Indications for Adjuvant Radiation Therapy in Cutaneous Squamous Cell Carcinoma: A Review

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MEDD 449: Flexible Enhanced Learning III
September 21, 2020

1. Introduction

Skin cancer is the most common human malignancy (1). Cutaneous squamous cell carcinoma (cSCC) is the second most common skin cancer after basal cell carcinoma (BCC), and represents 20-50% of all skin cancers in the United States (2,3). Several histopathological subtypes of cSCC have been identified which include lower risk variants like keratoacanthomas, verrucous, clear cell lesions and higher risk subtypes like acantholytic, adenosquamous, spindle cell (4) and desmoplastic cSCC (5). Grading of cSCC ranges from well- to poorly-differentiated.

The estimated lifetime risk of developing cSCC is 9-14% for men and 4-9% for women (6), and the majority of cases occur in people over the age of 60 (2,7,8). Approximately 4-5% of cSCC are found to be metastatic, most commonly to the first regional lymph node (9). Of the approximately 700,000 people diagnosed with cSCC annually in the United States, it is estimated that the disease-specific death is 1.5% (10), and this approaches the number of annual deaths from melanoma (11). The disease incidence is estimated to be increasing by 2-4% annually (12), perhaps due to older age or better screening; however, cSCC is not included in many nations' cancer registries, making the true incidence unknown (3,10,12).

The most prominent risk factors for cSCC include UV exposure, age, fair skin, and immunosuppression (2,11). It can be associated with precursor lesions such as actinic keratosis (a marker of UV exposure) and cSCC-in situ (Bowen's disease) (7). It is estimated that approximately 10% of actinic keratoses will transform into cSCC after 2 years (13). UV radiation is an important risk factor for both BCC and cSCC, however, cumulative lifetime UV exposure (ie. occupational) is related more with cSCC, whereas intermittent UV exposures (ie. during childhood) may be more important for BCC development (7,14,15). Immunosuppression is also a well-recognized risk factor for cSCC. In recipients of solid organ transplants on immunosuppressant therapy, cSCC risk is increased by a factor of 100, with higher metastasis and mortality rates (11,16). Moreover, patients who are immunocompromised secondary to chronic lymphocytic leukemia (CLL) have an 8- to 10-fold increased risk (2). Chronic sites of cutaneous inflammation secondary to burns or chronic wounds can also promote the development of cSCC (Marojlin's ulcer) (11,17). Moreover, familial syndromes associated with photosensitivity (ie. albinism) or defective DNA repair (ie. xeroderma pigmentosum) have markedly increased risk of cSCC (2,11).

cSCC typically presents in fair-skinned individuals on sun exposed sites as a non-healing ulcer or an abnormal cutaneous growth. Lesions manifest as papules or plaques that are firm, skin-coloured to pink, and smooth or hyperkeratotic in texture (18). The lesions may present with paresthesia or pain and this may suggest perineural invasion (PNI) of cancer (19).

PNI occurs in less than 5% of patients with cutaneous cancers (20,21), and is implicated in 2.5-14% of cSCC (22). It is traditionally thought to arise from contiguous spread of cancer, but growing evidence suggests the pathogenesis involves molecular interactions between supportive neuronal and malignant cells (23). PNI can be termed incidental when found on histology alone, or clinical when found on radiological imaging (typically MRI) or when presenting with neurological symptoms (22,24). cSCC clinical PNI nerve deficits most commonly affect the V2 branch of the fifth cranial nerve and the seventh cranial nerve (25). Clinical PNI is associated with higher local recurrence and death (22,24,26). The majority of patients (60-70%) with perineural invasion present with no clinical symptoms however symptoms may progress from skin paresthesia to pain, numbness, or motor deficit (27).

cSCC is treated by different modalities based on the location, stage, and patient preference. Radiotherapy (RT) is a treatment modality in the primary, adjuvant and palliative settings (28,29). Although the most effective treatment method for cSCC is surgery, radiation therapy after surgery for high risk lesions such as locally advanced tumours, positive margins, perineural involvement, or incomplete surgical excision could lead to improvement of local control. However, the precise group of patients who might benefit from adjuvant radiation has not been clearly determined, and there is variability of indications for this modality amongst practice guidelines. This review will focus on the literature around the utilization of adjuvant radiation for cSCC, and its indications.

2. Staging

2.1 AJCC Eighth Edition (AJCC-8)

The American Joint Committee on Cancer (AJCC) updated their staging criteria for cSCC in 2016 (2). It was developed within the head and neck committee, and although 80-90% of cSCC are located on the head (28,30) it is unclear as to how it applies in non head and neck cSCC. AJCC-8 stages cSCC based on tumour burden (T), nodal (N) involvement, and metastatic disease (M) (Table 1).

Table 1: AJCC-8 cSCC staging (2,31)

Category	Criteria
Tx	Primary tumour cannot be assessed
Tis	Carcinoma in situ
T1	Tumour ≤ 2 cm in greatest dimension
T2	Tumour > 2 cm but, ≤ 4 cm in greatest dimension
T3	Tumour > 4cm or minor bone erosion or perineural (≥ 0.1mm nerve calibre) or deep invasion (beyond subcutaneous fat or > 6mm)
T4a	Tumour with gross cortical bone/marrow invasion
T4b	Tumour with skull base invasion and/or skull base foramen involvement
N0	No regional lymph node metastasis
N1	Metastasis in a single ipsilateral lymph node, ≤3 cm in greatest dimension and extranodal extension (ENE) -
N2a	Metastasis in single ipsilateral node larger than >3 cm but not >6 cm in greatest dimension and ENE -
N2b	Metastasis in multiple ipsilateral nodes, none >6 cm in greatest dimension and ENE -
N2c	Metastasis in bilateral or contralateral lymph nodes, none >6 cm in greatest dimension and ENE -
N3a	Metastasis in a lymph node >6 cm in greatest dimension and ENE-
N3b	Metastasis in any node and ENE +
M0	No distant metastasis
M1	Distant metastasis

2.2 Brigham and Women's (BWH) Staging

The BWH cSCC staging system is based on tumour characteristics, but does not include N or M staging. There is no T4 in this classification in contrast to the AJCC-8 system. The number of high risk features is the criteria used in upstaging in this classification scheme (Table 2) (2).

Table 2: BWH Staging (2)

Stage	Number of Risk Factors	High Risk Features:
T1	0	• tumour diameter ≥ 2 cm • poorly differentiated histology • perineural invasion in nerves ≥ 0.1 mm in size • invasion beyond subcutaneous fat (except any bone invasion which is always classified as BWH T3)
T2a	1	
T2b	2-3	
T3	≥ 4	

3. Risk classification

Following the diagnosis of biopsy-confirmed cSCC, determining the risk level is integral in developing the management approach. Low risk is classified as T1 disease in the AJCC-8 staging system (32). T1 and T2a are low risk in the BWH staging systems, with T2b and T3 disease associated with greater than 20% risk of lymph node metastasis (32). One study found better performance of BWH classification in predicting nodal metastasis and disease specific death as compared to AJCC-8 (33). Although the National Comprehensive Cancer Network (NCCN) has defined many high risk criteria (Table 3), there is no single unified definition (28).

Table 3: NCCN cSCC high risk criteria (28)

History and Physical	• ≥ 20 mm on the trunk or extremities • ≥ 10 mm on the cheek, forehead, scalp, neck, and pre-tibia • any lesions on the “mask area” of the face (central face, eyelids, eyebrows, periorbital, nose, lips, chin, mandible, preauricular and post auricular skin/sulci, temple, and ear), genitalia, hands, and feet • poorly defined borders • recurrent tumour • Immunosuppression • site of prior RT/chronic inflammatory process • rapid growth • neurologic symptoms
Pathology	• poor differentiation • high risk subtypes (acantholytic, adenosquamous showing mucin production, desmoplastic or metaplastic) • >6mm in thickness or invasion beyond subcutaneous fat • perineural/lymphatic/vascular involvement

It is generally accepted that nodal involvement, increased diameter, depth of invasion, perineural involvement, immunosuppression, and recurrence are high risk features. Furthermore, a meta-analysis of 36 studies with 17248 patients found Breslow >2mm, invasion beyond subcutaneous fat, perineural invasion, diameter > 20mm, location on temple, and poor

differentiation were statistically significant risk factors for disease recurrence in descending order. For metastasis and disease-specific death, the highest risk ratio was associated with invasion beyond the subcutaneous fat and tumour diameter >20mm respectively. Moreover, immunosuppression was also significantly associated with metastasis (34). Similarly, a prospective study found key risk factors for recurrence were tumour thickness (HR 6.03 95% CI 2.71-13.43) and desmoplastic histopathology (HR 16.11 95% CI 6.57-39.49) (35).

Based on the assessment of tumour risk, preferred treatment options differ. Low risk cancers can be treated surgically with standard excision (4-6mm uninvolved skin margin), or curettage and electrodessication. Topical therapy (imiquimod or 5-fluorouracil) is an option for precancerous lesions but not recommended for treatment of cSCC(11,36). Primary RT is an option for non-surgical candidates due to functional limitations (ie. frail elderly) or improved cosmetic outcome (11,36).

High-risk cSCC could be treated with Mohs micrographic surgery (MMS) or excision with complete margin assessment and adjuvant RT when indicated (11,36). MMS is a specialized surgical technique which involves serial microscopic examination of excised tissue during surgery (17,26,28). A systematic review found a lower 5-year risk of local recurrence for high-risk cSCC when MMS was used as compared to primary curettage and electrodessication, standard excision, and RT in composite (30). More recently, systemic targeted and immunotherapies are under investigation for use in locally advanced and metastatic cSCC. Several immunotherapies are being studied (29) however are beyond the scope of this review.

4. Radiation Role

RT is a tissue-preserving approach which avoids post surgical morbidity and the need for surgical reconstruction by flaps or grafts. It can be especially useful for lesions where an improved cosmetic outcome is desired such as on the lip, ear, nose, forehead and periorbital areas (28). Radiation is well tolerated, however, acute side effects of desquamation and erythema are common. Moreover, there is risk for late side effects which include hypopigmentation, telangiectasia, epilation, subdermal fibrosis, and rarely, radiation induced malignancy (28). RT is not recommended in patients who are genetically prone to radiosensitivity such as ataxia telangiectasia, Gorlin syndrome, Li-Fraumeni syndrome as well as poorly controlled connective tissue disorders (37). RT is also not recommended for verrucous

cSCC as it has been associated with anaplastic transformation (38,39) and should be avoided in poorly vascularized sites (39,40).

4.1 Radiation techniques

RT works by using electromagnetic radiation (ie. x-rays), or particulate radiation (ie. electrons, protons, neutrons) to induce lethal DNA damage and mitotic cell death of cancer cells (28). This process of cell death is delayed, and may take multiple cell cycles (41). Broadly, RT techniques can be divided into external RT and brachytherapy. Brachytherapy places the source of radiation inside or in direct surface contact with the tumour.

The international unit used in RT is a Gray (Gy). Each single treatment is referred to as a fraction (28,41). When the total dose of radiation is given over less individual fractions and where the dose is more than 2Gy/fraction, the RT course is defined as hypofractionated. A typical adjuvant radiation course for skin cancers is mildly hypofractionated and uses 50 Gy over 20 fractions or 2.5 Gy/fraction, administered 5 days per week (28,41). More extremely hypofractionated regimens typically use 4-7 Gy/fraction which is useful for elderly patients who may not be able to come for treatment as frequently (28). However, more hypofractionated radiotherapy regimens have increased risk for poor cosmesis following treatment, when compared to fractionated regimens (28). As a result, these regimens are generally not recommended in younger patients, given the risk for late side effects.

A variety of techniques and regimens exist for administration of cutaneous RT. No single technique has been shown to be superior, and choice of technique should be individualized on patient specific factors and treatment center experience (36). RT may involve low-energy (kilovoltage or orthovoltage) or high energy techniques. Low energy techniques target superficial structures like skin, while sparing the deeper tissues. In contrast, high energy techniques using a linear accelerator can be useful to spare surface tissue and target deeper structures (28,41). This can be particularly useful for adjuvant treatment of cranial nerves affected by cancer spread.

4.2 Adjuvant RT

Adjuvant RT has the treatment goal of reducing cancer recurrence after primary excision (28). There is some consensus on patient indications for adjuvant RT among guidelines. It is recommended by a recent American Society for Radiation Oncology (ASTRO) guideline for

cSCC patients at high risk of cancer recurrence, perineural involvement, and regional spread to lymph nodes (37).

4.2.1 Indications for adjuvant RT

We could find no randomized controlled trials comparing adjuvant RT to surgery alone in cSCC, and available studies are limited by retrospective designs and potential selection bias.

A retrospective analysis by Harris et al. of patients with advanced head and neck cSCC found adjuvant RT to be associated with an improved overall survival (HR 0.59, 95% CI 0.38-0.90) compared to surgery alone. The study included a total of 349 patients, 9.5% were immunocompromised, 58.5% had recurrent tumours, 39% had PNI, 19.2% had extracapsular extension, 24.4% had poorly differentiated histologic features, and 37% had regional disease. In subset analysis, they found improved disease free and overall survival in patients with perineural invasion and regional disease who were treated with adjuvant radiation. However no such association was found for T3/T4 or poorly differentiated tumours (42).

Kim et al. conducted a small retrospective review of T3/T4 cSCC patients treated with definitive compared to adjuvant RT and found a benefit in three year disease specific survival for those treated with adjuvant RT (38.3%, 95% CI: 22.2-54.4 vs 92.9%, 95% CI: 77.9-95.5). However, this study is limited by selection bias for worse prognosis based on a higher number of older age patients, node positive disease and immune dysfunction in the definitive group (43).

In contrast to these studies, a 2009 systematic review by Jambusaria et al. found no significant difference with the addition of adjuvant RT when compared to surgery alone in patients with high risk cSCC. They defined high risk cSCC as tumour diameter > 2cm, depth to fat or deeper, >4mm deep, Clark IV or V, recurrent cSCC, location on anogenital region, ear, lip, or on scar or located on area of chronic inflammation, poorly differentiated or infiltrative histologic pattern, perineural, perivascular, perilymphatic invasion, concurrent CLL, and tumour after organ transplantation. However, data were not controlled for tumour stage, and they excluded those with known nodal metastasis at diagnosis (42). In addition a recent retrospective cohort of 104 patients treated with at least parotidectomy or neck dissection for advanced cSCC found no difference in the 2 year disease free survival for patients treated with surgery, surgery and adjuvant radiation, and surgery and adjuvant chemoradiotherapy (43).

Manyam et al. looked at patients treated with surgery and adjuvant RT, and compared immunocompetent with immunosuppressed patients and found the two year disease free survival to be lower in immunosuppressed patients (45% vs 62%; P=0.036) despite both groups receiving bimodal treatment (44). In keeping with this outcome, the immunosuppressed group had a higher incidence of high risk tumour features like poor differentiation, extracapsular extension, and lymphovascular invasion (44).

Overall, some of the most cited indications for adjuvant RT for cSCC include recurrence after prior excision, nodal metastasis, perineural invasion, and positive margins after surgery (36,37,41) which will be discussed separately.

4.2.1.1. Recurrence after prior excision

Strassen et al. found a benefit to the use of adjuvant radiation over surgery alone in an assessment on 67 patients with locoregional recurrence, of which 30% received adjuvant RT. Adjuvant RT was associated with an improved 5 year recurrence free interval (78% vs 30%; P=0.02) and overall survival (79% vs 46%; P < 0.05) (45). However, there were differences between cohorts in that the adjuvant group had lower T stages but more advanced N stages, whereas those without adjuvant treatment had higher T stages, but only up to N1 disease (45).

In contrast, Dean et al. did not find a benefit to adjuvant RT in patients with recurrent, advanced (stage III/IV) cSCC. Positive nodal metastasis was present in 43.7% of patients with recurrence and 66.7% received adjuvant RT. Although not statistically significant, patients with cervical node metastasis did trend toward improved locoregional control when compared to surgery alone (68 vs 25%; P=0.14), however there was no impact on overall disease free survival (P=0.42) or repeat cancer recurrence (P=0.85) (46).

4.2.1.2. Locoregional spread and nodal metastasis

The most commonly affected nodes are the parotid or cervical lymph nodes, and nodal metastasis is often an indication for adjuvant RT by guidelines after nodal dissection. However, Ebrahimi et al. found that those with metastatic disease to a solitary node $\leq$ 3cm in size without extracapsular extension or other poor clinicopathologic features (perineural invasion, involved or close surgical margins, immunosuppression, and concern for tumour contamination of the surgical field) may be treated with surgery alone as they found no significant difference in disease specific survival (90 vs 97% p=0.40) with the addition of adjuvant RT (47). Veness et al.

conducted a retrospective review of 167 patients with cSCC metastatic to the parotid or cervical nodes treated with surgery alone or surgery plus adjuvant RT, and found a lower locoregional recurrence (43% vs 20%) and a higher disease free survival (54% vs 73% P=.004) with the addition of adjuvant RT (48). Oddone et al. also found a survival benefit to adjuvant RT in 222 patients with metastatic cSCC to the parotid or cervical lymph nodes (HR 0.32; 95% CI 0.16-0.66) compared to surgery alone (49). Similar results were seen by Wang et al. in patients with only cervical node metastasis and found those that underwent surgery and adjuvant RT had a better 5 year disease free survival (74% vs 34%; p= 0.001) and overall survival (66% vs 27%; p=0.003) (50). Likewise, metastatic cSCC with parotid involvement has improved survival with a combined surgical and adjuvant RT approach (51–53). Moreover, in analysis of patients with regional disease, Harris et al. found adjuvant radiation was associated with improved disease free survival (HR, 0.36; 95% CI, 0.15-0.84) and overall survival (HR, 0.30; 95% CI, 0.15-0.61) (42).

Similarly, a 2019 systematic review and meta-analysis by Sahovaler et al. including 3534 patients with nodal metastatic cSCC of the head and neck found adjuvant RT to be associated with increased overall survival (HR,0.45; 95% CI, 0.26-0.78) and disease specific survival (HR, 0.52; 95%CI, 0.33-0.84). Interestingly, immunosuppression was found to have the highest risk for decreased overall survival and disease specific survival (54).

4.2.1.3. Perineural invasion

The calibre of nerve implicated by PNI greatly affects outcomes as patients with involvement of nerves $\geq$0.1mm have a high risk of recurrence (55,56). These larger nerves are associated with deeper invasion of cancer, and are usually found under the dermis. Carter et al. found cSCC PNI of large calibre nerves ($\geq$0.1mm) to be significantly associated with other high risk features like cSCC > 2 cm diameter, invasion beyond the subcutis, multiple nerve involvement, infiltrative growth, and lymphovascular invasion. They also found a 45 fold higher risk of death when these large calibre nerves are involved (57).

A case series by Warren et al. found a 75% disease specific survival and 62% recurrence free survival at 5 years for cSCC patients with clinical PNI treated with postoperative adjuvant RT suggesting good long term outcome with this treatment approach (24). Sapir et al. analyzed the outcomes of 102 patients with gross PNI (seen on MRI with or without cranial nerve deficit), microscopic focal (1-2 nerves on histological evaluation), and microscopic extensive ($\geq$2 nerves

on histological evaluation) PNI treated with or without RT. In patients with gross PNI, all patients received RT and the two year perineural recurrence free survival and disease free survival was 64% and 56% respectively with RT. Interestingly, those with microscopic extensive involvement had a benefit with adjuvant RT over observation alone, with a two year perineural recurrence free survival and disease free survival of 94% vs 25% (P=0.01) and 73% vs 40% (P=0.05) respectively. This effect was not seen in the microscopic focal PNI group, suggesting extensive nerve involvement may be an additional risk factor (58).

4.1.1.4. Positive margins

Guidelines generally recommend a 4-6 mm minimum excisional margin for low risk cSCC and even wider excisional margins for high risk cSCC (36). Despite this, as many as 17.6% of excised cSCC have positive pathologic margins after surgery (59). An analysis by Babington et al. of lip cSCC with close (defined as <2mm in this study) or positive margins saw a benefit to adjuvant RT and found a recurrence rate of 6%. In contrast, patients who had surgery or radiotherapy alone had a 53% and 19% recurrence rate respectively with a median time to recurrence of 12 months (1.2–37.8 months) (60).

4.2.2. Comparison of guidelines on the role of adjuvant radiotherapy

Despite a lack of prospective trials assessing the role of adjuvant radiotherapy in cSCC, there is some consensus defining its indications (61). ASTRO and NCCN guidelines are in alignment that at the presence of regional nodal metastasis, clinical PNI and positive margins after surgery, radiation is warranted (36,37). Both also suggest that a solitary metastatic node without extracapsular extension may be treated with surgery alone (36,37). NCCN however makes a distinction between trunk/extremity and head/neck cSCC with respect to defining cSCC risk (Table 3) (36). Journal of the American Academy of Dermatology (JAAD) guidelines do not make clear recommendations for adjuvant RT, but recommend its consideration for regional and nodal metastasis (62). The Canadian Non-melanoma Skin Cancer (NMSC) Guidelines Committee suggest any high risk cSCC may benefit from adjuvant RT (63). Interestingly, recent European Dermatology Forum (EDF), European Association of Dermato-Oncology (EADO) and the European Organization of Research and Treatment of Cancer (EORTC) joint guidelines do not explicitly list PNI as an indication in its recommendations in contrast to the other guidelines (64). Recent ASTRO guidelines are the most broad for adjuvant RT indications by including AJCC T3, T4, and desmoplastic or infiltrative tumours in the setting of chronic immunosuppression (37).

Table 4: Comparison of Guidelines

	ASTRO (US) - 2019	NCCN (US) - 2019	JAAD (US) - 2018	Canadian NMSC Guidelines Committee (Canada) - 2015	EDF/EADO/EORTC (Europe) - 2020
Indication for adjuvant RT	- Clinical or radiological PNI - Close or positive margins not amenable to surgery - Recurrence after a prior margin negative resection - AJCC T3/T4 tumours - Desmoplastic or infiltrative tumours in setting of chronic immunosuppression - Metastasis to clinically apparent regional lymph nodes, therapeutic lymphadenectomy followed by adjuvant RT is recommended, (except patients that have a single, small (<3 cm) cervical lymph node harboring carcinoma, without extracapsular extension) (37)	- Extensive perineural or large nerve involvement. - Positive tissue margins after definitive surgery - Nodal metastasis to the head and neck, although observation is a reasonable alternative for patients with only one small (≤3 cm) node and no ECE - Adjuvant RT to nodal bed should be considered in patients treated with dissection of nodes in the trunk and extremities (36)	- Surgical resection, with or without adjuvant RT and possible systemic therapy are recommended for regional lymph node metastases (62)	- May be added to the surgical treatment of high risk cSCC such as those with PNI (63)	- Should be considered in cSCC of the head and neck with regional nodal metastases and extracapsular extension - Should be considered after surgical excision for cSCC with positive margins and for which re-excision is not possible (64)

5. Conclusion

Although most cSCC cases are treated with surgery alone, adjuvant RT is indicated broadly by guidelines in advanced cases and has shown benefit over surgery alone. There is evidence for adjuvant RT in the management of regional nodal metastasis (42,48,49,51–54), recurrence (45), incomplete excision (60) and clinical PNI (24,58). Limited evidence suggests a role for T3/T4 tumours (43). There remains a lack of prospective randomized studies investigating its role, and the retrospective methodologies are a major limitation in the evidence for indications, given the risk for bias in such studies. Future high quality prospective randomized studies would add value and clarity on the benefits of adjuvant RT.

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