tooth Mechanical Integrity in high dose volume</td>
</tr>
<tr>
<td>5.2 Tooth Endodontic Status in high dose volume</td>
</tr>
<tr>
<td>5.0 Anticipated Vascular &amp; Cellular Changes</td>
</tr>
<tr>
<td>4.5 Salivation/Xerostomia Status</td>
</tr>
<tr>
<td>4.0 Anticipated Delicacy/Friability of Local Mucosa,</td>
</tr>
</tbody>
</table>

In addition to the results summarized in the Table above, respondents had the opportunity to supply some optional information. These responses lacked adequate quantity to achieve relative reliability, but are reported here. In response to the same root, "This factor, when pathologic, is usually a classic indication, rather than a modifying indication factor, in the decision to extract," the additional responses were:

• 2230 m. - local tissue characteristics other than k. & l. [Please specify:]
  Respondent 03/ "Keratinization; Overall healthful status."
  Respondent 04/ "Fibrosis, keratinization." "Type of tissue, alveolar mucosa or reconstructive tissue."

3030 r. Optional BLANKS For Suggestions.9 Respondent 10/ "Social/economic level" "Substance abuse"


Practically all quantitative ORN risk estimates requested in Section IV, the 44th through 53rd pages of the Survey (reproduced in the Appendix: Survey) lack sufficient central tendency and quality.

5. Outcomes (and Related)

Data of "inadequate" quality in this section were of two types:

1. "e. Osteoradionecrosis Severity Distributions:" quantitative estimates (# 3980)

2. large numbers of "one-off" categories of response qualitative responses associated with tables in Parts

- a. Criteria for Evaluating Severity of ORN Lesions
- b. ORN-Associated Factors That May Affect A Patient's Quality Of Life
- c. Anatomic Location and ORN Clinical Presentation
- d. Factors Skewing ORN Severity Distributions, and
- f. ORN Severity Category Associations With Pain & Function.

Additionally, Item 3960 produced some responses of low reliability that nevertheless may have relevance to future hypothesis testing or second Delphi rounds. The item was, "I think that a future quality of life scale would be incomplete were it not to include this factor/these factors along with the F4-->F0 and P4-->P0 scales just mentioned". The responses, categorized, were:

- 466. Inability, or impaired ability, to acquire nutrition (2 mentions)
- 616B. Oro-cutaneous Fistula (this and the others, 1 mention each)
- 660. Inability/ability to socially interact
- 670. Appearance; cosmesis
- 711. Support of the family.

---

6 ... Induced by high dose therapeutic radiation." Comment by Respondent 02:/ "Cannot anticipate" [these changes]
7 ... in combination with local supra-osseous tissue contours."
8 Re [k.: O2 perfusion; l.: friability of mucosa]. 02/ Comments: "Don't need to anticipate Can generally observe pre-treatment exam.
9 [Respondents were requested to ensure that the factors are independent, rather than contributory, to the factors listed above.]
APPENDIX 5. CLASS OF DATA GENERATING UNDEFINED QUARTILES

TABLE 72. ITEM 1770 DATA, TYPIFYING THAT GENERATING UNDEFINED QUARTILES.

<table>
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<tr>
<th>ITEM 1770 SUBMISSION</th>
<th>RESPONDENT:</th>
<th>SUMMARY:</th>
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<tbody>
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<td>AGREEMENT:</td>
<td>7 7 6 7 6 7</td>
<td>U:* 5 @ &quot;6&quot;, 8 @ &quot;7&quot;, 1 &quot;U&quot;</td>
</tr>
<tr>
<td>CONFIDENCE:</td>
<td>7 7 6 7 6 7</td>
<td>U:* 6 @ &quot;6&quot;, 7 @ &quot;7&quot;, 1 &quot;U&quot;</td>
</tr>
</tbody>
</table>

*: Item assumed not applicable to this physician correspondent; response to item was not requested.
U: Undefined  *: No response to this item by Respondent 15.

AGREEMENT: 25th %TILE 75th %TILE 75th % - 25th % TIE INTERQUARTILE RANGE CONSENSUS MEAN
AGREEMENT 6.1 6.6 6.9 Very small* Very high* 6.6
CONFIDENCE 6.0 6.5 6.6 Small* High* 6.5

+: Not determined by S.P.S.S. 3.1.2
*: Determined by inspection only, since 75th percentile is not calculated by S.P.S.S. 3.1.2 given these data. Please see explanation below.

The range of items identified in which (very high or high) consensus was assessable only by inspection all follow a pattern of responses similar to those in Item 1770, with expressed agreement or confidence very high, involving mostly "7"'s. For example, the agreement 75th percentile could not be calculated by S.P.S.S.3.1.2. for equally representative items #1780 (11 "7"'s and 3 "6"'s), #1820 (9 "7"'s, 4 "6"'s, and one "5"), and #1860 (8 "7"'s and 6 "6"'s).

High consensus in agreement is defined on page 177 as involving an agreement interquartile range of <2.0. Given calculated 25th percentiles of not less than 6.1 for all of these items, and 75th percentiles that cannot possibly be greater than 7.0, it can be seen that interquartile ranges for these items must be less than 1.0, i.e. "very high" consensus.

Item 1870\textsuperscript{10} data implies that the lack of calculability of the 75th percentile in these representative cases follows low variation in the values analyzed, and/or calculated 75th percentiles that approach the maximum possible value (i.e., the 100th percentile). In item 1870, 11 respondents each assess agreement and confidence in identical "pairs": (agreement & confidence "5" & "5", "6" & "6", "6" & "6", "6" & "6", "6" & "6", "6" & "6", "6" & "6", "7" & "7", "7" & "7", "7" & "7", "7" & "7", "7" & "7", "7" & "7", "7" & "7", "7" & "7", "7" & "7", and "7" & "7", "7" & "7", and "7" & "7", while three assess agreement and confidence differently: a) agreement "6", & confidence "7"; b) agreement "6", & confidence "7"; and c) agreement "1" & confidence "7". Variability in the agreement data was sufficient to calculate an agreement 75th percentile of 6.9, and an agreement interquartile range of 0.3. (Please see summary below.) In contrast, the final three confidence assessments of "7" would have resulted in confidence 75th percentiles even higher than 6.9, approximating the maximum value, 7.0. For whatever reason, this value could not be produced. Thus, quartiles approaching the extremes, and/or low variability in the data, result in undefined quartiles in S.P.S.S.3.1.2. Brief (1997) speculated that the reason for this type of result could involve an allocation of decimal points\textsuperscript{11} that was insufficient to permit successful percentile calculations involving very small differences.

<table>
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<td>6.6</td>
<td>6.1</td>
<td>-</td>
<td>-</td>
<td>6.6</td>
</tr>
</tbody>
</table>

\textsuperscript{10} "I need to consider the prognosis for patient attendance, and compliance with, recommended chair-side dental professional services, before establishing a treatment plan for ORN-prophylactic tooth extraction"

\textsuperscript{11} during this type of computation by S.P.S.S.3.1.2, a now-outdated program,