THE ACUTE EFFECTS OF CONSERVATIVE SURGERY PLUS

RADIOTHERAPY ON THE FUNCTIONAL CAPACITY AND

PSYCHOLOGICAL WELL BEING OF WOMEN

WITH EARLY STAGE BREAST CANCER

by

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# ABSTRACT

Seven women (54.1 ± 5.2 yrs) diagnosed with Stage I or II breast cancer who were treated with surgery and adjuvant radiotherapy served as subjects in a prospective investigation evaluating functional capacity and psychological well-being before, during, and after therapy. Physical measurements included height, body mass and sum of five skinfolds. Measures of spirometry (FVC, $FEV_1$, $FEF_{25\%-75\%}$, $FEV_1/FVC$, MVV) and single breath diffusing capacity of carbon monoxide ($DL_{CO}$, VA, $DL_{CO}/VA$) were recorded using a Collins DS I System (Warren E. Collins). To determine maximal oxygen consumption ($VO_2max$), minute ventilation (VE), heart rate (HRmax) and peak power output (PPO), subjects cycled until exhaustion on an electronically-braked cycle ergometer (Lode BV Excalibur V2.0). Percent arterial oxygen saturation ($\%SaO_2$) was monitored with a pulse oximeter (Ohmeda Box 3740). Subjects completed the Self-Esteem Questionnaire (Robson, 1989), a modified Quality of Life Index (Padilla *et al.*, 1983), and the Body Image Visual Analogue Scale (Mock, 1993). Measures were recorded after biopsy, prior to further surgery (Test 1), and repeated three weeks after surgery (Test 2), two weeks after commencement of radiotherapy (Test 3), as well as one week (Test 4) and two months (Test 5) after radiotherapy completion. Surgical, pathological and radiotherapy details were recorded, as was smoking history. In addition to relating pre-diagnostic activity, subjects kept a weekly log to record and subjectively rank their involvement in physical activity during treatment.

Repeated measures analysis of variances (RM ANOVAs) were implemented with subsequent Tukey HSD post-hoc analysis. A probability value of $<0.05$ was considered

significant for all tests. All pulmonary function measures, excluding FVC and $V_A$, decreased significantly between Test 1 and Test 5; changes were attributed to pulmonary inflammation. Nevertheless, deviations in spirometry and diffusing capacity were within normal limits, likely contributing to the maintenance of maximal exercise capacity. Body image and quality of life were significantly depressed at mid-radiation, yet self-esteem did not change over the course of treatment. Activity, smoking and age did not appear to play a role in either physiological or psychological health, yet sample size was small.

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| | |
|---|---|
| bpm | Beats per minute |
| $DL$ | Diffusing capacity of the lung (mL/min/mmHg): the volume of gas that diffuses through the alveolar-capillary membrane each minute for a pressure difference of 1 mmHg |
| $DL_{CO}$ | Diffusing capacity of the lung for carbon monoxide (mL/min/mmHg) |
| $DL_{CO}/VA$ | Specific diffusion of carbon monoxide per unit of alveolar volume |
| ECG | Electrocardiogram |
| $FEF_{25\%-75\%}$ | Forced expiratory flow (L/sec) during the middle half of the FVC |
| $FEV_1$ | Forced expiratory volume in the first second (L) of the FVC |
| FVC | Forced vital capacity (L): vital capacity performed with a rapid, maximally forced expiratory effort |
| Gy | Gray: One unit of absorbed dose of ionizing radiation |
| Hb | Hemoglobin (g/100 mL) |
| Hg | Mercury |
| HRmax | Maximum heart rate (bpm) |
| Kcal | Kilocalorie: unit of energy expenditure |
| MVV | Maximal voluntary ventilation (L/min): volume of air expired in a specified period during repetitive maximal respiratory effort |
| PFT | Pulmonary function test |
| PPO | Peak power output (watts) |

QOL          Quality of life

RER          Respiratory exchange ratio

rpm          Revolutions per minute

RT          Radiation therapy

$\%SaO_2$          Percentage of arterial oxyhemoglobin saturation

TLC          Volume (mL) of air contained within the lungs following a maximal inspiration

TNM          Breast cancer staging system

$V_A$          Alveolar volume (mL): the residual volume + inspiratory capacity

VC          Maximum volume (mL) of air exhaled following a maximum inspiration

VE          Expired ventilation per minute (mL/min)

$VO_2$          Rate of oxygen uptake (mL/min)

$VO_2max$          Maximal rate of oxygen uptake (mL/kg/min)

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# CHAPTER 1: INTRODUCTION

Breast cancer accounts for over 30% of newly diagnosed cancers and is the second-most-common cause of cancer deaths in women. Given 1996 incidence rates, it is estimated that one in nine women will develop breast cancer by the age of ninety. One in twenty-five will die from the disease. The National Cancer Institute of Canada has estimated that 18,400 new cases will be diagnosed and 5,100 will die from breast cancer in 1997 (National Cancer Institute of Canada, 1997). Although current therapy has led to a modest decrease in breast cancer mortality in the past decade, it includes a combination of systemic and local interventions that can affect major organ systems beyond its primary target. Surgery, radiation, and chemotherapy have multiple side effects, and pulmonary and cardiac complications arising from these treatments are not infrequent at any diagnostic stage.

An aging population, advances in mammographic technology, and increased education regarding breast self-examination, have contributed to a rise in detection of breast cancer cases; however technology and education have allowed detection at breast cancer's earliest stages. The maximum diameter of discovered tumours is consistently decreasing and T1 cancers (tumours measuring one centimetre or less in maximum diameter), as a proportion of all measured invasive breast cancers, is increasing (Cady *et al.*, 1996). Moreover, the fact that five year survival rates are up to 95% for Stage I, and 70% for Stage II diagnosed women (Olivotto *et al.*, 1995) affirms that life quality during and after treatment is of paramount importance, as Izack and Medialie suggested in their 1971 study of carcinoma:

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Survival rates while justifiably important in themselves cover only a portion of the total problem. These rates do not relate to how the patient survives; at what cost to his physical functioning; how he adapted to his condition from a psychological point of view; and how he is fulfilling his roles, in his family, at work, among friends and in the wider society.

Recurrence and survival rates show that conservative surgery (CS) plus radiotherapy (RT) is just as effective as mastectomy (Early Breast Cancer Trialists' Collaborative Group, 1995) and as a result, CS + RT has become an accepted treatment modality for women with an early stage (Stage I or II) diagnosis. Yet, concern has been considerable with respect to radiation's potential complications. The lungs are one of the more sensitive organs to radiation (Rubin, 1984) and because they are adjacent to the breast, lungs are easily susceptible to radiation effects including pulmonary pneumonitis and late-developing fibrosis (Cherniack *et al.*, 1994; Simpson, 1986). Some prospective observations on early stage breast cancer patients indicate that they have significantly reduced measurements of regional and overall lung function within four months of radiotherapy completion (Botterman *et al.*, 1990; Lund *et al.*, 1991; Roberts *et al.*, 1993; Kimsey *et al.*, 1994). Breast cancer RT is also associated with a variety of late cardiac complications (Burch, 1968; Simpson, 1986, Host *et al.*, 1986, Wallgren, 1992) especially when left breast lesions are treated.

The ability to maintain or resume normal activities is important for breast cancer patients (Kiebert *et al.*, 1991), yet literature indicates that functional capacity may be compromised as a result of radiation treatment effects on the heart and lungs. Functional capacity, defined as the highest metabolic rate an individual can achieve on exertion, is often used as a measure of ability to engage in physical activity (Vallbona, 1982). There is a direct

relationship between oxygen uptake and performance of endurance events, therefore maximum oxygen consumption is considered to be an objective physiological indicator of functional capacity. Oxygen uptake and delivery must match the demand of working muscles, and are contingent on an effective integrated response of the cardiovascular and pulmonary systems; therefore radiation treatment for breast cancer may pose a risk to exercise tolerance. Thus, any change in cardiopulmonary exercise capacity ($VO_2$max) from pre-surgery values may serve as a biological marker for surgical or radiation-induced injury. Since the aerobic and anaerobic systems provide energy for activities requiring endurance and strength, routine tasks, leisure activities, work requirements, and physical training may all require increased effort.

Depending upon the patient's perception of the disease, its potentially fatal outcome, and the possibility of disfigurement, diagnosis and treatment of breast cancer may also induce psychological reactions. Distress levels are influenced by medical factors (site, stage, type and number of treatments), psychological factors such as coping abilities and emotional maturity, and by the social context in which patients are treated (Massie and Holland, 1991). By assessing subjective experience of changes in self-esteem, quality of life, and body image, probing beyond the effects of treatment on physiological functional capacity to its effects on psychological well being is possible.

There is an absence of research investigating the effects of a complete treatment program (surgery and radiation), rather than a single therapy modality, on indices of either physiological or psychological health: few repeated measures or prospective investigations have been done, and there is a shortage of pre-surgery and mid-radiation examinations.

Repeat assessment before, during, and after treatment intervention is needed in order to assess temporal patterns of change in both physiological and psychological health. Moreover, few studies have examined the relationship between functional and psychological status.

## RESEARCH PROBLEM

The aim of this study was to determine if changes occur in pulmonary function, exercise capacity, quality of life, self-esteem, or body image during surgical and radiation treatment for breast cancer.

## RESEARCH HYPOTHESES

Hypotheses to be tested are

(1)   that a significant decrease in Forced Vital Capacity (FVC), Forced Expiratory Volume in one second ($FEV_1$), $FEV_1$/FVC, Forced Expiratory Flow during the middle half of the FVC ($FEF_{25\%-75\%}$) and the hemoglobin-adjusted Diffusing capacity of the Lung for Carbon Monoxide ($a.DL_{CO}$) will be seen one week after radiation treatment for breast cancer, as well as two months after completing radiotherapy in comparison to pre-surgery values

(2)   that there will be a small, but insignificant increase in patient's FVC, $FEV_1$, $FEV_1$/FVC, $FEF_{25\%-75\%}$ and $a.DL_{CO}$ between one week and two month post-radiation measures

(3)   that one week and two-month post-radiotherapy measures of the maximal rate of oxygen uptake ($VO_2max$), expired minute ventilation (VE) and Peak Power Output

(PPO) will be significantly decreased in patients in comparison with pre-surgery measures

(4)     that measures of $VO_2$, VE, and PPO will improve slightly between the one-week and two-month post-radiation evaluations

(5)     that self-esteem, quality of life (QOL), and body image (BI) measures will be significantly depressed at mid-radiation and one-week investigations, but will return to pre-surgery levels by the two-month post-radiation testing

(6)     that all psychological measures will improve significantly between mid-radiation and one-week post-radiation tests

## LIMITATIONS AND DELIMITATIONS

1. Limitations

The following may affect the ability to generalize to all women diagnosed with Stage I or II breast cancer receiving post-surgical RT:

- participation was restricted to volunteers, thus the self-selected sample may have personal qualities influencing response to treatment

- because of limited patient availability, it was not possible to control for radiotherapy treatment protocol

- the influence of disease progression upon the variables in question cannot be controlled

- subject recruitment proved difficult, and a small N resulted

- interpersonal influences as a result of investigator-patient relationship may have influenced the psychological indices

2. Delimitations

- women with unilateral disease

- women with no previous breast cancer or radiation exposure to heart or lungs

- women with early stage breast cancer

## STUDY SIGNIFICANCE

Functional improvement has been a goal of cancer therapy since the beginning of contemporary cancer treatment (Ganz, 1994), yet a gap exists in the literature with respect to the acute effects of current therapies. As a result, disruptions in physiological and psychological functioning may not be considered in current treatment planning. Acute treatment effects have important implications for early stage breast cancer management, therefore treatment techniques may have to be re-evaluated and counselling staff made available. This investigation may also enhance planning of successful early intervention, breast cancer rehabilitation programs that address both physiological and psychological factors. Although it has been shown that exercise programs can improve cardiopulmonary exercise tolerance and mood state of women treated for breast cancer (MacVicar and Winningham, 1986; MacVicar et al., 1989), pre and post-treatment values have not been assessed. Unknown, therefore, is whether low pre-exercise values for various parameters have been because of treatment, or because of factors such as age or inactivity.

The current study is first to investigate the effects of a complete treatment program, including surgery and radiotherapy, on the physiological and psychological capacity of women with breast cancer. It is one of few studies to take a prospective approach; second to test patients during, rather than only prior to and after therapy; first to follow maximal $VO_2$ through a radiotherapy program for breast cancer, and first to conduct a pre-surgery investigation.

# CHAPTER 2: METHODOLOGY

## SUBJECTS

Females between the ages of 35 and 65, diagnosed with breast cancer and whose

mammogram indicated a tumour <5 cm were invited to participate in the study by one of two

local breast surgeons immediately following diagnosis. Patients with metastases, multiple

tumours, bilateral cancer or previous breast cancer, and those with concurrent major health

problems (e.g. cardiovascular disease, respiratory disease) were excluded. A verbal

description and information sheet on the study's purpose and procedures were provided by the

physician. The principle investigator contacted potential subjects by telephone to provide

additional information and to confirm the patient's participation. Subjects received a detailed

written and verbal description of the investigation, including participation time, testing

procedures, associated risks, and assurances of confidentiality prior to providing informed

consent for participation. Any patient subsequently receiving chemotherapy was eliminated

from data analysis. Approval for the study was given from the University of British Columbia

Clinical Screening Committee for Research and Other Studies Involving Human Subjects, and

data collected from September, 1996 to August, 1997.

## INSTRUMENTS AND PROCEDURES

Body composition measurements, as well as resting systolic and diastolic blood

pressure (mmHg) (Baumanometer®, Copiague, NY) and resting heart rate, taken on each

subject's uninvolved side (to prevent onset, worsening, or influence of lymphedema), were

recorded. After calibration with a standard of known value (10.9 g/dL), a blood hemoglobin photometer (HemoCue AB, Ängelholm, Sweden) was implemented to determine subject's hemoglobin (Hb) concentration values using the methods described by Vanzetti (1966). Subjects were asked to respond to a modified Quality of Life Index (Padilla *et al.*, 1983), the Self-Esteem Questionnaire (Robson, 1989), and the Body Image Visual Analogue Scale (Mock, 1993). Subjects then underwent pulmonary function (PFT) and $VO_2max$ tests. On only the first test date, subjects were also asked to complete the PAR-Q readiness-to-exercise, pre-diagnostic activity, and demographics questionnaires, as well as a patient information form including affected side, current medication use, and smoking history. Tests were performed consecutively; subsequent assessments taken at or near the same time of day, and all performed in the exercise physiology lab at the Allan McGavin Sports Medicine Centre.

## BODY COMPOSITION

Anthropometric data included measurement of body mass (Detecto industrial scale) and height as well as skinfold thickness (mm) at five sites: biceps, triceps, subscapular, supra iliac and medial calf (Harpenden skinfold calliper, John Bull, British Indicators Ltd.). Skinfolds were measured on each patient's unaffected side and were summed.

## PULMONARY FUNCTION TESTS

Pulmonary function was tested using a Collins DS I System equipped with Collins PLUS Pulmonary Software (Warren E. Collins Inc., Braintree, MA). Testing included resting, seated measures of spirometry, and the diffusing capacity for carbon monoxide ($DL_{CO}$). Temperature, as indicated on the Collins System, and ambient barometric pressure were recorded before each test. The DS I System was calibrated for volume prior to both

spirometry and diffusion testing sessions using a three-litre syringe. All data obtained was recorded in absolute values.

**Spirometry**

Forced Vital Capacity (FVC), Forced Expiratory Volume in one second (FEV$_1$), the FEV$_1$/FVC ratio, and the Forced Expiratory Flow during the middle half of the FVC (FEF$_{25\%-75\%}$) were determined using the FVC manoeuvre. A minimum of three trials were performed and the best effort for each subject was determined using American Thoracic Society (ATS) criteria (1995b). In addition, at least two maximum voluntary ventilation (MVV) tests were performed over a twelve second period and the results automatically extrapolated to sixty seconds. Each subject's best MVV effort was selected.

**DL$_{CO}$**

After calibration of the helium (He) and carbon monoxide (CO) analyzers, DL$_{CO}$ was determined using the single breath method described by Ogilvie *et al.* (1957). Each test was performed using a gas mixture consisting of 0.3% CO, 10% He, 21% oxygen (O$_2$) in a balance of nitrogen (N$_2$). To prevent the possible influence of either the Valsalva or Müller manoeuvres on DL$_{CO}$, all subjects were asked to relax their accessory respiratory muscles against a closed glottis during the ten second breath-hold. A minimum of two trials meeting ATS criteria (Ferris, 1978) were performed a minimum of five minutes apart and averaged; and DL$_{CO}$, alveolar volume (VA), and the DL$_{CO}$/VA ratio were recorded. The Collins diffusion system used has been found to be highly reliable (r = 0.98) when measuring pulmonary diffusing capacity (Sheel, 1995).

It has been shown that there is a significant linear relationship between hemoglobin and

$DL_{CO}$ (r = 0.74), and that a 1 g per 100 mL decrease in hemoglobin is associated with a seven

percent decline in $DL_{CO}$ (Dinakara et al., 1970). To determine whether changes in diffusing

capacity throughout treatment can be attributed to lung damage via RT and not fluctuations in

hemoglobin status, a correction must be made. Values of both $DL_{CO}$ and $DL_{CO}/VA$ adjusting

to a hemoglobin value of 13.4 g/dL [the average Hb for adult women (ATS, 1995a)] were

automatically calculated by Excel software (Microsoft® Version 6.0) using a manually-

entered equation:

*(a). Hb adjusted $DL_{CO}$ (a. $DL_{CO}$):*

$$Hb\text{-adjusted} = [observed\ DL_{CO}][(9.38 + Hb)/(1.7)(Hb)]$$

[observed $DL_{CO}$ = Collins value (mL/min/mmHg); Hb = hemoglobin value (g/100 mL); 9.38,

1.7 = correction constants (ATS, 1995a)].

### EXERCISE CAPACITY TEST

Exercise was done on an electronically-braked cycle ergometer (Lode BV Excalibur

V2.0, Groningen, The Netherlands) using a ramp protocol, beginning at 0 watts and

increasing by 20 watts per minute to volitional fatigue. Winningham (1983) provides

adequate justification for use of the a cycle ergometer for testing and exercise prescription

with a breast cancer population. While adjusting the ergometer seat and handlebar for

comfort, subjects were advised that keeping a pace of approximately 70 rpm would facilitate

testing. Patients were verbally encouraged to continue until they were exhausted. In order to

enhance metabolic recovery, subjects finished the session with a three minute cool down

period with zero load at patient-preferred rpm. Volitional fatigue, a respiratory exchange

ratio [RER, the ratio of carbon dioxide production ($VCO_2$) to oxygen consumption ($VO_2$)] over 1.0, a heart rate >85% of age-predicted maximum, or a plateau in $VO_2$ with increasing work rate (Davis, 1995) were regarded as objective indicators of maximal aerobic performance.

Heart rate (HR) was continuously recorded using a direct lead electrocardiogram (ECG) (Lifepack 6®, Physio Control, Againcourt, Ontario) and diaphoretic electrodes (3M), and percent arterial oxygen saturation ($\%SaO_2$) measured using a pulse oximeter (Ohmeda Biox 3740, Louisville, CO) and averaged every fifteen seconds. The accuracy of pulse oximetry is plus or minus 3% (Frownfelter, 1994), and has been validated (r = 0.96) as a measure of arterial hemoglobin oxygen saturation in critically ill patients (Mihm and Bruce, 1985). To increase local perfusion, a topical vasodilator cream (Finalgon®, Boehringer/Ingeheim, Burlington, ON) was applied to an earlobe prior to placement of the ear oximeter sensor.

A sample of inspired and expired gas was continuously taken from a Medical Graphics CPX/D pneumotach and was analysed by $O_2$ and $CO_2$ fast-response gas analyzers (Medical Graphics Corporation, St. Paul, MN) calibrated with two gases of known concentration before each test, which enabled the monitoring of $VO_2$ and VE on a breath-by-breath basis. The computer system calculated and displayed the average values every fifteen seconds, and output was recorded on a IBM computer interfaced with the metabolic cart. According to Lamarra and Whipp (1995), it is routinely possible to measure respired gas concentrations with errors below 0.1% or even 0.01% using fast-response, automated computational systems.

Maximum oxygen uptake was defined as the average of the four highest consecutive $VO_2$ (mL/min) values measured at the end of the test. If the last recorded value differed by more than 10% from the previous fifteen second value, it was not included as one of the four values for determining $VO_2$max. Decreased exercise tolerance was observed by recording PPO and $VO_2$max. The Rate of Perceived Exertion (RPE) (Borg, 1982) was determined by using the most recently developed rating scale constructed as a category scale with ratio properties. Verbal anchors and rapid conversion to a percentage of total effort allowed the interpretation of 0 - 10 range scale without difficulty. Results of all physiological tests were discussed so as to provide subject feedback and allow for return to pre-exercise heart rate and blood pressure conditions. Subjects were not permitted to leave the site until their heart rate was less than 100 bpm.

## QUALITY OF LIFE EVALUATION

Quality of life (QOL) was defined as patients' "appraisal of and satisfaction with their current level of functioning compared with what they perceive to possible or ideal" (Cella and Cherin, 1988). In order to assess changes in QOL, subjects were asked to complete the Quality of Life Index (Padilla *et al.*, 1983)--an index designed for cancer patients receiving either radiotherapy or chemotherapy, which was modified slightly to make it more applicable to those receiving only radiotherapy. This was accomplished by replacing items #2 and #3-- regarding nausea and vomiting--with a question investigating how much fatigue the patient was experiencing. In addition, question #13--regarding worry about the cost of medical care-- was omitted because of the Canadian Medicare support system. Subjects were asked to complete the questionnaire on how they felt during the visit, the "normal for me" descriptor

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indicating what was normal prior to illness. Twelve questions investigated three components of quality of life: psychological well-being, physical well-being and symptom control, which were applied using analogue scale. Two anchor words denoting the extremes of subjective response were positioned at either end of a 100 mm scale. Subjects placed an "X" on the line corresponding to their degree of agreement with the question, the distance from the "0" mark (mm) corresponding with the subjects' scores. All eleven items of the original fourteen item index used in the modified questionnaire have shown significant test-retest reliability ($r \geq 0.64$) for outpatient radiotherapy patients; both construct and discriminant validity have been indicated.

An overall Quality Life Index (QLI) was calculated as the mean of all twelve items. A psychological well-being subscore was calculated for each subject as the mean of satisfaction, general QOL, feelings of usefulness, fun and sleep scores; a physical well-being subscore was determined by averaging the scores in levels of appetite, eating, working, strength, and sexual activity; and a symptom control factor was calculated using the mean of the pain and fatigue scores.

### SELF-ESTEEM EVALUATION

Subjects were asked to respond to the Self-Esteem Questionnaire (Robson, 1989), which consists of thirty items in seven categories: significance (5), worthiness (5), appearance/social acceptability (5), resilience and determination (5), competence (4), control over personal destiny (4), value of existence (2). "Completely disagree" and "completely agree" were positioned at either end of a zero to seven scale, and subjects circled the number

corresponding to how they felt at that visit. Reliability and validity for the questionnaire are r = 0.96 and r = 0.80 respectively (Robson, 1989).

A total self-esteem score was calculated as the sum of responses to all thirty questions; subscores for each of the seven categories described were calculated by adding the questions investigating each respective category.

## *BODY IMAGE EVALUATION*

The Body Image Visual Analogue Scale (BIVAS) (Mock, 1993), a 100 mm horizontal scale with "complete dissatisfaction" at the left end and "complete satisfaction" at the right, was also administered. Subjects were asked to place an "X" upon the line which represented intensity of satisfaction or dissatisfaction with physical self on the day of the test; distance from the "0" mark (mm) constituted the subject's score. Data is not available on the BIVAS reliability or validity, but visual analogue scales are considered to be both reliable and valid (Gift, 1989).

## *WEEKLY ACTIVITY LOG*

To determine the influence of participation in activity or absence from it, all women were asked to keep a weekly log in which to record, and subjectively rank, involvement in physical activity. Activities that were recorded included bicycling, conditioning exercises (such as callisthenics, rowing, weight lifting), dancing (including aerobics), lawn and garden, running, sports, walking, water activities (including swimming), and winter activities (such as downhill and cross-country skiing); subjective intensity level was listed as light, moderate, vigorous, or very vigorous. A metabolic equivalent (MET) level for each activity was assigned using the Compendium of Physical Activities (Ainsworth, 1993); energy cost was

calculated for each activity session by multiplying the average body mass in kilograms by the assigned MET value and duration of activity/sixty minutes in order to estimate energy expenditure (Kcal). Logs were collected at the last testing session and daily totals were added to obtain a total for each test date. Activity for the year preceding diagnosis was also recorded using the same descriptors and MET assignment implemented in the weekly activity log. The energy cost of the activity was multiplied by both its duration/sixty minutes and frequency per week to obtain an annual total. Activity totals were summed to obtain an energy expenditure in Kcal for the year preceding diagnosis, allowing evaluation of the influence of pre-diagnostic physical status upon the response to treatment.

## TESTING TIMELINE

Initial subject testing occurred prior to surgical intervention (Test 1). Subjects repeated all measures three weeks after surgery, prior to the onset of radiotherapy (Test 2); type of breast surgery as well as the number of axillary nodes removed and involved were noted. Subjects also repeated all measures two weeks after commencement of radiotherapy (Test 3), as well as one week (Test 4) and two months (Test 5) after completion of radiation delivery. Subjects were tested two weeks after RT began in order to avoid the confounding effect of fatigue that follows radiation therapy (Greenberg *et al.*, 1992). Clinical radiotherapy treatment parameters such as beam quality (e.g. photons or electrons, the energy), total dose given, number of individual fractions, dose per fraction, overall treatment time, technique, nodes irradiated, and any cases of radiation pneumonitis were recorded once radiotherapy had been completed by referring to subjects' medical records. The study's progression in relation to treatment interventions is best displayed graphically:

```
D  T1  S    T2              BRT  T3        ERT  T4                    T5

⇓----⇓-----⇓--------⇓----------------⇓--------⇓-----------⇓--------⇓------------------------⇓--
0   21   28    53              93    106       118   124                    172
                            (Days)
```
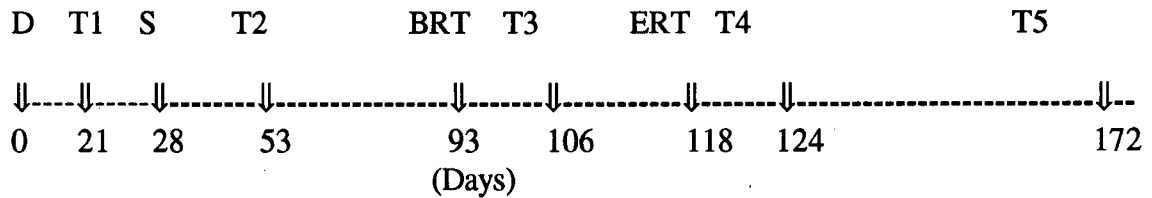
D = diagnosis; T# = test number; S = surgery; BRT = begin radiotherapy; ERT = end

radiotherapy  * Days compiled from Appendix D, Table 48.

## DESIGN AND STATISTICAL ANALYSES

Although FVC, $FEV_1$, $FEV_1$/FVC, a.$DL_{CO}$, VA, a.$DL_{CO}$/VA, $VO_2$max, self-esteem,

quality of life, and body image were the major areas of study interest, several related

parameters were also examined:

(a) body weight in kg

(b) SOS

(c) VE

(d) MVV

(d) PPO in watts

(e) max. heart rate in bpm

Within group analysis for all variable were analyzed by single factor (time) repeated

measures (RM) analysis of variance (ANOVA). Post-hoc comparisons using Tukey's

Honestly Significant Difference (HSD) procedure were used to determine individual

differences between test visits. The level of significance ($\alpha$) was set at $p<0.05$ for all

comparisons. RM ANOVAs were performed using SPSS Release 6.0, and Tukey's HSD tests

were calculated manually.

# CHAPTER 3: RESULTS

Of the fifteen women who volunteered for the study, one voluntarily withdrew from testing after being given a mastectomy and recommendation against further therapy; a second withdrew after deciding against adjuvant therapy (attempting alternative methods) despite physician recommendation, and a third withdrew citing constant fatigue and time constraint. Another five subjects, whose surgery indicated nodal involvement, transferred to a study investigating chemotherapy's effects on exercise tolerance in women with a Stage II diagnosis. The resulting group of seven women ranged in age from 47-62 (age = 54.1 ± 5.2 yrs; ht = 163.0 ± 7.0 cm; mass = 64.7 ± 12.3 kg), one with Stage 0 (TisN0M0), five with Stage I (T1N0M0) and one with Stage II (T1N1M0) breast cancer. Demographic information is summarized in Appendix D, Table 13.

## TREATMENT DETAILS

Subjects received primary treatment from either of two local physicians specializing in surgical breast cancer management. After considering pathological results of the breast biospy, surgery type was decided through surgeon and patient consultation. Individual data is summarized in Table 1.

Table 1. Surgical Details, individual subject data

| Subject | Surgery | Tumour size | Nodes | Nodes + |
|---------|---------|-------------|-------|---------|
| A | r. partial | 1.0 cm | 21 | 0 |
| B | r. mastect | 1.9 cm | 09 | 0 |
| C | l. partial | 1.5 cm | 15 | 0 |
| D | r. partial | 0.7 cm | 10 | 0 |
| E | l. partial | 1.0 cm | 14 | 4 |
| F | l. partial | 1.5 cm | 17 | 0 |
| G | l. partial | 1.0 cm | 10 | 0 |

r = right; l = left; partial = partial mastectomy; mastect = mastectomy; tumour size = maximum tumour diameter; nodes = axillary lymph nodes removed during in surgery; nodes + = number of axillary lymph nodes positive for carcinoma

A portion of tissue removed during surgery, examined in detail (Table 2), gave additional information which allowed for treatment determination through greater understanding of tumour behaviour.

Table 2. Pathological Details, individual subject data

| Subject | Type | Histology | Stage | ER Status |
|---------|------|-----------|-------|-----------|
| A | IFDC/DCIS | I/III | T1N0M0 (I) | 3+ |
| B | LCIS/DCIS | -/II | TisN0M0 (0) | 3+ |
| C | IFDC | I | T1N0M0 (I) | 1+ |
| D | IFDC | I | T1N0M0 (I) | 2+ |
| E | IFLC | - | T1N1M0 (II) | 3+ |
| F | IFDC/DCIS | I/I | T1N0M0 (I) | 3+ |
| G | IFDC/DCIS | I/III | T1N0M0 (I) | 2+ |

IFDC = infiltrating ductal carcinoma; DCIS = ductal carcinoma in situ; LCIS = lobular carcinoma in situ; IFLC = infiltrating lobular carcinoma; ER = estrogen receptor (See Appendix A--Staging and the Treatment for Early Stage Breast Cancer for more information on pathology)

Radiotherapy was the treatment choice of all subjects. Five women in the current investigation received 44 Gy treated to the whole breast, using a pair of opposed tangential fields in sixteen daily fractions--a schedule deemed acceptable by the local division of radiation oncologists (Olivotto *et al.*, 1996). Subject G received a slightly higher dose in twenty-five fractions as she was larger breasted than the other subjects. A lower total dose was given to subject B, who had undergone mastectomy rather than conservative surgery.

Photon beam axes were angled three to six degrees anteriorly so posterior beam edges were coplanar. Physics plans were calculated for each subject using the mid plane contour and 30° wedge filters to improve dose uniformity within the tangential fields. No subject received supraclavicular field radiotherapy. Nodal field irradiation was employed only for subject E, who had pathologically node-positive breast cancer. The amount of healthy lung tissue irradiated was determined by medial field chest film examination; greatest actual physical depths in centimeters are reported (Table 3).

Table 3. Radiation Details, individual subject data

| Subjects | Dosage (Gy) | Fractions | Dose/Fract (Gy) | Duration (days) | Quality | Lung Depth Hit |
|---|---|---|---|---|---|---|
| A | 44 | 16 | 2.75 | 23 | 4 MeV | 0.9 cm |
| B | 40 | 16 | 2.50 | 24 | 6 MeV | 1.4 cm |
| C | 44 | 16 | 2.75 | 22 | 6 MeV | 1.9 cm |
| D | 44 | 16 | 2.75 | 26 | 6 MeV | 1.6 cm |
| E | 44 | 16 | 2.75 | 22 | 6 MeV | # |
| F | 44 | 16 | 2.75 | 22 | 4 MeV | 1.2 cm |
| G | 50 | 25 | 2.00 | 35 | 6 MeV | 0.3 cm |

# information not available; subject A also received a direct boost dose of 7.5 Gy in three fractions in three days using 9 MeV electrons, subject G using 12 MeV; subject E also received 37.5 Gy to the left axillary nodes

All initial study measures (Test 1) were recorded prior to patient surgery, excluding subject G, whose Test 1 physiology, quality of life, and body image were estimated by first determining the average percentage change from pre-surgery (Test 1) to pre-radiation (Test 2) measures of the other subjects, and then adding this percentage to G's pre-radiation measures (Test 2). Activity/day between Test 1 and 2 was also estimated in this manner for subject G. Self-esteem measures for subject G's Test 1 were estimated by determining the average numerical change from pre-surgery (Test 1) to pre-radiation (Test 2) of the other subjects. In addition, missing Test 2 physiology data for subject A was calculated using the percentage change from pre-radiation (Test 2) to pre-surgery (Test 1). Although estimation of a variable may contribute to a more homogenous response to treatment, prediction of a single test for two of seven participants (i.e. two of thirty-five total tests) is unlikely to have large influence. In a repeated measures design, missing data for a single test results in the loss of all data for that participant, therefore calculations were made to avoid sacrificing sample size.

**PHYSIOLOGICAL DATA**

*ANTHROPOMETRY*

Body mass showed a small and consistent, but non-significant [$F(4,24) = 2.71$, $p = 0.054$, $ES = 0.526$] increase during treatment which continued two months after therapy completion (Table 4). Sum of skinfolds did significantly change over the testing period however [$F(4,24) = 4.61$, $p = 0.007$, $ES = 0.919$]. Subsequent Tukey's HSD tests revealed that the 13.0% and 12.9% increase in SOS between pre-surgery (Test 1) and one-week (Test 4) and two-month post-radiotherapy (Test 5) tests was significant [$p<0.05$]. Individual data can be found in Appendix D, Tables 15 and 16.

Table 4. Body Mass and Sum of Skinfolds, group data (n=6)

| | Test 1 | Test 2 | Test 3 | Test 4 | Test 5 |
|---|---|---|---|---|---|
| Mass (kg) | $64.7 \pm 17.3$ | $65.0 \pm 17.4$ | $66.2 \pm 17.7$ | $65.9 \pm 17.9$ | $66.1 \pm 16.7$ |
| SOS (mm) | $83.3 \pm 39.6$ | $91.3 \pm 42.4$ | $91.8 \pm 41.9$ | $94.1 \pm 44.5*$ | $94.0 \pm 39.9*$ |

Values are means ($\pm$ SD) * significantly different from Test 1 (p<0.05)


## PULMONARY FUNCTION

All spirometry measures, except FVC, changed significantly over the testing period.

Statistical information is related below (Table 5).


Table 5. Statistical Results, Pulmonary Function

| Measure | $F(4,20)$ | $p$ | $ES$ |
|---|---|---|---|
| FVC | 0.94 | 0.460 | 0.350 |
| $FEV_1$ | 4.26 | 0.012 | 0.976 |
| $FEF_{25-75\%}$ | 4.06 | 0.014 | 0.853 |
| $FEV_1/FVC$ | 5.53 | 0.004 | 0.943 |
| MVV | 3.13 | 0.038 | 0.974 |


$FEV_1$, $FEF_{25-75\%}$, and $FEV_1/FVC$ each decreased over the treatment period (Test 1-Test 4) [$p<0.05$], improving slightly between Tests 4 and 5. For $FEF_{25-75\%}$ and $FEV_1/FVC$ measures, improvement, however, was still decreased compared with pre-surgery values [$p<0.05$].

$FEV_1$ did not remain significantly depressed at Test 5, but marked reduction from pre-surgery measures was earlier, at Test 3 [$p<0.05$]. Changes from pre-surgery values were also seen in MVV values at both Test 2 and Test 5. Figure 1 shows group spirometry values; individual measures can be found in Appendix D, Tables 18-22. Subject E had difficulty performing

spirometry maneuvers due to an inability to open her jaw large enough to hold the apparatus, therefore her data was excluded from analysis.

Figure 1. Spirometry (n=6)
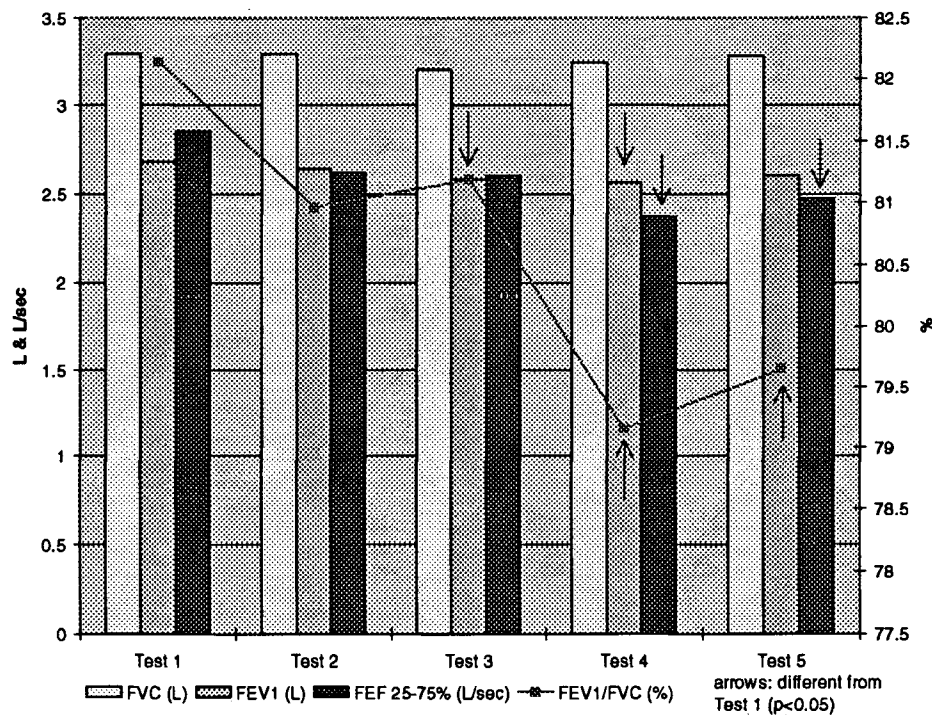


Hemoglobin-adjusted pulmonary diffusing capacity for carbon monoxide also declined significantly across the testing period $[F_{(4,20)} = 2.89, p = 0.049, ES = 0.787]$. There was a significant decline from pre-surgery values one week after radiotherapy completion $[p<0.05]$, yet a.DL$_{CO}$ showed a small, but insignificant increase between one-week (Test 4) and two-month (Test 5) post-radiation measures. Hemoglobin-adjusted DL$_{CO}$/VA showed a similar trend $[F_{(4,20)} = 5.34, p = 0.004, ES = 0.981]$, yet continued to decline from Test 4. Tukey's

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HSD tests revealed that changes from pre-surgery values were statistically significant at both Test 4 and 5. Alveolar volume steadily increased throughout treatment, but did not change significantly [$F(4,20) = 2.35$, $p = 0.089$, $ES = 0.689$. Figure 2 represents group values over the therapy program, and individual data is displayed in Appendix D, Tables 23-25. Individual hemoglobin data, which did not show modification [$F(4,20) = 0.64$, $p = 0.642$, $ES = 0.449$], can be viewed in Appendix D, Table 17. Subject A did not complete the diffusing capacity tests until Test 4 therefore her data was not included in the analysis.

Figure 2. Diffusing Capacity (n=6)



a. DLCO/VA    VA (mL)    a. DLCO (mL/min/Hg)    arrows: different from Test 1 (p<0.05)
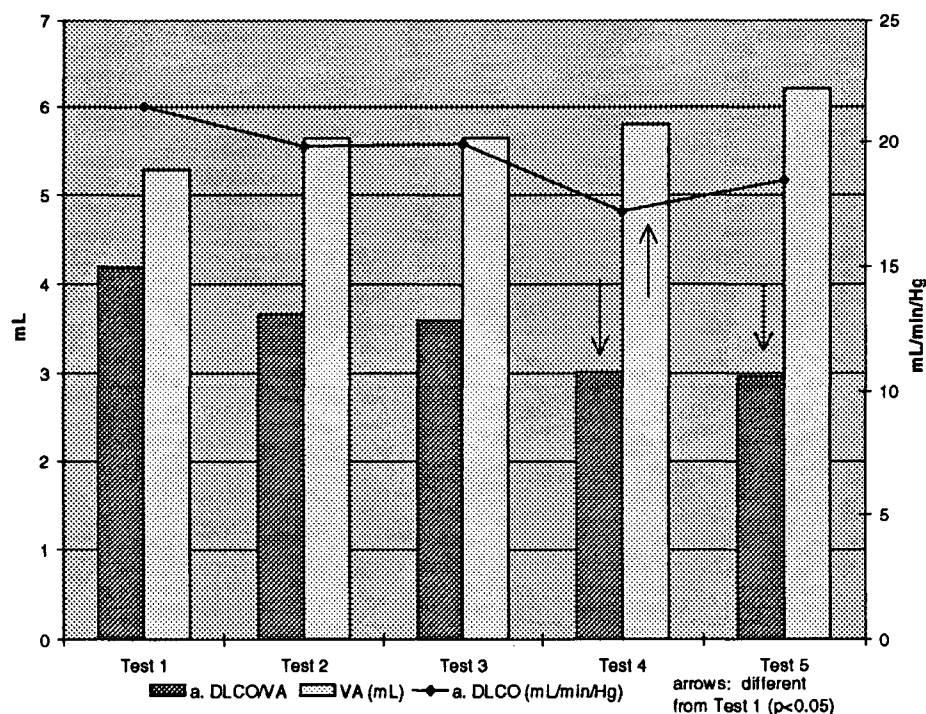
## EXERCISE CAPACITY

The ability to exercise maximally did not change significantly over a course of surgery and radiotherapy for early stage breast cancer when expressed in absolute $VO_2$max values [$F$ (4,24) = 1.73, $p = 0.177$, $ES = 0.693$] or $VO_2$max values relative to body mass [$F$ (4,24) = 1.38, $p = 0.271$, $ES = 0.456$]. Both values are presented in Table 6. Individual data is summarized in Appendix D, Tables 26 and 27. Like $VO_2$max values, there were no significant changes in HRmax [$F(4,24) = 2.08$, $p = 0.115$, $ES = 0.411$] or PPO [$F(4,24) = 2.30$, $p = 0.088$, $ES = 0.450$], however there was a significant change in $VE$ [$F(4,24) = 3.17$, $p = 0.032$, $ES = 0.529$] during the therapy program (Table 6). Post-hoc multiple comparisons indicated that two-month post-radiotherapy values were significantly different from both pre- and post-radiation values [$p<0.05$]. Individual data is related in Appendix D, Tables 28-30.

Table 6. Metabolic Response to Maximal Exercise, group data (n=7)

|  | Test 1 | Test 2 | Test 3 | Test 4 | Test 5 |
|---|---|---|---|---|---|
| $VO_2$ (L/min) | 1.27 ± 0.29 | 1.23 ± 0.24 | 1.31 ± 0.30 | 1.28 ± 0.32 | 1.39 ± 0.46 |
| $VO_2$ (mL/min/kg) | 20.2 ± 5.0 | 19.6 ± 4.6 | 20.3 ± 4.6 | 19.9 ± 4.6 | 21.6 ± 7.5 |
| VE (L) | 62.2 ± 15.9* | 63.7 ± 9.2* | 68.9 ± 16.6 | 68.0 ± 13.9 | 77.0 ± 23.3 |
| HRmax (bpm) | 152  15 | 154 ± 13 | 164 ± 23 | 165 ± 22 | 160 ± 19 |
| PPO (watts) | 131 ± 29 | 130 ± 21 | 132 ± 31 | 148 ± 31 | 146 ± 32 |

Values are means (± SD) * significantly different from Test 5 (p<0.05)

Interestingly, three subjects experienced exercise-induced hypoxemia, indicated by percent arterial oxygen desaturation ($SaO_2 \leq 90\%$). Subject D and F reached a value of 89%

before ceasing exercise on Test 5 and 3 respectively; subject G obtained 90% upon the completion of Test 4. All values can be found in Appendix D, Table 31.

## DATA SUMMARY AND PREDICTED VALUES

To establish norms and determine the significance of changes during therapy, values for healthy patients with the same mean age, body mass, and height as the sample population were estimated using the PLUS DS I software (Collins 2). The predicted value for MVV was calculated using the equation of Baldwin *et al.* (1948); $DL_{CO}$ using the equation of Gaensler and Wright (1966), and all other spirometry using the equations of Knudson *et al.* (1983). $VO_2$max and HRmax predicted values were obtained from the equations of Wasserman *et al.* (1987). Information can be found in Table 7.

Table 7. Physiology Summary and Predicted Values

| Measure | Predicted | Test 1 | % Predicted | Test 4 | % Predicted |
|---------|-----------|--------|-------------|--------|-------------|
| FVC (L) | 3.12 | 3.29 | 105 | 3.24 | 104 |
| $FEV_1$ (L) | 2.55 | 2.68 | 105 | 2.55 | 100 |
| $FEF_{25-75\%}$ (L/sec) | 2.68 | 2.86 | 107 | 2.37 | 88 |
| $FEV_1$/FVC (%) | 81.3 | 84.1 | 103 | 79.2 | 97 |
| MVV (L) | 77.6 | 107.5 | 139 | 101.4 | 131 |
| a.$D_{LCO}$ (mL/min/Hg) | 19.6 | 21.4 | 109 | 17.2 | 88 |
| $VO_2$ (L/min) | 1.46 | 1.27 | 87 | 1.28 | 88 |
| HRmax (bpm) | 166 | 152 | 92 | 165 | 99 |

**PSYCHOLOGICAL DATA**

*QUALITY OF LIFE*

Subject measures of the overall QLI [$F(4,20) = 5.13$, $p = 0.005$, $ES = 0.886$], as well

as each subscore--physical [$F(4,20) = 6.78$, $p = 0.001$, $ES = 0.994$], psychological [$F(4,20) =$

4.91, $p = 0.006$, $ES = 0.765$], and symptom [$F(4,20) = 2.96$, $p = 0.045$, $ES = 0.990$]--changed

significantly during treatment. Subsequent Tukey's test for multiple comparisons indicated

low values at mid-radiation (Test 3) were statistically different from Test 5 for psychological

QOL, but from both pre-surgery (Test 1) and two-month post radiation tests (Test 5) for

physical, symptom, and overall QOL. It is interesting to note that Test 5 measures are

actually higher than those for Test 1 in all QOL parameters, except the physical subscore.

Group relationships are represented graphically in Figure 3; Tables 32-35 (Appendix D)

contain individual data. Quality of life and body image indices were not completed by subject

A for tests 1 or 2, nor did she complete any of the self-esteem questionnaires; therefore her

psychological data was not included in the analysis.

Figure 3. Quality of Life Index and Subscores (n=6)
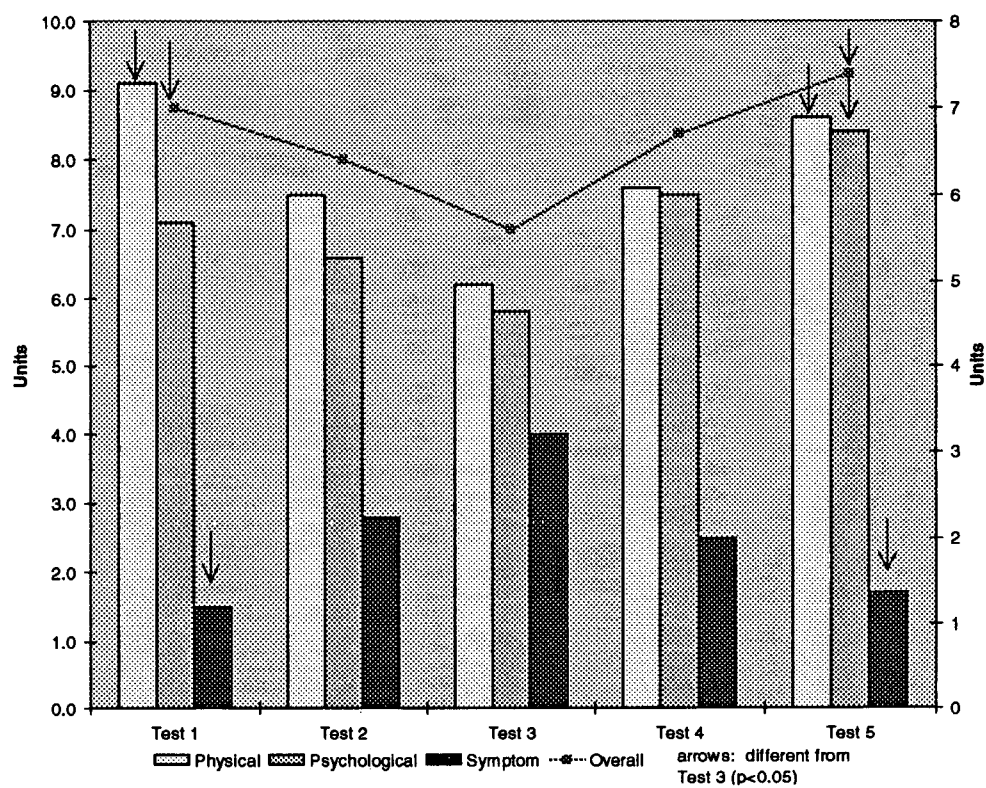


## SELF-ESTEEM

Unlike QOL, self-esteem did not change globally or in any subgroup over the surgery

and radiotherapy treatment protocol. Statistical information in summarized in

Table 8.

Table 8.  Statistical Results, Self-Esteem

| Measure | F(4,20) | p | ES |
|---|---|---|---|
| Appearance | 0.49 | 0.742 | 0.763 |
| Competence | 0.93 | 0.468 | 0.470 |
| Control | 1.54 | 0.230 | 0.646 |
| Resilience | 0.83 | 0.520 | 0.611 |
| Significance | 1.45 | 0.253 | 0.710 |
| Value | 0.59 | 0.675 | 0.818 |
| Worthiness | 0.36 | 0.837 | 0.709 |
| Global | 1.18 | 0.350 | 0.753 |

Group data is presented in Table 9, and individual subject data in Appedix E, Tables 36-43.

Table 9.  Self-Esteem, group data (n=6)

| | Test 1 | Test 2 | Test 3 | Test 4 | Test 5 |
|---|---|---|---|---|---|
| Appearance | 18.5 ± 5.8 | 20.2 ± 3.8 | 18.8 ± 5.1 | 18.2 ± 2.9 | 18.7 ± 2.7 |
| Competence | 12.3 ± 2.7 | 14.0 ± 4.2 | 15.0 ± 3.7 | 14.0 ± 2.8 | 14.5 ± 3.6 |
| Control | 12.7 ± 4.4 | 11.7 ± 3.9 | 12.8 ± 4.9 | 10.0 ± 3.0 | 11.0 ± 1.7 |
| Resilience | 14.3 ± 3.9 | 15.3 ± 2.2 | 14.8 ± 1.7 | 13.8 ± 1.7 | 13.0 ± 3.2 |
| Significance | 20.3 ± 3.8 | 20.5 ± 2.7 | 20.7 ± 2.9 | 19.0 ± 2.8 | 19.2 ± 2.5 |
| Value | 11.3 ± 2.3 | 10.3 ± 2.3 | 10.8 ± 1.8 | 11.0 ± 2.5 | 11.2 ± 1.8 |
| Worthiness | 18.2 ± 2.8 | 17.5 ± 1.8 | 17.5 ± 2.0 | 17.7 ± 2.3 | 18.3 ± 1.9 |
| Global Total | 106.8 ±15.1 | 109.5 ± 13.1 | 110.5 ± 13.5 | 103.8 ± 14.8 | 107.5 ± 11.5 |

Values are means (± SD)

## BODY IMAGE

Group measures for body image mirrored the results of QOL--changes were significant over the testing period [$F(4,20) = 3.04$, $p = 0.041$, $ES = 0.806$], with higher values at Tests 1 and 5 and the lowest values at Test 3.  Tukey's HSD tests indicated mid-radiation BI was significantly lower than BI measured two months following radiotherapy [$p<0.05$], yet it was not statistically lower than pre-surgery BI.  Figure 4 shows the change in body image

during a therapy program which included both surgery and radiotherapy. Individual changes may be viewed in Appendix D, Table 44.

Figure 4. Body Image (n=6)
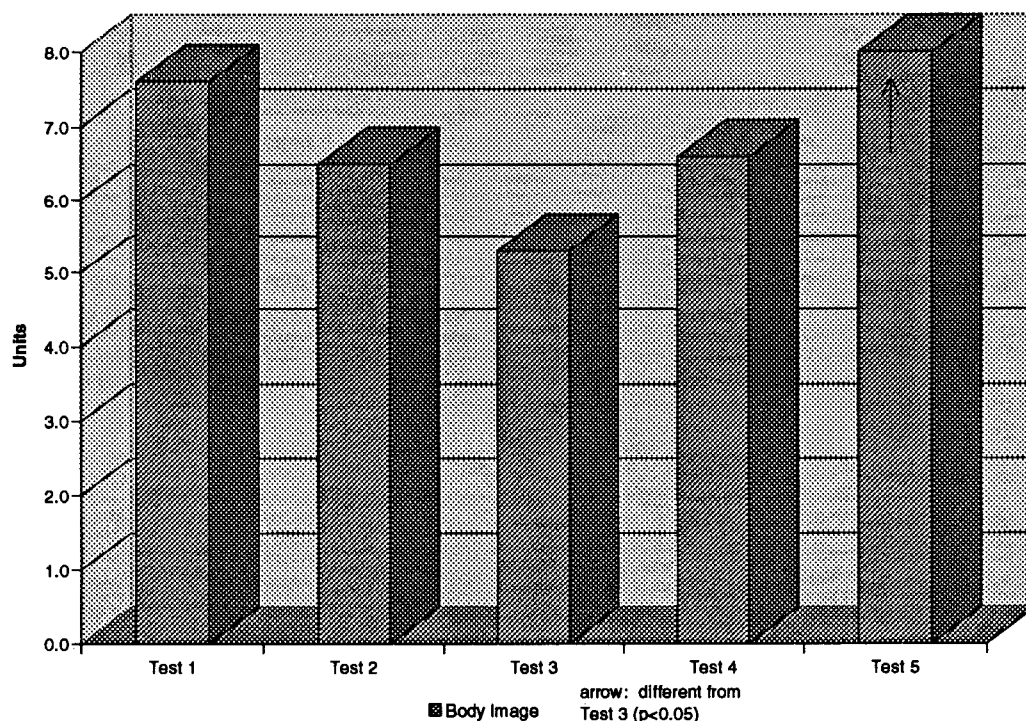


ACTIVITY LEVELS

Subjects' daily activity levels did not change significantly over the course of the treatment program [$F(4,20) = 2.14$, $p = 0.138$, $ES = 0.375$], however daily activity ($193 \pm 137$) was significantly different from the activity practiced for the year preceding diagnosis averaged over 365 days ($406 \pm 250$). It should be noted, however, that some changes in individual activity levels during the treatment period were masked by assessing the mean.

Group activity over each testing period is shown in Table 10; individual data summarized in Appendix D, Tables 45 and 46. Subject A did not return the activity log therefore her activity is not included in the analysis.

Table 10. Activity Levels, group data (n= 6)

| | Test 1-2 | Test 2-3 | Test 3-4 | Test 4-5 | Mean | Pre-diag/dy |
|---|---|---|---|---|---|---|
| MEAN Kcals ± SD | 2 992 ± 2 775 | 8 465 ± 6 928 | 6 009 ± 8 463 | 11 526 ± 10 314 | - | - |
| MEAN days ± SD | 31 ± 5 | 55 ± 36 | 17 ± 5 | 49 ± 7 | - | - |
| MEAN Kcals/day ± SD | 104 ± 77 | 159 ± 82 | 292 ± 300 | 221 ± 166 | 193* ± 137 | 406 ± 250 |

Pre-diag/day = activity the year preceding diagnosis ÷ 365 days/year; * significantly different from Pre-diag/day (p<0.05)

**SMOKING ACTIVITY**

Although all subjects were non-smoking during therapy, four were previously regular smokers. Pre-diagnostic lifetime smoking activity is summarized in Appendix D, Table 47 with group data described below (Table 11).

Table 11. Smoking Activity, group data (n=7)

| SUBJECTS | Smoke-yrs | Pack/wk | Packs/yr | Total Packs Smoked | Smoke-free yrs |
|---|---|---|---|---|---|
| MEAN ± SD | 17 ± 20 | 2 ± 3 | 115 ± 171 | 4387 ± 7596 | 4.3 ± 6.0 |

# TREATMENT AND TESTING TIMELINE

Planned study interventions--one week prior (Test 1) and three weeks after surgery (Test 2), two weeks after the commencement of RT (Test 3) and one week (Test 4) and two months (Test 5) after the completion of RT--showed little time deviation. However, the timing between diagnosis and surgery, as well as surgery and radiotherapy varied considerably among subjects. The mean time between treatment and test interventions are contained in Table 12. Individual data can be viewed in Appendix D, Table 48.

Table 12. Treatment and Testing Timeline, group data (n = 7)

| SUBJ. | D-T1 | T1-S | S-T2 | T2-BRT | BR-T3 | T3-ERT | ERT-T4 | T4-T5 |
|-------|------|------|------|--------|-------|--------|--------|-------|
| MEAN | 21 | 7 | 25 | 40 | 13 | 12 | 6 | 48 |
| ± SD | ± 13 | ± 7 | ± 7 | ± 33 | ± 3 | ± 5 | ± 2 | ± 7 |

D = diagnosis, T# = test number, S = surgery, BRT = begin radiotherapy, ERT = end radiotherapy

# CHAPTER 4: DISCUSSION

Breast cancer incidence is on the rise. Yet, thankfully, tumours are at an earlier stage; with better long term prognosis--tumours for which surgery and adjuvant radiotherapy is often prescribed. Breast cancer mortality is on the decline. Consequently, women treated for the disease are "survivors" longer than they are "patients" and functional issues have come to the forefront. The current investigation is the first to describe acute effects of a complete therapy program for early stage breast cancer on both physiological and psychological health.

Although it has been suggested that no gross abnormalities in lung function occur before four to eight weeks after radiation delivery (McDonald *et al.*, 1995), significant changes one week and two months following radiotherapy's termination were demonstrated in this study. Maintenance of FVC with concurrent decreases in $FEV_1$ and $FEV_1/FVC$ indicate treatment-induced airflow limitation. A decline in $FEF_{25-75\%}$, a measure indicative of medium-to small-airway status, helps confirm the trend toward airway obstruction. These findings are in support of a variety of previous research demonstrating post-radiation obstructive changes within four months of radiotherapy completion (Kaufman *et al.*, 1986; Botterman *et al.*, 1990; Lund *et al.*, 1991).

Although Kimsey and colleagues (1994) reported no mid-treatment changes in spirometric parameters in women receiving a total dose of 40-50 Gy; changes from pre-surgery measures were evident in the study population after delivery of an average of eleven fractions at a mean 2.6 Gy/fraction--for a total dose of 28.6 Gy. Mid-radiation changes in $FEV_1$ reached statistical significance. This suggests that damage to pulmonary tissue may be

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immediate and that injury worsens with increasing dose. Higher dosage has been shown to be associated with greater lung injury (Van Houtte, 1987; Wallgren, 1992).

Obstructive changes observed within one week and two months following therapy are likely a result of direct lung damage. Pneumonitis, an inflammation of lung tissue, is one of the early signs of radiation damage to the lungs (Wallgren, 1992), symptoms appearing six to twelve weeks after therapy (Gross, 1977). Symptomatic presentation of radiation pneumonitis is infrequently associated with breast cancer radiotherapy (Botterman et al., 1990; Lingos et al., 1991; Roberts et al., 1993; Kimsey et al., 1994), yet computed tomography has indicated radiological changes without patient cough, fever, or dyspnea (Schratter-Sehn et al., 1993). It appears that the onset of inflammation, a problem linked to obstructive lung disease, is responsible for changes observed in the current sample. Inflammatory processes increase small airway resistance by edema, mucus production and smooth muscle constriction (Ruppel, 1994). In addition, the fact that pneumonitis is transient supports findings that suggest a move towards "recovery" in both $FEF_{25-75\%}$ and $FEV_1/FVC$ two months after the cessation of radiation treatment.

Alveolar exudation, edema and excess surfactant production resulting from damage to not only type I and II pneumocytes, but also capillary endothelial cells may also result in impaired gas exchange (Coggle et al., 1986; McDonald et al., 1995). The 20% decrease in a.$DL_{CO}$ one week after radiotherapy completion was significant when compared with pre-surgery measures. A decrease in a.$DL_{CO}/VA$ from pre-surgery values, which proved to be significant at both one-week and two-month post-radiation evaluations, with a simultaneous, consistent increase in VA confirms obstructive damage. Diffusion limitation is likely the result

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of an inflammatory increase in the alveolar-capillary membrane's thickness. A reduction in

membrane diffusion capacity (DM), rather than a change in the amount of blood in the

vascular bed (Vc) would confirm this hypothesis. Concurrent obstructive changes in $FEF_{25-75\%}$ and diffusion suggest that obstruction lies in the small airways and alveoli. According to

Deeley (1976), the lung's acute reaction to radiation is a filling of alveoli with exudate,

necrotic cells and lymphocytes in addition to thickening of the intra-alveolar septa.

Although airflow limitation was induced by the surgery and radiotherapy program,

subjects maintained "normal" spirometry and diffusing capacity. All values in Table 7 are

within the average deviation from predicted that is accepted as normal-- FVC and $FEV_1 \pm$

20%; $FEF_{25-75\%} \pm 30\%$, $FEV_1/FVC < 0.80$ only in the presence of impaired previous measures,

$DL_{CO} \pm 15-20\%$ (Wagner, 1992), and MVV $\pm 30\%$ (Ruppel, 1994). Confirmation of

normality comes from the guidelines for grading the severity of pulmonary function

impairment provided by Morgan and Seaton (1984). It is interesting to note that although

$FEF_{25-75\%}$, $a.DL_{CO}$, and $VO_2$max were all 88% of predicted after a surgery and radiation

program (Test 4), it was only pulmonary function measures that were decreased as a result of

the treatment--$VO_2$max was already low (87%) prior to therapy's commencement.

Literature suggesting deleterious effects of radiotherapy on the heart and lungs have

often addressed technology implemented ten to fifteen years ago. With current three-

dimensional dose planning, both acute and long term effects may be minimized. Moreover,

given current techniques, functional changes may be rare due to the relatively small lung

volume irradiated in combination with the physical reserve capacity of the lungs (Bentzen *et*

*al.*, 1996). Having compared perfusion scans with pulmonary function tests, Lund and colleagues (1991) concluded that changes in most cases have minimal functional significance. While acute changes were not clinically significant, and subjects were absent of symptoms, late effects may still pose a risk for this group.

Although there is a trend toward "recovery" only two-months following radiotherapy in the study population, spirometry and diffusing capacity have been reported to not return to pre-radiation values until up to two years following therapy completion (Kimsey *et al.*, 1994). However, reports of late recovery (Kaufman *et al.*, 1986; Groth *et al.*, 1989; Kimsey *et al.*, 1994) may be linked to the use of supra-infraclavicular and axillary nodal radiation which include greater lung volumes. Lack of a boost dose in the subjects under study may also have helped to reduce long-term changes in pulmonary function. Retrospective observation indicates that early stage breast cancer patients with negative margins do not benefit from boosting; therefore it may not be recommended. As Galinsky *et al.* (1994) have pointed out, it is associated with increases in both pigmentation and telangiectasia.

In patients who receive daily therapy, the heart and lungs may not have the ability to repair injury before subsequent radiation dosages. In fact, radiation may affect the ability of these organs to repair themselves even if weeks or months separate the first and second treatments (Cherniack *et al.*, 1994). Although literature indicates that breast cancer radiotherapy may pose a great risk to healthy tissue and therefore patients' ability to exercise, no significant change in exercise capacity ($VO_2$max, HRmax, or PPO) was demonstrated in this group. Results do not support the hypothesis, but do advocate previous literature examining exercise performance before and after radiation (Strender *et al.*, 1986; Greenberg

*et al.*, 1992) or chemotherapy treatment (MacVicar and Winningham, 1986; Mock *et al.*, 1994). Exercise capacity also changed little (8.4%) in women treated with radiotherapy compared with a healthy control group (McKenzie *et al.*, 1996). Women treated with chemotherapy have shown 24.6% lower values than a control group recently diagnosed with the disease (Earle *et al.*, 1996). Values for $VO_2max$ in study participants were not 20-40% below predicted, therefore the sample would not be considered to have even mild impairment (Ruppel, 1994). Healthy pulmonary function status may aid to maintain exercise capacity values.

The general increase in minute ventilation (VE) over the testing period, which became significantly different from pre-surgery and pre-radiation values at Test 5, may be an attempt to better ventilate alveoli reduced in function. According to Madama (1993), decreases in the effective alveolar ventilation (VAeff) can cause hypoxemia, and compensatory ventilation acts to prevent hypoxemia in subjects with minor pulmonary limitation. Interestingly, three subjects exhibited exercise-induced arterial hypoxemia ($SaO_2<90\%$) after the commencement of RT. Measurement of $\%SaO_2$--a hypoxemic index--is often used to detect and assess the severity of respiratory disease (Wagner, 1992). The significant decrease in diffusing capacity over the testing period supports this explanation of increased VE, as low $DL_{CO}$ is often used as a predictor of desaturation (Ruppel, 1994). Furthermore, maximum ventilation rarely exceeds 70% of the MVV (Wagner, 1992), but may approach the MVV if there is a ventilatory limitation to exercise. Rather than using mean values of MVV, which showed inconsistent results, the product of $FEV_1$ and 35 (a measure highly correlated with, and often used in replacement of MVV) was implemented in this study to determine ventilatory capacity. At

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Test 1 and 5, the women had VE values corresponding to 66% and 86%, respectively, of their maximal ventilatory response. This supports the hypothesis that increased ventilation may act to counteract changes in the quality of gas exchange. Ventilatory reserve [1 - (VE/MVV)] is often compromised in patients with obstruction (Ruppel, 1994). It should be noted, however, ventilatory changes may be partially attributed to higher peak power outputs at Tests 4 (148 watts) and 5 (146 watts) as compared with pre-surgery (131 watts)--VE increases with increasing work. Relief of finishing a long therapy program, undoubtedly resulting in increased motivation, likely contributes to higher values for PPO. Tests 4 and 5 were conducted one week and two months after radiotherapy's termination. The increase in PPO was not statistically significant.

Several factors are associated with exercise-induced hypoxemia (EIH), including hypoventilation, veno-arterial shunts, ventilation/perfusion (V/Q) mismatch and diffusion limitation. According to Sheel (1995) hypoventilation and veno-arterial shunts have little influence on EIH, V/Q mismatch and diffusion limitation have the greatest effect. The proposed inflammation of the alveolar-capillary membrane would be considered a limitation in the diffusing capacity of carbon monoxide. Hypoxemia did not appear to be related to any other variable, however one subject who experienced desaturation received twenty-five rather than sixteen fractions with a higher total dose to the breast.

It appears that activity in the year preceding diagnosis may act to influence the severity of change in $DL_{CO}$ --those subjects more active prior to surgery and radiotherapy experienced smaller changes in diffusing capacity. However, spirometric changes did not seem to correlate with activity levels. Surprisingly, neither diffusing capacity nor spirometry measures appear to

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be affected by smoking activity, age or the amount of healthy lung tissue irradiated. However, conclusions are limited due to the modest sample.

In order to properly assess the effects of only treatment on functional capacity, post-diagnostic activity was followed. Daily activity levels were halved (from 406 to 193 Kcal) between activity measured for the previous year and activity over the treatment period. The patients who exhibited the most dramatic changes were no longer able to maintain regular activities which contributed largely to their exercise frequency--tennis, golf, swimming, and gardening--all of which were hampered by the surgical side-effects of pain, decreased mobility and lymphedema.

Activity may have played a role in subjects' maintenance of maximal exercise tolerance. Although statistically different from pre-diagnostic activity, activity levels were maintained throughout the treatment program as well as two months following RT. Patients who did show some deviation in activity during the program (Subjects E and G) also did not experience a change in exercise tolerance. It has been suggested that cancer patients become entangled in a negative cycle of debilitation and reduced physical conditioning that fosters a further decrease in physical activity (MacVicar and Winningham, 1986). Progressive inactivity resulting from the side-effects of treatment is likely to influence patient ability to perform maximal exercise. Exercise tolerance in women treated for left breast cancer, where the heart may be at risk of radiation exposure, was similar to those treated for the cancer in the right. It should be noted that patients who volunteer for an "exercise" study may be younger, or more active or motivated than those not tested. As a result, maximal exercise capacity, as well as pulmonary function, may change to a greater extend in those who

potentially have lower pre-surgery health status. The stability of exercise tolerance, in addition to an absence of change in HRmax, may indicate that cardiac function is maintained through surgery and radiation. Conclusions can not be made without a more accurate measure of cardiac function, however.

Activity logs also allowed investigation of physical activity's influence on feelings of decreased quality of life, self-esteem, and body image that may be associated with a breast cancer program. Upon subjective examination of individual data, it appears that neither pre-diagnostic nor treatment activity levels influenced subject response to psychological measures.

Regardless of age, marital status, or physical activity levels, significant changes in quality of life and body image were evident during the therapy program. A preliminary visit to the oncologist as well as communication with their primary physician left the women well informed of the treatments they would receive, the reason for them, as well as potential side effects. After they had interviewed various radiotherapy patients, Peck and Boland (1977) stated that appreciation was expressed by patients who had been warned about possible side effects. Those not informed felt disappointed, angry, and often misinterpreted symptoms as signs of treatment failure. Women involved in this study similarly reported that preparation procedures for RT such as films, a mock visit, and pamphlets helped alleviate concern, and that radiotherapy staff were very supportive. However, many subjects noticed special precautions taken by staff members, the presence of thick doors, and their being left alone during exposure. Furthermore, some felt as if they had become "one of those" [with cancer] and only a file number. Massie and Holland (1991) report that many do not feel the emotional impact of a breast cancer diagnosis until they begin the daily routine of radiation therapy. It is

suggested that the emotional response is aided by frequent visits with exposure to others with cancer, as well as cumulative fatigue. Exhaustion was most commonly cited as a reaction to radiotherapy sessions. General weakness may also foster a sense of disability and poor life quality.

Undesirable side-effects imposed by treatment, such as fatigue as well as surgical scars, are likely responsible for declines in QOL and BI measures as values were highest prior to any treatment intervention and returned to pre-surgical values two months after radiotherapy completion. Interestingly, body image, overall QOL and physiological and psychological QOL subscores were higher on Test 5 than Test 1. This suggests that these parameters were already depressed as a result of breast cancer diagnoses. Both BI and QOL were lowest at the mid-radiation test. Tattoo marks and cosmetic changes on an organ rich in meaning may contribute to decreases in these variables. Feelings of claustrophobia, and being around frightening machinery on a daily basis may also be of influence (Payne *et al.*, 1996). Low QOL and BI may also be fostered by unproductive feelings while taking time off employment.

It has been suggested that anxiety may be higher at RT completion due in part to the loss of close observation and emotional support of the radiotherapy clinic (Massie and Holland, 1991), and that uncertainty, anger, and depression increase at this time (Holland *et al.*, 1979; Leigh, 1994). Yet, QOL, as hypothesized, returned to pre-surgery values two months after RT; subjects relieved to finish a stressful and time-consuming program. Relief would also explain the increase between mid-radiation and one week post-radiation tests--one week appears to be sufficient for a move towards "recovery". Although the length of the

surgery-radiotherapy interval has not been associated with an increased risk of recurrence (Nixon *et al.*, 1994), waiting periods of up to eight weeks for women participating in the current study may have had great influence on perceived QOL.

Even though it is not unusual for cancer patients to feel as if they have lost control over their lives (Hinterbuchner, 1978), subject global self-esteem and subscores remained stable throughout the course of treatment. Interestingly, body image, which changed dramatically, is often thought of as an integral part of self-esteem (Mock, 1993). The lack of change in self-esteem is most conceivably related to its static nature and the fact that the women who volunteered for the study were of a certain type--secure, out-going and confident in their return to good health. Nelson (1991) reported that self-esteem was not significantly different in women who received surgery without adjuvant therapy when compared to healthy controls.

Changes in QOL and BI may also be related to body mass and subcutaneous fat consistently gained over therapy's duration. Segal *et al.* (1996) found that compared with women measured prior to receiving adjuvant therapy, breast cancer patients who had undergone a mean nine and a half weeks of adjuvant chemotherapy had 16.2% higher body mass and a sum of skinfolds 50% larger. Changes may be related to an increased consumption of "comfort" foods high in calories, or possibly greater access to food as there is more time spent at home--all women in the study took leave from work. Furthermore, although activity levels did not change over the course of treatment, the quality of the activity (i.e. energy expenditure) may have been lower even though effort was subjectively evaluated

to be the same. Subjects may have believed exertion was equivalent due to confounding fatigue.

Although activity logs did not provide evidence supporting the use of exercise as a rehabilitation strategy for breast cancer management, the advantages of exercise in the general population have been well described not only on physiological, but also on psychological measures. In a review of eleven studies addressing exercise as rehabilitation from breast cancer treatment, Friedenreich and Courneya (1996) conclude that planned physical activity appears to improve both physiological and psychological well-being. Patients may choose to engage in an exercise program to alleviate fatigue and reduce side effects of treatment. Furthermore, group interaction may help foster a positive sense of life quality. Respondents to surveys in *Runner's World* and *Bicycling* magazines indicated that they felt physically and mentally better as a result of activity and many advised that exercise helped them cope with the stress of treatment (MacVicar and Winningham, 1986). Regular activity may also explain the lack of change in exercise capacity in the current study. This implies that normal physical activities during breast cancer treatment are important for maintaining functional capacity, and suggest that increased activity through an exercise program may help control changes in pulmonary function.

## SUMMARY

Study results corroborated previous research suggesting that radiation in the treatment of breast cancer induces obstructive changes in pulmonary tissue. Decreases in spirometry and diffusing capacity were suspected to be due to inflammation. Yet, findings indicated that recovery began within two months of radiotherapy completion. Results also confirmed

affirmations that exercise capacity is uncompromised as a result of therapy. Self-esteem remained stable throughout surgery and radiation, yet quality of life and body image decreased as the program progressed, improving gradually after mid-radiation evaluation. Smoking, activity levels and demographic variables did not appear to have an effect on the physiological or psychological response to treatment.

**RECOMMENDATIONS**

Although many problems exist with modalities for breast cancer treatment, it must be remembered that those treatment modalities exist because of their established role in extending patient life and disease-free survival. Research has shown the failure of radiation therapy to improve overall survival (Host *et al.*, 1986; Fisher and Anderson, 1994), yet meta-analyses allowing for both increased power and sample size suggest that modern radiation techniques may reduce the risk of death from breast cancer. Levitt *et al.* (1995) and Rutqvist (1996) report that it can, yet others suggest that there are still no definite differences in overall survival for those receiving adjuvant RT compared with those who choose surgery only (Early Breast Cancer Trialists' Group, 1995). Yet because it has been shown that cardiovascular mortality is correlated with both dosage and irradiated volume (Rutqvist *et al.*, 1992), procedures must minimize radiation doses to cardiac tissue and coronary arteries. Individual patient preparation and attention to dose distributions will obviate the development of either acute or late effects on the heart and lungs.

Techniques that avoid the exposure of healthy tissue to radiation must be explored. Merchant and McCormick (1994) suggest that irradiating breast cancer patients in the prone, rather than the commonly used supine position, may help reduce significant doses to normal

tissue and may increase breast dosage homogeneity. An advertisement in a radiation journal proclaims the benefits of the Alderson Breast Dosimetry System (ABDS™)--a brassiere designed to direct the breast away from potentially damaging radiation to the heart, lungs and ribs. Although the risk of secondary cancer is insufficient to influence treatment decisions (Mark *et al.*, 1994; Inskip *et al.*, 1994), radiation techniques must evade underlying ipsilateral organs and the contralateral breast to help avoid the risk of inducing malignancy in healthy tissue. These alternatives must be clinically investigated: breast cancer patients should not die as a result of a treatment designed to extend the length and quality of life.

Identification of a group with low risk of recurrence and with, therefore, no need of adjuvant radiotherapy after conservative surgery, would be beneficial in terms of patient comfort and economic cost. In a review of prospective investigations, Recht and Houlihan (1995) found that local recurrence rates were unacceptably high for women treated with conservative surgery alone; on the other hand, in their retrospective evaluation of 759 women, Dalberg *et al.* (1997) reported that node-negative patients $\geq 50$ yrs of age were a low-risk group. The sample had a cumulative recurrence risk at 10 years of 9% without radiotherapy and 5% after receiving adjuvant treatment. The Ontario Clinical Oncology Group (OCOG) was not able to identify a subgroup for whom recurrence rates were acceptably low: women >50 yrs with tumours <2 cm were reported to have a 13.5% local recurrence rate at a median follow-up of 43 months (Clark *et al.*, 1992); 22% at a median 7.6 years (Clark *et al.*, 1996). At present, there is no consensus concerning which factors distinguish a group of patients for

whom the risk for recurrence is sufficiently low to deny adjuvant therapy, which emphasizes the need for improved techniques to help avoid negative early and late treatment effects.

Patient care must not focus solely on medical treatment, but on the person as a "whole"; rehabilitation efforts must be directed not only at physical recovery, but also at potential disruptions in psychology during and after treatment. Patients should not be passive recipients of the "standard" treatment, but educated to access information and utilize available resources. This will help ensure confidence about choices as well as about treatment, which may be reflected in higher self-esteem and quality of life. The rehabilitation effort should begin at initial diagnosis of cancer, or perhaps prior to it, in preparation for possibly poor biopsy results.

Although current breast cancer therapies improve disease-free survival (Host *et al.*, 1986), they have focused little upon quality of life following treatment. It has been shown that damage to the cardiovascular system may pose a risk to the performance of daily and exercise activity. Established principles of physical training have been proven effective in patients who have undergone breast cancer therapies (Winningham, 1983; MacVicar and Winningham, 1986; MacVicar *et al.*, 1989). However, an appropriate exercise prescription must be ensured as these individuals may be limited by ventilation, gas exchange, cardiac contractility abnormalities, or anaemia.

Several studies have pointed to the protective effect exercise may have on breast cancer due to better control of body composition, immunity and ovulatory cycles (Hoffman-Goetz and Husted, 1994). These results may well apply to breast cancer recurrence and are, therefore, applicable to women who have already experienced treatment. Furthermore,

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according to a review by Shepard and Shek (1995), several researchers have concluded that physical therapy has proven to have emotional and psychological benefits. In fact, patients who exercise have a significantly higher quality of life compared with that of non-exercisers (Young-McCaughan and Sexton, 1991); and those receiving chemotherapy have reported decreased feelings of nausea and fatigue (Winningham and MacVicar, 1988; Mock *et al.*, 1994). Hopefully, programs which encourage personal physical and psychological growth through exercise and adventure, such as the "Women in Nature" effort (Johnson and Kelly, 1990) will become more widespread. Health must be a reflection of successful adaptation.

Specifically in regard to the current study, statistical analysis and conclusions are somewhat limited because of the small sample size. It naturally would be beneficial to investigate a larger group of women so as to allow greater generalization of results and identification of predisposing factors for tissue injury such as menopausal status or age. Computerized tomography or magnetic resonance imaging would also be useful in determining whether inflammation linked to pneumonitis is responsible for changes seen in pulmonary function. It would also be beneficial to assess acute effects of surgery and radiation on cardiac function more directly than by assessing exercise tolerance; for example, ejection fraction. Treatment effects on the physiological and psychological status of those of different diagnostic stages and receiving chemotherapy should also be probed. Subjects should also be followed for an extended period to investigate late effects with known pre-treatment values.

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## APPENDIX A: REVIEW OF LITERATURE

## STAGING AND THE TREATMENT OF EARLY STAGE BREAST CANCER

Staging is the grouping of patients according to the extent of disease; it is useful in determining treatment for individual patients, estimating their prognosis, and comparing the results of different treatment programs. Clinical staging is based on all of the information available prior to the first definitive treatment and includes physical examination findings, imaging studies, operative findings, and pathologic examination of the breast or other tissues (Harris, 1996). Briefly, cancers that are small and confined to the breast are considered to be at an early stage, whereas those that have spread to other parts of the body are "advanced" or "metastatic". The TNM staging system, based on histopathological examination, defines the extent of cancer based on three features of breast tumours: the size and extent of the tumour (T), axillary lymph node involvement (N), and the presence or absence of metastases (M). There are nine T, four N, and two M categories (Appendix B). Roman numeral staging is a simpler system that defines five stages of breast cancer (Appendix C): Stage 0 includes non-invasive cancers; Stage I represents a small tumour and no cancerous spread to axillary lymph nodes; Stage II is associated with a larger tumour and possible spread to the nodes; in stage III, the tumour is progressively more advanced; Stage IV refers to metastatic disease that has spread to other areas of the body.

Several types of breast cancer exist; divided into two principal groups. Non-invasive breast cancers include ductal carcinoma in situ (DCIS) where disease has formed in only the milk ducts, and lobular carcinoma in situ (LCIS), where only milk glands contain cancerous

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cells. When malignant cells spread beyond the breast's primary structures and into fatty tissue, the cancer becomes "invasive" or "infiltrating". Subtypes include cancers originating from the milk ducts--infiltrating ductal carcinoma (IFDC)--as well as those arising from the glands--infiltrating lobular carcinoma (IFLC). The most common type of malignant breast disease is IFDC, yet it is not uncommon for more than one type of disease to be present in breast tissue (Crowe and Lampejo, 1996).

Histologic grading considers the growth pattern of ductal carcinomas and the cytological features of differentiation. The parameters measured for IFDC are the (a) pattern of tubular arrangement, (b) nuclear pleomorphism and (c) the degree of mitotic activity. Each feature scores one to three points, and the individual scores are added to give a tumour grade expressed as well differentiated [grade I: 3-5 points], moderately differentiated [grade II: 6-7 points], or poorly differentiated [grade III: 8-9 points] (Crowe and Lampejo, 1996). A three-tiered classification, using primarily nuclear features and orientation, is also used in DCIS. A higher histologic grade is associated with a higher rate of local recurrence (Clarke et al, 1985).

Breast tumour growth appears to be stimulated by the hormone, estrogen. However, drugs inhibiting estrogen's action (e.g. tamoxifen) have been developed; working by blocking a tumour's estrogen receptors. If a tumour is estrogen-receptor positive (ER+), hormonal drug therapy is a viable adjuvant treatment option in breast cancer management. If there is less than ten to fifteen estrogen receptors (ER-), anti-estrogen therapy is of little benefit (Olivotto *et al.*, 1995). Anti-estrogen drugs are frequently used in postmenopausal women, but have yet to show sufficient benefit in those with premenopausal status. Immunohistochemical analysis, a method used to determine tumour-estrogen receptor levels,

relates quantity using 0 (negative), 1+ (low), 2+ (moderate), or 3+ (high) classification (Wittliff, 1995). Estrogen receptor status is also a prognostic index--several researchers have reported that patients with positive ER status experience longer disease-free survival than those with negative status (Wittliff, 1995).

Virtually unanimous agreement in favour of the Halsted radical mastectomy as the operation choice for treatment of breast cancer existed for almost half a century (Margolese, 1988), but women no longer need to face a certainty of long-term disfigurement and disability. Less invasive options such as total, subcutaneous, or modified radical mastectomies are now available, and breast-conserving surgery such as lumpectomy and partial mastectomy are now frequent choices of both surgeons and patients. Breast conservation, when combined with adjuvant therapy, often leads to a better cosmetic result and has been associated with a low incidence of recurrence, as well as a survival rate equivalent to that achieved by mastectomy. As a result, conservative surgery, including axillary lymph node sampling, and radiation therapy (CS+RT) has become an established method for effective treatment of early stage breast cancer; indeed it has been suggested that breast conservation treatment should become the standard therapy for early stage disease (National Institutes of Health Consensus Conference, 1991). Although primarily a treatment program for women with Stages 0 and I breast cancer; surgery and radiotherapy, without adjuvant chemotherapy, may also be implemented when treating Stage II cancers if a chemotherapeutic program is not advisable.

The main goal of surgery is to excise the breast tumour with negative margins yet to maintain cosmetic appearance. However, because there is risk of residual microscopic cancer remaining in the breast after excision, surgery is considered only potentially curative.

Adjuvant RT is necessary to eradicate any residual microscopic cancer remaining in the breast after excision. The larger fraction of a radiation dosage is delivered to the whole breast, and occasionally the regional lymph nodes, as two opposing tangential fields in an attempt to bypass the lung. As nodal irradiation has proven unnecessary, current standard procedure includes irradiating the breast tissue only (Clark, 1996). RT begins approximately four weeks after surgery and is administered using high-energy photons from a linear accelerator with daily treatments of approximately 2 Gy five days per week. Sixteen to twenty-five treatments are commonly given with a typical total dose of 40 to 50 Gray (Olivotto *et al.*, 1995). A subsequent boost dose using an electron beam, may be given directly to the tumour area as the region of the primary tumour is the most common site of residual disease and loco-regional recurrence (Boyages and Harris, 1989). Boosting, however, is more commonly practiced when surgical margins around the tumour site have signs of residual disease. RT may be given after lumpectomy, partial mastectomy, or modified radical mastectomy and continues for three and a half to six weeks depending on the severity of the cancer (Olivotto *et al.*, 1995). Treatment including diagnosis, surgery, and radiation takes approximately sixteen weeks to complete.

Although much of the success in treating early stage breast cancer is attributed to the development of CS+RT, complications in muscle, lung, and heart function still arise as a result of therapy. In order to facilitate patient rehabilitation and quality of life, physicians must ensure proper surgical and radiotherapeutic techniques.

## TREATMENT EFFECTS ON PHYSIOLOGICAL VARIABLES

### *PULMONARY TISSUE*

The use of radiation therapy in the thorax is limited by pulmonary complications. In his comprehensive review, Gross (1977) reported that clinical radiation damage occurs in over 11% of breast cancer patients. In addition to treatment volume and fraction number (Wallgren, 1992), Van Houtte (1987) remarks that damage to the lung is time and dose related. According to Wallgren (1992), a dose of 20 Gy in one to two weeks is considered to produce permanent changes in lung tissue.

Certain investigations into radiation's influence on pulmonary tissue appear to indicate a two-phase development of lung damage; acute and late. Increases in lung density (Rotstein *et al.*, 1990; Svane *et al.*, 1995) and septal thickening (Majurin *et al.*, 1995), assessed by computer tomography (CT), are indicators of early pulmonary injury that does not persist but may follow a two-phase trend. Pneumonitis--characterized by cough, fever, and mild dyspnea--and lung fibrosis constitute two of the most commonly recorded early and late effects of breast cancer radiotherapy on the lungs (Wallgren, 1992). Acute, transient radiation pneumonitis may occur six to twelve weeks after therapy (Gross, 1977) and fibrosis may arise in the following six to twelve months (Gross, 1977; Simpson, 1986; Roberts *et al.*, 1993). Fibrosis, confined to the area of radiation, has been reported to occur in up to 75% of irradiated breast cancer patients exposed to doses in excess of 30-40 Gy (Roberts *et al.*, 1993; Van Houtte, 1987). In a review of the physiologic effects associated with cancer therapy, Loescher *et al.* (1989) stated that fibrosis involving the alveolar walls and endothelial damage

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may not present themselves until three to six months after irradiation, and may progress over one to two years before stabilizing.

The few prospective observations on the occurrence of radiation pneumonitis in early stage breast cancer patients which have been published (Botterman *et al.*, 1990; Roberts *et al.*, 1993; Kimsey *et al.*, 1994) suggest that early acute pneumonitis develops after treatment in 5% to 15% of women receiving RT for breast cancer (Roberts *et al.*, 1993; Cherniack *et al.*, 1994). After noting changes seen in the non-irradiated lung, Roberts *et al.* (1993) have suggested that pneumonitis may be due to a lymphocyte-mediated hypersensitivity reaction and that pneumonitis is not confined to the irradiation field; yet the findings of Lund *et al.* (1991) do not support the suggestion that hypersensitivity mechanisms play a role in radiation-induced injury.

In their retrospective review of 1,624 early stage breast cancer patients treated with CS+RT, Lingos *et al.* (1991) reported clinical or radiographic pneumonitis in only seventeen women. The 1% incidence rate observed is apparently supported by other researchers (Lichter, 1988). The major factor predicting increased risk of pneumonitis was the use of the two standard tangential fields plus a third nodal field combined with chemotherapy. Thus chemotherapy may act to potentiate radiation damage. This hypothesis is supported by the results of Roberts *et al.* (1993) who, in a study of seventeen women receiving postoperative radiotherapy for breast cancer, reported two cases of pneumonitis in patients who had also received adjuvant chemotherapy; moreover, in a study involving twenty-five patients treated only by radiotherapy, Lund *et al.* (1991) reported no cases of pneumonitis.

Most clinicians believe that RT for primary breast cancer is generally well tolerated, and is associated with a low incidence of radiation pneumonitis (Lingos *et al.*, 1991) and because of the rarity of the problem, it has been concluded that the tangential beam technique safely preserves pulmonary function (Lund *et al.*, 1991; Botterman *et al.*, 1990). Significant decreases in pulmonary function measures have been reported with the use of this technique however. Kaufman *et al.* (1986) studied the effects of radiation therapy on lung function in twenty-one patients who had received modified radical mastectomy. A statistically significant decline from pre-radiation measures in FVC, $FEV_1$, $FEV_1/FVC$ and the $FEF_{25\%-75\%}$, suggestive of an obstructive lung defect, was evident in some patients within three months following therapy and persisted for a year. The results of Botterman *et al.* (1990) affirm obstructive lung defect within three months of radiation therapy. This is also corroborated by Kimsey *et al.* (1994), who reported a 5-10% decrease in all pulmonary function parameters in early stage patients one to four months after therapy but which, fortunately, was resolved within two years. Lund *et al.* (1991) suggest that although a concurrent decrease in $FEV_1$ and FVC suggests an obstructive element, damage may also be restrictive in nature due to a near significant decline in total lung capacity; the limitation in pulmonary function possibly due to structural changes of the lung parenchyma as well as altered elastic properties of the chest wall. The fact that Kaufman *et al.* (1986) did not find a correlation between radiographic changes and lung function supports such an alternative. In the only long-term investigation of spirometry changes after radiation treatment for breast cancer, Strender *et al.* (1986) reported that only ten of sixty-nine patients had below-normal vital capacity ten years after radiation delivery. One patient experienced decreased $FEV_1$, and $FEV_1/FVC$.

Generally, previous research has appeared to discount any effect of radiation on lung volume. Kimsey et al. (1994) observed a 10-15% decrease in lung volume that did not return to pre-treatment values, but, as in the investigation by Lund et al. (1991), this change was not clinically significant. Other studies have found insignificant change in lung volume (Botterman et al., 1990), but near-significant findings suggest that RT may have a restrictive influence on the lung. Groth et al. (1989) concluded that post-mastectomy thoracic irradiation causes changes consistent with restrictive lung disease after having reported significant decreases in both total lung capacity (TLC) and vital capacity (VC) three months after therapy completion with secondary changes in $FEV_1$. In what has been the only mid-radiation investigation of RT, Kimsey et al. (1994) reported that no changes were observed in FVC, $FEV_1$ or the $FVC/FEV_1$, indicating a possible time or dosage threshold for radiation damage.

· Unlike spirometry and lung volumes, pulmonary diffusing capacity is not dependent upon the function of the chest wall: changes in $DL_{CO}$ reflect factors that affect the diffusion of carbon monoxide across the alveolar-capillary membrane. These may include alveolar volume, haematocrit or hemoglobin, carboxyhemoglobin, alveolar pressure of carbon dioxide, and pulmonary capillary blood volume (Ruppel, 1994). Decreased $DL_{CO}$ may be a result of lung volume loss (restrictive), uneven ventilation/perfusion ratio (V/Q) (obstructive), or uneven distribution of inspired gas to alveolar volume ($V_A$) (obstructive). Measuring both $V_A$ and $DL_{CO}/V_A$ will allow differentiation between disease processes. A decrease in diffusing capacity may be due to a small loss in functional lung parenchyma and a decrease in $DL_{CO}/V_A$ ($K_{CO}$) may indicate alteration of the lung interstitium (Botterman et al., 1990). Although significant effects were seen in both perfusion and ventilation three months after therapy, it

has been reported that regional V/Q remains relatively constant for up to a year following completion of treatment (Groth et al., 1989).

Decreases in $DL_{CO}$ have been reported from one to four months after completion of RT (Kaufman et al, 1986; Groth et al., 1989; Botterman et al., 1990; Lund et al., 1991; Kimsey et al., 1994), with changes from the pre-radiation value ranging from 0% (Lund et al., 1991) to 22% (Kimsey et al., 1994). The latter investigation included women diagnosed with Stage II breast cancer which suggests that age or inactivity may be influences, as women diagnosed with Stage II cancer are generally older and complete a lengthier therapy program than those diagnosed with Stage I breast cancer. No difference was found in the pulmonary function of patients treated with or without chemotherapy, indicating that additional adjuvant chemotherapy of Stage II cancer does not play a role in changes to $DL_{CO}$: the number of patients receiving chemotherapy was small, however.

Changes in pulmonary function may be a result of direct lung tissue injury from radiation. The lungs' primary response may be an increase in vascular permeability and damage to type I and II pneumocytes, resulting in excess surfactant production which contributes to atelectasis, reduced ventilation, and abnormal gas exchange values (Coggle et al., 1986). Microcapillary vascular damage can also produce ischemic tissue injury resulting in fibrotic healing (Gross, 1981). McDonald et al. (1995) report that damage to the lung becomes evident within weeks of radiation therapy and continues for years. Alveolar exudation and edema leads to early impairment of gas exchange and possibly pneumonitis--a process closely linked to damage to both type II pneumocytes and capillary endothelial cells.

As the process continues, alveoli shrink and vessel walls thicken, leading to the development of fibrosis.

## *CARDIAC TISSUE*

Few have investigated the acute effects of radiation on cardiac tissue. There have been reports of temporary, acute cardiovascular changes such as rhythm alterations, ECG aberrations, and blood pressure changes during breast cancer radiotherapy (Stewart *et al.*, 1995). Using serum cardiac troponin T as a marker of myocardial cell injury, Hughes-Davies and associates (1995) have suggested that no acute myocyte death occurs after irradiation, and its effects are minor. But scinigraphy has shown myocardial perfusion changes one year after radiotherapy in women choosing breast-conserving surgery, which suggest that changes may reflect microvascular damage to the myocardium (Gyenes *et al.*, 1996). It has also been shown that the pericardium is susceptible to radiation damage causing inflammation and fibrinous exudation (Schneider and Edwards, 1979). In fact, pericarditis with effusion is the most common acute cardiac manifestation of radiation injury (Stewart *et al.*, 1995).

When evaluating cause-specific mortality in 7,941 long-term survivors of breast cancer who received only radiotherapy, Cuzick *et al.* (1994) found that cardiac-related deaths were increased in comparison with patients who did not receive radiotherapy. Yet, in the only prospective study involving breast cancer patients, Strender *et al.* (1986) concluded that regardless of treatment side, perimyocardial damage manifested over a period of ten years was normal for an aging population; that the incidence of cardiac disease was not increased after radiotherapy. Long-term retrospective evaluation of patients appears to indicate that radiation

plays a significant role in late effects on the heart following treatment for a tumour in the left breast however.

There have been various reports of radiation-induced heart problems including ECG abnormalities (Strender *et al.*, 1986), as well as pericardial, myocardial and coronary artery disease (Stewart *et al.*, 1995). Gyenes *et al.* (1994) found that radiotherapy for left breast cancer may be an independent risk factor in the development of ischemic heart disease; the patients involved, however, received radiation to the internal mammary nodes located close to the heart. In a study involving 960 breast cancer patients, Rutqvist *et al.* (1992) found those treated for left-sided tumours had a significantly greater risk of dying from ischemic heart disease in comparison with those who received surgery only. Wallgren (1992) has also documented that patients treated for cancer in the left breast are significantly more likely to suffer from myocardial infarction than those treated for cancer in the right. The notion that damage to the heart occurs most often upon irradiation of the left field is supported by other researchers, including Burch (1968), Simpson (1986), and Host *et al.* (1986). But concern should not be absent if a tumour in the right breast is being treated. Although damage seems more likely when treating the left breast, the medial and right sections of the heart are susceptible to radiation damage by primary radiation beams upon treatment for a carcinoma in the right breast (Strender *et al.*, 1986). Furthermore, individuals with additional risk factors for cardiovascular disease (e.g. smoking, hypertension, obesity) may be more susceptible to radiation-induced cardiac damage.

The "vascular hypothesis" is believed to explain late cardiac morbidity in patients who have undergone thoracic irradiation. This hypothesis states that because of inherent sensitivity

of supporting endothelial cells, radiation damages the heart's vast capillary network. Both

injury of the endothelial cells leading to capillary swelling and microvascular damage of the

myocardium are indicative of the first stage of radiation-induced heart disease (Stewart and

Fajardo, 1984). Stewart et al. (1995) add that progressive radiation may also damage the

myocytes, resulting in their proliferation and migration. After evaluating a patient who had

received irradiation to the mediastinum for thyroid carcinoma, Burch and his associates (1968)

concluded that radiation exposure can cause significant changes in subcellular myocardium,

including myofibrillar disintegration and atrophy, a decrease in mitochondrial cristai, and

damage to both the cardiac capillary walls and sarcolemma. In addition to pericardial and

myocardial fibrosis, conduction disturbances and valvular defects have been frequently

reported (Rutqvist et al., 1992; Stewart et al., 1995). Tritto and Calabrese (1995) give a

review of morphological changes and clinical manifestations of radiation-induced cardiac

damage in both the acute and late periods.

It has been suggested that high, single fractions (>2.5 Gy) currently in use may

predispose patients for late cardiovascular effects (Cuzick et al., 1994; Clark, 1996). In much

the way radiotherapy affects the lung, Loescher et al. (1989) report that cardiac damage in the

cancer patient is affected by the dose, duration and field size. They also note, however, that

most patients with radiation-induced cardiac disease show no symptoms of disease.

### CARDIOPULMONARY EXERCISE CAPACITY

The processes involved in the transport of oxygen to the tissues include ventilation,

diffusion, circulation and delivery to skeletal muscle. To meet the demands of physical

activity effectively, each of these processes must function synchronously and without

hindrance. It has been shown, however, that radiotherapy for breast cancer can damage the cardiovascular and pulmonary systems and may lower resilience to activity.

Lungs are responsible for the first two steps of the oxygen delivery process: irregular mechanics, impaired gas exchange, and/or ventilatory muscle fatigue resulting from radiation to the lung may limit exercise performance. Several recorded effects of breast cancer treatment have been associated with decreased lung function. Fibrosis results in reduced flexibility and elasticity of pulmonary tissue, and shrinking due to scarring reduces the lung's internal volume (Marieb and Mallatt, 1992). As exercise demands an increase in ventilation and relies on the resilience of lung tissue, fibrosis may challenge exercise potential. Similarly, type II cell hyperplasia may result in increased surfactant production and, therefore, disrupted lung compliance. Damage such as alveolar septal thickening and intraalveolar edema, which has also been associated with therapy, results in a diametric increase of the alveolar-capillary membrane and therefore impairs gas exchange. Since inadequate diffusion increases the ventilation required to maintain oxygen transfer between the alveoli and the pulmonary capillaries, increasing demands on the respiratory muscles result in limited performance (Frontera and Adams, 1986). Complications in the lung can ultimately lead to a decrease in arterial oxygen content--one factor related to the ability to perform ($VO_2$):

$$VO_2 = (\text{stroke volume})(\text{heart rate})(\text{arterial } O_2 - \text{venous } O_2)$$

The heart is responsible for circulating blood for oxygen delivery. Cardiac complications associated with the administration of adjuvant therapy affects the ability to perform physical activity if the heart cannot meet the oxygen demands of the working muscle. Breast cancer therapy has not only been shown to be linked to cardiovascular disease, but

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also to trauma affecting the pericardium, myocardium and coronary arteries. The heart normally responds to increased muscular oxygen demand during activity by increasing cardiac output--the product of stroke volume and heart rate-- in order to supply additional blood to the tissue. Contraction failure because of cardiomyopathic scarring or ischemic heart disease can inhibit increase of stroke volume during exercise however. To compensate, the heart responds with tachycardia, resulting in a higher myocardial oxygen demand (Frontera and Adams, 1986). Decreased blood flow to the arteries, associated with coronary heart disease, also inhibits the pumping ability of the heart. The heart's role in supplying blood to oxygen-needy tissue is also compromised because of reduced blood flow to the tissues associated with peripheral vascular disease. With less blood in the tissue, diffusion is jeopardised.

Literature points to specific damage to the heart and lung in the breast cancer patient, but little attention has been directed to how they function collectively during exercise performance. There have been only four prospective studies that have examined the effect treatment had on cardiopulmonary exercise capacity in those with breast cancer. In an investigation of fatigue syndrome due to radiation, Greenberg *et al.* (1992) tested five early stage breast cancer patients receiving six to nine weeks of radiotherapy. Subjects were tested prior to radiotherapy as well as at six and twelve weeks after the commencement of radiation delivery by using cycle ergometry. Exercise capacity, as well as pulmonary function, was maintained in all subjects, but sample size was small. Using a sample of ninety-six patients, Strender *et al.* (1986) examined physical working capacity at both a heart rate of 150 bpm (PWC 150) and after six minutes (PWCmax 6 min) of cycle ergometry before, as well as six months and ten years after radiation completion. No significant changes in PWC 150 were

observed, and a ten percent change in PWCmax 6 min from pre-treatment values at the ten year follow-up was attributed to aging of those involved. It was concluded that there was no correlation between maximum work load an individual could perform and radiation dose to the heart. Mock *et al.* (1994) found the number of meters subjects were able to walk in twelve minutes were essentially maintained when prospectively evaluating exercise tolerance in fourteen early stage breast cancer patients receiving adjuvant chemotherapy. It was suggested however, that the method used to evaluate exercise capacity was not adequate and that a more comprehensive measure of functional status might be more reflective of changes in patient ability to perform daily activities. In an investigation by MacVicar and Winningham (1986), four breast cancer patients receiving chemotherapy and not participating in an exercise program experienced a 1.8% decline in peak $VO_2$--from 1.11 to 1.09 L of oxygen--measured by cycle ergometry, in the ten week period between pre and post-chemotherapy evaluation.

Two control-group studies have also investigated treatment's effects on exercise capacity in women with early stage breast cancer. Earle *et al.* (1996), using the Canadian Aerobic Fitness Test (CAFT) to estimate measures of $VO_2max$, found a 24.6% lower functional capacity in eight women measured a mean nine and a half weeks into chemotherapy than that of seven diagnosed with breast cancer assessed prior to receiving adjuvant therapy. McKenzie *et al.* (1996) found that eighteen healthy controls had an 8.4% higher $VO_2max$ (1.67 L/min) than fifteen women who, on average, had completed a program of surgery plus radiotherapy (Stage I) five years prior to evaluation (1.54 L/min). There was a 6.5% decrease in minute ventilation, and a 5.8% decrease in maximal work, as measured by cycle ergometry, from the healthy to affected women. Changes, however, were not significant. There was no

difference in HRmax between groups. A prospective investigation of the relationship between complete treatment for early stage breast cancer--a program including surgery and radiation -- and cardiopulmonary exercise capacity remains to be performed.

## TREATMENT EFFECTS UPON PSYCHOLOGICAL VARIABLES

Many factors contribute to the psychological responses of women diagnosed with, and treated for, breast cancer (Massie and Holland, 1991; Rowland and Massie, 1996), including sociocultural context, available treatment options, and medical factors such as the stage of cancer and the type of treatment received. In addition, personal influences such as coping ability, life-cycle stage, familial and social environment, and the available emotional support may affect adaptation to the disease. A family or friend who received a cancer diagnosis may also influence patient perception.

### *QUALITY OF LIFE*

Quality of life is a complex arrangement of factors, with physical/occupational function, psychological state, sociability, and somatic comfort as the major contributors (Schipper and Levitt, 1985). According to Cella and Cherin (1988), quality of life of the cancer patient is most often affected by disease site, treatment selection, patient age and current clinical status.

With the breast being so closely linked with self-esteem and body image, it treatment can particularly interfere with both interpersonal and sexual relationships. Surgical treatment produces apprehension, and is also associated with physical difficulties in shoulder range of motion, as well as with lymphedema. Radiotherapy is associated with fatigue and decreased appetite, and may cause soreness of the breast.

Age plays an integral role in perception of life quality during breast cancer diagnosis and management, as does marital status and whether a woman has had children. Energy and physical capacity to work is also of great significance for those who have not chosen retirement.

Quality of life is also highly dependent upon where the patient is in the therapy program. Reactions to a breast cancer diagnosis often includes heightened vulnerability and fear of dying (Leigh, 1994) in addition to worry about surgery choices, sadness, despair, and rage (Payne *et al.*, 1996). Patients who hypothesize that unhealthy or stressful lifestyles contributed to cancer development can also experience feelings of guilt. Massie and Holland (1991) report that most women say the days prior to surgery are the worst because of the flood of emotion and uncertainty. Post-operative stress may also occur waiting for pathology results and the beginning of adjuvant treatment. According to Payne *et al.* (1996), patients receiving radiotherapy may be greatly affected by frightening machinery, feelings of claustrophobia, and daily reminders of the disease. Furthermore, tattoo marks and cosmetic changes in the breast surface and tissue compounds a sense of being "damaged". At the beginning of treatment patients may be appeased by the thought that treatment is the lesser of two evils, yet as toxic effects increase, optimism declines (Cella and Cherin, 1988).

In one of the few prospective investigations, Holland *et al.* (1979) found that anxiety tended to decrease during radiotherapy treatment, yet concluded that depression and anger increased significantly from pre-radiation measures at both the second and sixth treatment weeks; it was also reported that hope showed a consistent, but non-significant, decline during therapy. Subjects in this study had, however, positive nodal status--a prognostic factor that

could strongly influence the response to treatment. Women with small tumours and negative nodes--a favorable prognosis--may feel relieved to have completed a lengthy and stressful therapy program. In a study including all cancer types, nearly 75% of which were early stage cancers, mean scores for uncertainty, hope, and adjustment problems remained relatively stable during radiotherapy (Christman, 1990). Upon completion of treatment there may be feelings of uncertainty about the loss of a medical support system, as well as fear of recurrence (Leigh, 1994). Earle *et al.* (1996) found that women, measured a mean nine and a half weeks into chemotherapy, had 14.8% and 14.3 % lower values for the Medical Outcomes Study Short Form (SF-36) physical and mental subscales than women assessed prior to receiving chemotherapy. The Functional Assessment of Cancer Therapy questionnaire reflected a 3.5% and 6.8 % decline on the General and Breast-specific scores respectively. Each stage of the therapy protocol is likely to influence feelings of quality of life, as well as those of self-esteem and body image.

## SELF-ESTEEM

Self-esteem has been defined as "the sense of contentment and self acceptance that results from a person's appraisal of his own worth, significance, attractiveness, competence, and ability to satisfy his aspirations" (Robson, 1989). Nelson (1991), reported that women who have experienced Stage I breast cancer do not have significantly different self-esteem from those who have not, but patients in the investigation received mastectomy only without adjuvant therapy and had been out of treatment for four to five years. Completion of a joint chemo/radiotherapy program has been associated with patient reports of problems with respect to sense of competency, as well as the ability to prepare for the future (Ward *et al.*,

1992). Self-esteem has never been evaluated during treatment for early stage breast cancer, nor has pre-surgical status been measured.

## *BODY IMAGE*

The main objective in breast surgery is maintaining the cosmetic appearance of the breast--an organ of great psychological significance for many women. Alteration of what has traditionally been a symbol of femininity, sexual attractiveness, and nurturing may easily have negative effects on body image. It has been suggested that cancer patients experience greater stress when a surgical scar is on, or near, a primary or secondary sex organ (Cella and Cherin, 1988). Ward *et al.* (1992) reported that seven of thirty-eight (18%) of those who received both chemotherapy and radiation reported problems with self-image at the termination of treatment. Some studies have compared body image responses among surgery options (i.e. mastectomy, mastectomy plus immediate reconstruction, or conservative surgery) (Mock, 1993), yet investigation into how body image may change over the course of surgery and radiotherapy is lacking.

# APPENDIX B: TNM STAGING SYSTEM

| TNM staging system |
| --- |
| TUMOUR Stages: (T)<br><br>T(x): primary tumour cannot be assessed<br>T(0): no identifiable tumour in the breast<br>T(is): in-situ, non-invasive cancer<br>T(1): invasive cancer 2 cm or less in diameter<br>T(2): invasive cancer 2 cm to 5 cm in diameter<br>T(3): invasive cancer larger than 5 cm without skin or chest wall involvement<br>T(4): tumour of any size with direct extension to chest wall or skin |
| NODE Stages: (N)<br><br>N(0): no evidence of palpable lymph nodes<br>N(1): palpable, mobile lymph nodes in the armpit only<br>N(2): lymph nodes in the axilla are fixed to each other or to adjacent structures such as nerves, muscles, skin or bones<br>N(3): involved lymph nodes beside the breast bone |
| METASTASIS Stages: (M)<br><br>M(0): no evidence of metastases<br>M(1): metastases present including spread to lymph nodes above the collarbone |

Olivotto *et al.*, 1995; Harris, 1996.

## APPENDIX C:  FIVE STAGES OF BREAST CANCER

| Roman Numeral Staging | TNM Staging |
|---|---|
| STAGE O<br><br>Non-invasive cancers, including ductal carcinoma in-situ<br>lobular carcinoma in-situ | Tis, N0, M0 |
| STAGE I<br><br>Tumour less than 2 cm, no metastases, no cancer in lymph nodes | T1, N0, M0 |
| STAGE II<br><br>Tumour 2-5 cm but not involving skin and chest wall.  If lymph nodes are involved they must be movable | (IIA)<br>T0, N1, M0<br>T1, N1, M0<br>(IIB)<br>T2, N0, M0<br>T2, N1, M0<br>T3, N0, M0 |
| STAGE III<br><br>Advanced local tumour, fixed to the skin or chest wall, or presence of lymph nodes 'attached' to structures in the axilla | (IIIA)<br>T0, N2, M0<br>T1, N2, M0<br>T2, N2, M0<br>T3, N1, M0<br>T3, N2, M0<br>(IIIB)<br>T4, any N, M<br>Any T, N3, M0 |
| STAGE IV<br><br>Cancer spread beyond the breast and axilla, to lymph nodes above the collarbone, or to distant organs | Any T, any N, M1 |

Olivotto *et al.*, 1995 and Harris,1996.

# APPENDIX D: RAW DATA

## DEMOGRAPHICS

Table 13. Demographic Information

| | |
|---|---|
| Race | |
|     Caucasian | 6 |
|     Asian | 1 |
| Marital status | |
|     Married | 4 |
|     Separated | 1 |
|     Divorced | 1 |
|     Living with significant other | 1 |
| Education | |
|     Post-graduate work | 1 |
|     University graduate | 2 |
|     Some university | 2 |
|     High school graduate | 2 |
| Employment | |
|     Full-time | 4 |
|     Part-time | 1 |
|     Retired | 2 |
| Hormonal status | |
|     Pre-menopausal | 4 |
|     Post-menopausal | 3 |

## ANTHROPOMETRIC DATA

Table 14. Pre-surgery Age and Mean Height, individual subject data

| SUBJECT | Age (yrs) | Height (cm) |
|---|---|---|
| A | 58.5 | 161.9 |
| B | 50.2 | 173.0 |
| C | 52.0 | 162.8 |
| D | 47.6 | 162.7 |
| E | 62.9 | 164.3 |
| F | 55.2 | 150.2 |
| G | 52.1 | 166.7 |
| MEAN ± SD | 54.1 ± 5.2 | 163.1 ± 6.8 |

Table 15. Body Mass (kg), individual subject data

| SUBJECT | Test 1 | Test 2 | Test 3 | Test 4 | Test 5 | MEAN |
|---|---|---|---|---|---|---|
| A | 59.0 | **59.2** | 58.1 | 57.2 | 58.2 | 58.3 |
| B | 67.7 | 67.8 | 69.3 | 68.7 | 69.1 | 68.5 |
| C | 69.5 | 69.5 | 69.0 | 70.4 | 69.8 | 69.6 |
| D | 52.5 | 52.7 | 55.7 | 55.8 | 57.1 | 54.8 |
| E | 53.9 | 53.7 | 54.0 | 54.3 | 54.6 | 54.1 |
| F | 50.4 | 51.3 | 53.7 | 51.8 | 53.0 | 52.0 |
| G | **100.2** | 100.8 | 103.4 | 103.1 | 100.7 | 101.6 |
| MEAN ± SD | 64.7 ± 17.3 | 65.0 ± 17.4 | 66.2 ± 17.7 | 65.9 ± 17.9 | 66.1 ± 16.7 | |

• Bold numbers have been estimated


Table 16. Sum of Skinfolds (mm), individual subject data

| SUBJECT | Test 1 | Test 2 | Test 3 | Test 4 | Test 5 |
|---|---|---|---|---|---|
| A | 107.2 | **117.7** | 112.3 | 101.5 | 102.8 |
| B | 76.6 | 83.1 | 79.7 | 83.4 | 88.3 |
| C | 146.3 | 157.4 | 158.5 | 165.8 | 156.2 |
| D | 40.3 | 45.9 | 51.0 | 51.7 | 60.8 |
| E | 38.3 | 40.7 | 40.8 | 39.1 | 39.8 |
| F | 66.0 | 75.3 | 76.9 | 82.8 | 79.8 |
| G | **108.3** | 119.1 | 123.6 | 134.4 | 130.4 |
| MEAN ± SD | 83.3 ± 39.6 | 91.3 ± 42.4 | 91.8 ± 41.9 | 94.1 ± 44.5 | 94.0 ± 39.9 |

• Bold numbers have been estimated


Table 17. Hemoglobin (g/100 mL), individual subject data.

| SUBJECT | Test 1 | Test 2 | Test 3 | Test 4 | Test 5 |
|---|---|---|---|---|---|
| A | 13.8 | - | - | 14.6 | 12.3 |
| B | 10.8 | 12.1 | 12.4 | 11.4 | 14.6 |
| C | 12.1 | 15.1 | 11.5 | 13.1 | 11.9 |
| D | 13.6 | 14.1 | 12.9 | 11.5 | 13.9 |
| E | 14.5 | 12.4 | 11.6 | 11.3 | 11.3 |
| F | 13.8 | 12.6 | 13.4 | 14.0 | 13.8 |
| G | **11.1** | 11.3 | 11.8 | 10.6 | 10.5 |
| MEAN ± SD | 12.7 ± 1.5 | 12.9 ± 1.4 | 12.3 ± 0.8 | 12.0 ± 1.3 | 12.7 ± 1.7 |

• Bold numbers have been estimated; means do not include subject A

## PULMONARY FUNCTION DATA

Table 18. FVC (L), individual subject data

| SUBJECT | Test 1 | Test 2 | Test 3 | Test 4 | Test 5 |
|---|---|---|---|---|---|
| A | 2.68 | **2.67** | 2.80 | 2.80 | 2.71 |
| B | 4.37 | 4.38 | 4.04 | 4.29 | 4.30 |
| C | 3.46 | 3.52 | 3.50 | 3.36 | 3.42 |
| D | 3.78 | 3.90 | 3.65 | 3.77 | 3.68 |
| E | 3.20 | 3.09 | 3.17 | 3.17 | 3.03 |
| F | 2.69 | 2.52 | 2.40 | 2.60 | 2.68 |
| G | **2.74** | 2.73 | 2.78 | 2.64 | 2.87 |
| MEAN ± SD | 3.29 ± 0.70 | 3.29 ± 0.76 | 3.20 ± 0.63 | 3.24 ± 0.69 | 3.28 ± 0.64 |

• Bold numbers have been estimated; means do not include subject E

Table 19. $FEV_1$ (L), individual subject data

| SUBJECT | Test 1 | Test 2 | Test 3 | Test 4 | Test 5 |
|---|---|---|---|---|---|
| A | 2.17 | **2.13** | 2.21 | 2.21 | 2.14 |
| B | 3.49 | 3.41 | 3.27 | 3.29 | 3.37 |
| C | 2.73 | 2.74 | 2.68 | 2.57 | 2.66 |
| D | 3.00 | 3.04 | 2.93 | 2.96 | 2.91 |
| E | 2.73 | 2.54 | 2.79 | 2.69 | 2.51 |
| F | 2.39 | 2.23 | 2.12 | 2.18 | 2.23 |
| G | **2.32** | 2.28 | 2.28 | 2.12 | 2.28 |
| MEAN ± SD | 2.68 ± 0.50 | 2.64 ± 0.51 | 2.58 ± 0.46 | 2.55 ± 0.48 | 2.60 ± 0.48 |

• Bold numbers have been estimated; means do not include subject E

Table 20. $FEF_{25-75\%}$ (L/sec), individual subject data

| SUBJECT | Test 1 | Test 2 | Test 3 | Test 4 | Test 5 |
|---|---|---|---|---|---|
| A | 2.05 | **1.89** | 1.75 | 1.89 | 2.00 |
| B | 3.40 | 2.86 | 3.23 | 2.78 | 3.20 |
| C | 2.49 | 2.33 | 2.08 | 2.04 | 2.19 |
| D | 2.61 | 2.54 | 2.61 | 2.70 | 2.59 |
| E | 3.07 | 2.73 | 3.67 | 3.09 | 3.27 |
| F | 3.59 | 3.37 | 3.45 | 2.75 | 2.86 |
| G | **2.99** | 2.75 | 2.47 | 2.08 | 2.00 |
| MEAN ± SD | 2.86 ± 0.58 | 2.62 ± 0.50 | 2.60 ± 0.65 | 2.37 ± 0.41 | 2.47 ± 0.49 |

• Bold numbers have been estimated; means do not include subject E

Table 21. FEV$_1$/FVC (%), individual subject data

| SUBJECT | Test 1 | Test 2 | Test 3 | Test 4 | Test 5 |
|---------|--------|--------|--------|--------|--------|
| A | 81.00 | **79.79** | 79.02 | 79.02 | 78.97 |
| B | 79.85 | 77.87 | 80.86 | 76.65 | 78.45 |
| C | 79.00 | 77.80 | 76.59 | 76.41 | 77.77 |
| D | 79.30 | 78.04 | 80.24 | 78.44 | 79.09 |
| E | 85.30 | 82.15 | 87.97 | 85.02 | 82.72 |
| F | 88.80 | 88.59 | 88.36 | 84.12 | 83.44 |
| G | **84.89** | 83.64 | 82.06 | 80.24 | 79.65 |
| MEAN ± SD | 82.14 ± 3.91 | 80.96 ± 4.35 | 81.19 ± 3.98 | 79.15 ± 2.83 | 79.56 ± 2.00 |

• Bold numbers have been estimated; means do not include subject E

Table 22. MVV (L/min), individual subject data

| SUBJECT | Test 1 | Test 2 | Test 3 | Test 4 | Test 5 |
|---------|--------|--------|--------|--------|--------|
| A | 84.00 | **74.68** | 96.99 | 82.71 | 84.23 |
| B | 138.01 | 117.41 | 111.01 | 117.80 | 107.34 |
| C | 98.82 | 88.95 | 88.13 | 95.77 | 83.92 |
| D | 123.37 | 115.64 | 118.21 | 130.71 | 117.37 |
| E | 102.39 | 71.75 | 83.98 | 72.16 | 104.50 |
| F | 98.44 | 86.54 | 73.87 | 93.84 | 86.56 |
| G | **102.57** | 91.02 | 97.08 | 87.79 | 93.88 |
| MEAN ± SD | 107.54 ± 19.58 | 95.71 ± 17.10 | 97.55 ± 15.86 | 101.44 ± 18.72 | 95.55 ± 13.87 |

• Bold numbers have been estimated; means do not include subject E

Table 23. Hb-adjusted DL$_{CO}$ (mL/min/mmHg), individual subject data

| SUBJECT | Test 1 | Test 2 | Test 3 | Test 4 | Test 5 |
|---------|--------|--------|--------|--------|--------|
| A | - | - | - | 18.69 | 15.90 |
| B | 23.35 | 20.36 | 23.10 | 15.36 | 17.12 |
| C | 24.21 | 18.18 | 21.51 | 17.29 | 22.15 |
| D | 12.83 | 13.23 | 12.87 | 11.69 | 10.34 |
| E | 24.46 | 21.96 | 20.99 | 19.92 | 17.65 |
| F | 15.85 | 19.22 | 19.60 | 17.35 | 15.67 |
| G | **27.92** | 25.90 | 21.39 | 21.33 | 27.80 |
| MEAN ± SD | 21.44 ± 5.79 | 19.81 ± 4.20 | 19.91 ± 3.63 | 17.16 ± 3.41 | 18.45 ± 5.95 |

• Bold numbers have been estimated; means do not include subject A

Table 24. VA (mL), individual subject data

| SUBJECT | Test 1 | Test 2 | Test 3 | Test 4 | Test 5 |
|---------|--------|--------|--------|--------|--------|
| A | - | - | - | 4.64 | 5.06 |
| B | 6.59 | 7.07 | 6.96 | 6.81 | 6.97 |
| C | 5.42 | 6.31 | 5.70 | 6.53 | 7.62 |
| D | 5.86 | 5.74 | 5.83 | 5.68 | 5.65 |
| E | 5.04 | 5.60 | 5.65 | 5.55 | 5.24 |
| F | 4.40 | 4.42 | 4.27 | 4.98 | 4.60 |
| G | **4.34** | 4.61 | 5.41 | 5.24 | 7.20 |
| MEAN ± SD | 5.28 ± 0.87 | 5.63 ± 1.01 | 5.64 ± 0.86 | 5.80 ± 0.72 | 6.21 ± 1.22 |

• Bold numbers have been estimated; means do not include subject A


Table 25. Hb-adjusted $DL_{CO}$/VA, individual subject data

| SUBJECT | Test 1 | Test 2 | Test 3 | Test 4 | Test 5 |
|---------|--------|--------|--------|--------|--------|
| A | - | - | - | 4.03 | 3.14 |
| B | 3.54 | 2.88 | 3.32 | 2.26 | 2.46 |
| C | 4.47 | 2.88 | 3.77 | 2.65 | 2.91 |
| D | 2.19 | 2.31 | 2.21 | 2.06 | 1.83 |
| E | 4.85 | 3.92 | 3.72 | 3.59 | 3.37 |
| F | 3.60 | 4.35 | 4.59 | 3.48 | 3.41 |
| G | **6.51** | 5.62 | 3.95 | 4.07 | 3.86 |
| MEAN ± SD | 4.19 ± 1.46 | 3.66 ± 1.22 | 3.59 ± 0.79 | 3.02 ± 0.81 | 2.97 ± 0.74 |

• Bold numbers have been estimated; means do not include subject A


**EXERCISE CAPACITY DATA**

Table 26. $VO_2$max (mL/min), individual subject data

| SUBJECT | Test 1 | Test 2 | Test 3 | Test 4 | Test 5 |
|---------|--------|--------|--------|--------|--------|
| A | 1096 | **1071** | 1055 | 943 | 1023 |
| B | 1797 | 1625 | 1779 | 1757 | 2198 |
| C | 978 | 986 | 1024 | 993 | 1137 |
| D | 1337 | 1362 | 1434 | 1413 | 1856 |
| E | 1193 | 1130 | 1228 | 1108 | 1098 |
| F | 1033 | 1042 | 1047 | 1106 | 1048 |
| G | **1434** | 1399 | 1597 | 1626 | 1388 |
| MEAN ± SD | 1267 ± 285 | 1231 ±235 | 1309 ± 300 | 1278 ± 321 | 1392 ± 460 |

• Bold numbers have been estimated

Table 27. VO₂max (mL/kg/min), individual subject data

| SUBJECT | Test 1 | Test 2 | Test 3 | Test 4 | Test 5 |
|---|---|---|---|---|---|
| A | 18.6 | **18.1** | 18.2 | 16.5 | 17.6 |
| B | 26.5 | 24.0 | 25.7 | 25.6 | 31.8 |
| C | 14.0 | 14.2 | 14.8 | 14.1 | 16.3 |
| D | 25.5 | 25.8 | 25.8 | 25.3 | 32.5 |
| E | 22.1 | 21.0 | 22.7 | 20.4 | 20.1 |
| F | 20.5 | 20.3 | 19.5 | 21.3 | 19.8 |
| G | **14.3** | 13.9 | 15.4 | 15.8 | 13.3 |
| MEAN ± SD | 20.2 ± 5.0 | 19.6 ± 4.6 | 20.3 ± 4.6 | 19.9 ± 4.6 | 21.6 ± 7.5 |

- Bold numbers have been estimated

Table 28. VE (L/min), individual subject data

| SUBJECT | Test 1 | Test 2 | Test 3 | Test 4 | Test 5 |
|---|---|---|---|---|---|
| A | 48.9 | **51.9** | 58.8 | 55.3 | 61.4 |
| B | 91.8 | 73.1 | 97.6 | 85.9 | 114.7 |
| C | 41.8 | 55.7 | 48.2 | 52.6 | 57.2 |
| D | 57.5 | 68.9 | 81.8 | 87.5 | 105.2 |
| E | 63.4 | 55.1 | 58.9 | 68.1 | 63.4 |
| F | 66.8 | 74.1 | 71.7 | 66.4 | 75.3 |
| G | **65.5** | 66.9 | 65.0 | 60.3 | 62.0 |
| MEAN ± SD | 62.2 ± 15.9 | 63.7 ± 9.2 | 68.9 ± 16.6 | 68.0 ± 13.9 | 77.0 ± 23.3 |

- Bold numbers have been estimated

Table 29. HRmax (bpm), individual subject data

| SUBJECT | Test 1 | Test 2 | Test 3 | Test 4 | Test 5 |
|---|---|---|---|---|---|
| A | 155 | **157** | 145 | 162 | 158 |
| B | 161 | 145 | 154 | 155 | 163 |
| C | 128 | 140 | 172 | 160 | 156 |
| D | 160 | 167 | 199 | 202 | 174 |
| E | 136 | 138 | 131 | 129 | 122 |
| F | 157 | 161 | 169 | 174 | 176 |
| G | **169** | 171 | 177 | 172 | 171 |
| MEAN ± SD | 152 ± 15 | 154 ± 13 | 164 ± 23 | 165 ± 22 | 160 ± 19 |

- Bold numbers have been estimated

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Table 30. PPO (watts), individual subject data

| SUBJECT | Test 1 | Test 2 | Test 3 | Test 4 | Test 5 |
|---------|--------|--------|--------|--------|--------|
| A | 108 | **109** | 100 | 193 | 189 |
| B | 183 | 166 | 183 | 175 | 182 |
| C | 93 | 105 | 98 | 101 | 104 |
| D | 150 | 145 | 155 | 155 | 161 |
| E | 126 | 121 | 117 | 121 | 121 |
| F | 121 | 130 | 132 | 140 | 140 |
| G | **136** | 136 | 139 | 150 | 127 |
| MEAN ± SD | 131 ± 29 | 130 ± 21 | 132 ± 31 | 148 ± 31 | 146 ± 32 |

• Bold numbers have been estimated

Table 31. SaO$_2$(%), individual subject data

| SUBJECT | Test 1 | Test 2 | Test 3 | Test 4 | Test 5 |
|---------|--------|--------|--------|--------|--------|
| A | 96 | - | 94 | 97 | 95 |
| B | 96 | 96 | 96 | 96 | 97 |
| C | 96 | 97 | 97 | 97 | 95 |
| D | 97 | 95 | 97 | 96 | 89 |
| E | 92 | 95 | - | - | 99 |
| F | 97 | 97 | 89 | 94 | 93 |
| G | - | 97 | 94 | 90 | 97 |

## QUALITY OF LIFE DATA

Table 32. Physical QOL, individual subject data

| SUBJECT | Test 1 | Test 2 | Test 3 | Test 4 | Test 5 |
|---------|--------|--------|--------|--------|--------|
| A | - | - | - | - | - |
| B | 8.5 | 6.0 | 5.3 | 6.1 | 8.3 |
| C | 7.5 | 7.1 | 5.1 | 8.8 | 9.9 |
| D | 9.0 | 8.9 | 7.6 | 7.5 | 8.1 |
| E | 10.0 | 5.6 | 5.7 | 5.0 | 6.6 |
| F | 10.0 | 10.0 | 7.2 | 10.0 | 9.6 |
| G | **9.4** | 7.5 | 6.0 | 8.2 | 9.1 |
| MEAN ± SD | 9.1 ± 1.0 | 7.5 ± 1.7 | 6.2 ± 1.0 | 7.6 ± 1.8 | 8.6 ± 1.2 |

• Bold numbers have been estimated; means do not include subject A

Table 33. Psychological QOL, individual subject data

| SUBJECT | Test 1 | Test 2 | Test 3 | Test 4 | Test 5 |
|---------|--------|--------|--------|--------|--------|
| A | - | - | - | - | - |
| B | 6.7 | 5.6 | 3.8 | 6.4 | 8.3 |
| C | 6.7 | 6.2 | 5.1 | 8.4 | 9.7 |
| D | 6.7 | 8.2 | 7.7 | 7.2 | 8.5 |
| E | 7.5 | 5.4 | 5.3 | 5.3 | 5.9 |
| F | 10.0 | 9.9 | 8.7 | 9.9 | 9.9 |
| G | **4.9** | 4.5 | 4.1 | 8.0 | 8.2 |
| MEAN ± SD | 7.1 ± 1.7 | 6.6 ± 2.0 | 5.8 ± 2.0 | 7.5 ± 1.6 | 8.4 ± 1.4 |

• Bold numbers have been estimated; means do not include subject A


Table 34. Symptom QOL, individual subject data

| SUBJECT | Test 1 | Test 2 | Test 3 | Test 4 | Test 5 |
|---------|--------|--------|--------|--------|--------|
| A | - | - | - | - | - |
| B | 0.6 | 4.6 | 6.7 | 4.9 | 0.9 |
| C | 3.6 | 3.8 | 4.1 | 0.8 | 0.8 |
| D | 1.6 | 1.6 | 4.6 | 4.1 | 1.8 |
| E | 0.5 | 2.2 | 2.7 | 2.7 | 3.1 |
| F | 0.6 | 0.7 | 1.2 | 0.4 | 2.2 |
| G | **2.5** | 4.0 | 4.7 | 2.0 | 1.3 |
| MEAN ± SD | 1.6 ± 1.3 | 2.8 ± 1.5 | 4.0 ± 1.9 | 2.5 ± 1.8 | 1.7 ± 0.9 |

• Bold numbers have been estimated; means do not include subject A


Table 35. Overall QOL individual subject data

| SUBJECT | Test 1 | Test 2 | Test 3 | Test 4 | Test 5 |
|---------|--------|--------|--------|--------|--------|
| A | - | - | - | - | - |
| B | 0.6 | 4.6 | 6.7 | 4.9 | 0.9 |
| C | 3.6 | 3.8 | 4.1 | 0.8 | 0.8 |
| D | 1.6 | 1.6 | 4.6 | 4.1 | 1.8 |
| E | 0.5 | 2.2 | 2.7 | 2.7 | 5.7 |
| F | 0.6 | 0.7 | 1.2 | 0.4 | 2.2 |
| G | **2.5** | 4.0 | 4.7 | 2.0 | 1.3 |
| MEAN ± SD | 7.0 ± 0.8 | 6.4 ± 1.3 | 5.6 ± 1.1 | 6.7 ± 1.3 | 7.4 ± 1.0 |

• Bold numbers have been estimated; means do not include subject A

## SELF-ESTEEM DATA

Table 36. Appearance, individual subject data

| SUBJECT | Test 1 | Test 2 | Test 3 | Test 4 | Test 5 |
|---------|--------|--------|--------|--------|--------|
| A | - | - | 21 | 20 | 18 |
| B | 19 | 21 | 15 | 15 | 18 |
| C | 12 | 16 | 16 | 16 | 17 |
| D | 17 | 16 | 17 | 16 | 16 |
| E | 19 | 20 | 18 | 20 | 17 |
| F | 15 | 22 | 18 | 22 | 22 |
| G | **29** | 26 | 29 | 20 | 22 |
| MEAN ± SD | 18.5 ± 5.8 | 20.2 ± 3.8 | 18.8 ± 5.1 | 18.2 ± 2.9 | 18.7 ± 2.7 |

• Bold numbers have been estimated; means do not include subject A

Table 37. Competence, individual subject data

| SUBJECT | Test 1 | Test 2 | Test 3 | Test 4 | Test 5 |
|---------|--------|--------|--------|--------|--------|
| A | - | - | 9 | 6 | 10 |
| B | 12 | 14 | 15 | 10 | 11 |
| C | 11 | 8 | 14 | 13 | 13 |
| D | 10 | 10 | 11 | 12 | 11 |
| E | 17 | 19 | 13 | 17 | 17 |
| F | 10 | 17 | 15 | 16 | 20 |
| G | **14** | 16 | 22 | 16 | 15 |
| MEAN ± SD | 12.3 ± 2.7 | 14.0 ± 4.2 | 15.0 ± 3.7 | 14.0 ± 2.8 | 14.5 ± 3.6 |

• Bold numbers have been estimated; means do not include subject A

Table 38. Control, individual subject data

| SUBJECT | Test 1 | Test 2 | Test 3 | Test 4 | Test 5 |
|---------|--------|--------|--------|--------|--------|
| A | - | - | 12 | 10 | 9 |
| B | 10 | 7 | 13 | 8 | 9 |
| C | 13 | 12 | 11 | 11 | 12 |
| D | 6 | 9 | 7 | 7 | 9 |
| E | 14 | 10 | 9 | 8 | 12 |
| F | 14 | 14 | 17 | 15 | 13 |
| G | **19** | 18 | 20 | 11 | 11 |
| MEAN ± SD | 12.7 ± 4.4 | 11.7 ± 3.9 | 12.8 ± 4.9 | 10.0 ± 3.0 | 11.0 ± 1.7 |

• Bold numbers have been estimated; means do not include subject A

Table 39. Resilience, individual subject data

| SUBJECT | Test 1 | Test 2 | Test 3 | Test 4 | Test 5 |
|---------|--------|--------|--------|--------|--------|
| A | - | - | 15 | 13 | 14 |
| B | 16 | 15 | 14 | 14 | 15 |
| C | 11 | 17 | 16 | 14 | 17 |
| D | 12 | 14 | 15 | 14 | 13 |
| E | 21 | 18 | 115 | 12 | 13 |
| F | 15 | 16 | 17 | 17 | 16 |
| G | **11** | 12 | 12 | 13 | 14 |
| MEAN ± SD | 14.3 ± 3.9 | 15.3 ± 2.2 | 14.8 ± 1.7 | 13.8 ± 1.7 | 13.0 ± 3.2 |

- Bold numbers have been estimated; means do not include subject A

Table 40. Significance, individual subject data

| SUBJECT | Test 1 | Test 2 | Test 3 | Test 4 | Test 5 |
|---------|--------|--------|--------|--------|--------|
| A | - | - | 18 | 16 | 14 |
| B | 14 | 17 | 17 | 17 | 15 |
| C | 19 | 19 | 22 | 19 | 19 |
| D | 19 | 19 | 18 | 15 | 18 |
| E | 22 | 23 | 25 | 19 | 21 |
| F | 24 | 21 | 21 | 21 | 22 |
| G | **24** | 24 | 21 | 23 | 20 |
| MEAN ± SD | 20.3 ± 3.8 | 20.5 ± 2.7 | 20.7 ± 2.9 | 19.0 ± 2.8 | 19.2 ± 2.5 |

- Bold numbers have been estimated; means do not include subject A

Table 41. Value, individual subject data

| SUBJECT | Test 1 | Test 2 | Test 3 | Test 4 | Test 5 |
|---------|--------|--------|--------|--------|--------|
| A | - | - | 12 | 12 | 11 |
| B | 8 | 8 | 8 | 8 | 10 |
| C | 10 | 10 | 10 | 10 | 10 |
| D | 11 | 12 | 10 | 11 | 12 |
| E | 11 | 8 | 12 | 9 | 9 |
| F | 14 | 10 | 13 | 14 | 14 |
| G | **14** | 14 | 12 | 14 | 12 |
| MEAN ± SD | 11.3 ± 2.3 | 10.3 ± 2.3 | 10.8 ± 1.8 | 11.0 ± 2.5 | 11.2 ± 1.8 |

- Bold numbers have been estimated; means do not include subject A

Table 42. Worthiness, individual subject data

| SUBJECT | Test 1 | Test 2 | Test 3 | Test 4 | Test 5 |
|---|---|---|---|---|---|
| A | - | - | 18 | 18 | 16 |
| B | 14 | 16 | 15 | 16 | 16 |
| C | 18 | 18 | 19 | 19 | 20 |
| D | 19 | 18 | 18 | 15 | 19 |
| E | 16 | 15 | 19 | 16 | 16 |
| F | 21 | 18 | 19 | 21 | 19 |
| G | **21** | 20 | 15 | 19 | 20 |
| MEAN ± SD | 18.2 ± 2.8 | 17.5 ± 1.8 | 17.5 ± 2.0 | 17.7 ± 2.3 | 18.3 ± 1.9 |

• Bold numbers have been estimated; means do not include subject A

Table 43. Global Total, individual subject data

| SUBJECT | Test 1 | Test 2 | Test 3 | Test 4 | Test 5 |
|---|---|---|---|---|---|
| A | - | - | 107 | 99 | 95 |
| B | 93 | 98 | 97 | 88 | 94 |
| C | 94 | 100 | 108 | 102 | 108 |
| D | 94 | 98 | 96 | 90 | 98 |
| E | 120 | 113 | 111 | 101 | 105 |
| F | 113 | 118 | 120 | 126 | 126 |
| G | **127** | 130 | 131 | 116 | 114 |
| MEAN ± SD | 106.8 ± 15.1 | 109.5 ± 13.1 | 110.5 ± 13.5 | 103.8 ± 14.8 | 107.5 ± 11.5 |

• Bold numbers have been estimated; means do not include subject A

## BODY IMAGE DATA

Table 44. Body Image, individual data

| SUBJECT | Test 1 | Test 2 | Test 3 | Test 4 | Test 5 |
|---|---|---|---|---|---|
| A | - | - | - | - | - |
| B | 8.9 | 5.7 | 3.2 | 7.0 | 8.4 |
| C | 7.9 | 7.8 | 5.3 | 5.1 | 9.1 |
| D | 8.7 | 7.4 | 7.1 | 4.8 | 7.4 |
| E | 6.9 | 4.4 | 3.0 | 4.3 | 4.7 |
| F | 8.0 | 9.2 | 9.8 | 10.0 | 10.0 |
| G | **5.4** | 4.4 | 3.1 | 8.2 | 8.2 |
| MEAN ± SD | 7.6 ± 1.3 | 6.5 ± 2.0 | 5.3 ± 2.8 | 6.6 ± 2.2 | 8.0 ± 1.8 |

• Bold numbers have been estimated; means do not include subject A

# ACTIVITY DATA

Table 45. Activity Levels (Kcal), individual data

| SUBJECT | Test 1-2 | Test 2-3 | Test 3-4 | Test 4-5 |
|---|---|---|---|---|
| A | - | - | - | - |
| | ( - ) | ( - ) | (20) | (43) |
| B | 2 246 | 8 827 | 2 300 | 5 240 |
| | (27) | (118) | (16) | (48) |
| C | 1 544 | 2 869 | 1 435 | 5 560 |
| | (37) | (30) | (18) | (50) |
| D | 2 347 | 3 552 | 1 266 | 2 974 |
| | (34) | (36) | (17) | (46) |
| E | 968 | 21 554 | 5 685 | 16 830 |
| | (24) | (77) | (14) | (47) |
| F | 7 853 | 4 900 | 2 352 | 8 428 |
| | (33) | (25) | (12) | (43) |
| G | - | 9 088 | 23 014 | 30 126 |
| | ( - ) | (43) | (27) | (62) |
| MEAN | 2 992 ± | 8 465 ± | 6 009 ± | 11 526 ± |
| ± SD | 2 775 | 6 928 | 8 463 | 10 314 |
| | (31 ± 5 ) | (55 ± 36) | (17 ± 5) | (49 ± 7) |

(Number of days between tests); means do not include subject A

Table 46. Activity (Kcal)/day, individual data

| SUBJ. | Test 1-2 | Test 2-3 | Test 3-4 | Test 4-5 | MEAN | Pre-diag. --1 yr | Pre-diag/ day [Rank] |
|---|---|---|---|---|---|---|---|
| A | - | - | - | - | [-] | 35 616 | 98 [-] |
| B | 83 | 74 | 143 | 109 | 102 [4] | 107 712 | 295 [4] |
| C | 41 | 95 | 79 | 111 | 82 [5] | 85 071 | 233 [5] |
| D | 69 | 98 | 74 | 64 | 76 [6] | 25 334 | 69 [6] |
| E | 40 | 279 | 406 | 356 | 271 [2] | 274 372 | 752 [1] |
| F | 237 | 196 | 196 | 196 | 206 [3] | 198 800 | 545 [2] |
| G | **152** | 211 | 852 | 485 | 516 [1] | 198 364 | 543 [3] |
| MEAN | 104 | 159 | 292 | 221 | 193 | 148 276 | 406 |
| ± SD | ± 77 | ± 82 | ± 300 | ± 166 | ± 137 | ± 37 290 | ± 250 |

• Bold numbers have been estimated; means do not include subject A; Pre-diag = activity the year preceding diagnosis; Pre-diag/day = activity the year preceding diagnosis ÷ 365 days/year

## SMOKING DATA

Table 47. Smoking History, individual data

| SUBJECT | Smoke-yrs | Packs/wk | Packs/yr | Total Packs Smoked (Rank) | Smoke-free yrs |
|---|---|---|---|---|---|
| A | 0 | - | - | - | - |
| B | 14 | 0.5 | 26 | 286 (4) | 3.0 |
| C | 30 | 7.0 | 364 | 10738 (2) | 0.5 |
| D | 35 (+18) | 3.0 (+3) | 364 | 19110 (1) | 0.5 |
| E | 0 | - | - | - | - |
| F | 0 | - | - | - | - |
| G | 24 | 1.0 | 52 | 572 (3) | 13.0 |
| MEAN ± SD | 17 ± 20 | 2 ± 3 | 115 ± 171 | 4387 ± 7496 | 4.3 ± 6.0 |

* (Subject D also smoked marijuana)

## TIMELINE DATA

Table 48. Timeline, individual data

| SUBJ. | D-T1 | T1-S | S-T2 | T2-BRT | BRT-T3 | T3-ERT | ERT-T4 | T4-T5 |
|---|---|---|---|---|---|---|---|---|
| A | 9 | 20 | - | - | 10 | 13 | 2 | 43 |
| B | 15 | 5 | 22 | 104 | 11 | 13 | 7 | 48 |
| C | 18 | 4 | 33 | 12 | 18 | 4 | 8 | 50 |
| D | 36 | 11 | 23 | 21 | 14 | 12 | 7 | 46 |
| E | 10 | 33 | 22 | 32 | 14 | 8 | 8 | 47 |
| F | 40 | 1 | 32 | 41 | 10 | 12 | 6 | 43 |
| G | - | - | 15 | 29 | 14 | 21 | 7 | 62 |
| MEAN | 21 | 7 | 25 | 40 | 13 | 12 | 6 | 48 |
| ± SD | ± 13 | ± 7 | ± 7 | ± 33 | ± 3 | ± 5 | ± 2 | ± 7 |

D = diagnosis; T# = test number; S = surgery; BRT = begin radiotherapy; ERT = end radiotherapy