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Locally advanced non-melanomatous skin cancer: Contemporary radiotherapeutic management

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ABSTRACT

Non-melanomatous skin cancers (NMSC), comprising both cutaneous squamous cell carcinomas (SCC) and basal cell carcinomas (BCC), are the most common malignancies in fair-skinned persons, frequently arising in the sun-exposed head and neck region. Simple surgical excision is usually curative in the majority of low-risk cases, when functional and cosmetic preservation is typically easily achieved. A number of factors portend a more aggressive course in localised lesions, including pathological features such as an involved surgical margin, moderate to poor differentiation, or perineural or lymphovascular invasion, and clinical features including immunosuppression and recurrent cancer status. Though high-level evidence is lacking, consensus guidelines consistently recommend adjuvant radiotherapy in high-risk NMSCs, most commonly in the setting of a positive margin or extensive perineural disease. In non-operative candidates, high-dose radiotherapy can provide long-term control and survival. In SCC, high risk lesions pose an increased risk of regional spread, and consideration should be given to elective nodal treatment, either with neck dissection or irradiation. Development of regional disease, often to the parotid or cervical nodes in the head and neck region, shifts the prognosis substantially and combined therapy consisting of surgery and radiotherapy is then recommended. Limited evidence supports the use of the emerging technologies of protons, heavy particles or stereotactic treatment, but they may be considered in the setting of intracranial perineural spread or the reirradiation setting, when the radiation dosimetry is exceptionally complex. This review aims to provide an update on the current use of radiation in the treatment of locally advanced NMSCs.

Introduction

Basal cell carcinoma (BCC) and squamous cell carcinoma (SCC) are the most common malignancies in fair-skinned persons [1,2]. Most commonly, these non-melanomatous skin cancers (NMSC) occur in the sun-exposed areas of the head and neck [3]. The lifetime intensity and frequency of ultraviolet radiation exposure (UVA and UVB) accounts for the majority of NMSCs [4–8], although other risk factors such as chronic ulceration or inflammation [9], arsenic exposure [10], prior exposure to ionizing radiation [11], genetic conditions and immunosuppression [12,13] are also implicated. Immunosuppression, in particular, as result of iatrogenic causes (medication, transplant) or immunological dysfunction (i.e. chronic lymphocytic leukaemia, human immunodeficiency virus) imparts a high vulnerability to developing multiple, recurrent and biologically aggressive SCCs, with a marked propensity for regional and distant recurrence and subsequent death [14–17]. However, the overwhelming majority (>90%) of NMSC exhibit relatively indolent behaviour and simple surgical excision is usually curative.

Locoregionally advanced NMSC (LA-NMSC) refers to the minority of cases presenting with an extensive primary lesion (T3-4) or regional nodal metastases (Table 1) [18]. All nonmelanomatous skin cancers of the head and neck except for Merkel cell carcinoma are covered in the current AJCC TNM staging system. Whereby the majority of early-stage tumours are surgically cured with limited morbidity, the development of locoregionally advanced disease heralds a shift towards higher risk of recurrence and death [14–16], with the concomitant result of higher treatment-related morbidity due to requirement for more intense therapies.

The objective of this review is to provide an up-to-date review of the literature and techniques used in the radiotherapeutic management of LA-NMSC.

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Table 1
AJCC TNM pathological staging of cutaneous squamous cell carcinoma of the head and neck, 8th ed [18].

Primary Tumour	
T category	**T criteria**
T1	Tumor ≤ 2 cm in diameter
T2	Tumor > 2 cm, but ≤ 4 cm in diameter
T3	Tumor > 4 cm in diameter or minor bone erosion, perineural invasion or deep invasion*
T4	
T4a	Tumor with gross cortical bone/marrow invasion
T4b	Tumor with skull base invasion and/or skull base foramen involvement
Regional Disease	
N category	**N criteria**
N0	No regional lymph node metastasis
N1	Metastasis in a single ipsilateral lymph node, ≤3 cm and no ENE
N2	
N2a	Metastasis in a single ipsilateral lymph node ≤ 3 cm and ENE; or a single ipsilateral node > 3 cm but ≤ 6 cm and no ENE
N2b	Metastases in multiple ipsilateral nodes, none > 6 cm and no ENE
N2c	Metastases in bilateral or contralateral lymph node(s), ≤6 cm and no ENE
N3	
N3a	Metastasis in a lymph node > 6 cm and no ENE
N3b	Metastasis in a single ipsilateral node > 3 cm and ENE; or multiple ipsilateral, contralateral, or bilateral nodes, any with ENE

ENE = extranodal extension.
* Deep invasion = beyond subcutaneous fat or >6 mm; perineural invasion = tumor cells within the nerve sheath deeper than the dermis or with nerve diameter calibre ≥0.1 mm, or clinical/radiological involvement of named nerves without skull base invasion or transgression.

Current standards of care

Surgical resection is the optimal primary management of LA-NMSCs (Table 2) [19,20]. The goal of surgery is to obtain clear surgical margins and maximise function and cosmesis. Furthermore, surgical resection allows for comprehensive pathological assessment which may identify additional factors resulting in improved risk stratification not possible with non-surgical treatment. This information will also allow for the most appropriate adjuvant radiotherapy (aRT) treatment volumes, including for example cases where irradiation of a nerve or elective nodal irradiation (ENI) are indicated. In the locoregionally advanced setting, pathological radial margins of at least 4 mm and 10 mm are recommended for high risk BCC and SCC, respectively [21]. The minimum pathologic margin required at the deep aspect of the tumour to reduce the risk of recurrence has not been well characterised in the literature.

However, widely clear margins are not always achievable in the head and neck anatomic region without cosmetic or functional compromise, and aRT is often utilised to compensate for tighter margins. There is little evidence to support the use of wider surgical margins with functional compromise where aRT can be safely utilised, such as sacrificing a normal facial nerve in cases where there is metastatic cutaneous head and neck SCC (cHNSCC) within a parotid node in adjacency to the nerve. Where margin status is the only indication for aRT (although in locoregionally advanced tumours this is often not the case), and additional surgery would not compromise function, strong consideration should be given to further resection and its potential implications, weighed against the potential toxicities of aRT.

There are no randomised trials comparing surgery to definitive RT in LA-NMSC, although retrospective series report improved rates of locoregional control when surgery with or without aRT rather than definitive radiation alone is used, particularly where SCC is concerned [27–29]. Primary radiation management is usually reserved for the surgically or medically inoperable, patients who refuse surgery or those requiring palliation. However, contrary to the opinion of some, definitive radiotherapy alone can be an extremely effective treatment modality for superficial BCC and SCC, and patients can expect moderate rates of control in locoregionally advanced SCC, and even higher rates of control in cases of locally advanced BCC (Table 3) [28–33].

Primary radiation therapy for locally advanced disease

Although there is a long history of successful treatment of small superficial NMSCs including both BCCs and SCCs with radiotherapy alone [28,35–40], combined modality treatment is preferred in medically and surgically suitable patients with LA-NMSC. Though it is clear radiotherapy alone is sufficient treatment for some LA-NMSC, no predictive biomarkers are available to select these patients. In particular, neither HPV nor p16 status are prognostic or predictive markers in cHNSCC and should not be used to determine management [41].

Local disease

The published radiotherapy literature in NMSC stretches over many decades, predating contemporary radiotherapy techniques (Table 3). Considering the technological limitations, as well as recent refinements in staging [97], radiotherapy alone demonstrates moderate efficacy. In some series, radiotherapy appears to be more effective in locally advanced BCC compared to SCC [28,29], although other series do not discriminate by histology or have failed to find a difference in response [30,32]. Larger lesions, higher T-stages and recurrent tumours consistently demonstrate inferior rates of control [28–30,32,34,39]. LA-NMSC with perineural tumor spread, including retrograde intracranial spread, is a distinct clinical entity associated with worse prognosis [36,42–44]. Where gross surgical clearance is not possible, definitive radiotherapy is recommended in suitably fit patients. The radiotherapeutic approach with large-nerve perineural tumor spread, including through the base of skull with or without intracranial extension is the subject of another paper in this special series on skin cancer [98].

Nodal disease

Although most series focus on the treatment of primary lesions, some also include patients treated with clinically positive neck disease. Where compared, radiation alone is less effective than a combined approach of surgery followed by aRT [45,46], although it is highly likely that selection bias exists in these comparisons, with the more fit patients eligible for surgery. Drawing firm conclusions about the effectiveness of RT alone in this setting is challenging owing to the small number of patients not suitable for surgical treatment, but who are suitable for radical treatment. While some small series have reported high rates of regional control with RT alone [28,30], at least one series reporting on definitive concurrent chemoradiation reported much lower rates of regional control, largely in the setting of macroscopic evident nodal disease [47]. Where surgery is not feasible, the data does support that radical radiotherapy should be discussed and offered to appropriately suitable patients.

Concurrent systemic therapy

The benefit of adding concomitant chemotherapy to definitive radiotherapy in cHNSCC is unknown, as it has only been reported in small series [33,47,48]. To date the only prospective series of concurrent platinum-based chemoradiation was reported by Nottage et al. from Brisbane, Australia [47]. The majority of the 19 assessable patients had nodal disease (with or without local disease) and were treated with platinum-based concurrent chemotherapy. They reported a locoregional control rate of 61.9% at six months. However, this series is small and only limited conclusions can be drawn. In line with the recommendations from the NCCN [19], largely extrapolating from the benefit seen in the mucosal SCC setting [49], adding concurrent

Table 2
Selected international guidelines on management of cutaneous squamous and basal cell carcinomas.

Group	Year	Indications for radiotherapy				RT dose guidelines	Concurrent chemotherapy indications
		Definitive low risk	Adjuvant primary	Adjuvant regional	Elective regional		
Squamous cell carcinoma							
National Comprehensive Cancer Network [19]	2018	Non-surgical candidates (inoperable, patient preference)	Extensive, large or named PNI, SM+	aRT in all cases; Single node ≤ 3 cm no ENE – can consider RT or observation	NR	Yes	Consider in: selected high risk cases treated with primary RT, high-risk regional disease, residual disease after surgery, inoperable regional disease
American Academy of Dermatology [22]	2018	Surgery not feasible or patient preference in low risk (accepting cure rate may be lower)	PNI	No firm recommendation (Surgery ± aRT)	NR	NR	Consider concurrent treatment in inoperable locally advanced cases
Cancer Council of Australia* [23]	2008	Surgery not feasible, patient refusal, significant cosmetic or functional morbidity	Indicated: incomplete excision; Consider in: T4, rapidly growing, Recurrent, Margins < 5 mm, PNI, LVSI, In-transit metastases	Indicated in: any parotid node, ≥ 2 neck nodes, ≥ 3 cm node, significant ENE, close or involved margins, skin infiltration, major nerve involvement, recurrent nodal disease, nodes in unusual sites, nodal metastases with local relapse	NR	NR	NR
British Association of Dermatologists*† [24]	2009	Unresectable	NR	NR	END mentioned, NR	NR	NR
Basal cell carcinoma							
National Comprehensive Cancer Network [20]	2018	Non-surgical candidates (inoperable, patient preference)	SM+, large nerve or extensive PNI	N/A	N/A	Yes	N/A
American Academy of Dermatology [25]	2018	Surgery not feasible or patient preference in low risk cases (accepting cure rate may be lower)	NR	N/A	N/A	NR	N/A
Cancer Council of Australia* [23]	2008	Surgery not feasible	Indicated in: incomplete excision and surgery not feasible. Consider in: T4, multifocal recurrence, multiple recurrences, poor prognosis subtypes‡, inadequate margins, PNI	In cases of node-positive BCC consider with multiple nodes, ENE, close or involved margins	N/A	NR	N/A
British Association of Dermatologists*† [26]	2008	Not considered treatment of choice, but may be good or fair option in selected situations based on histology, size and site	NR	N/A	N/A	NR	N/A

PNI = perineural invasion; SM+ = positive surgical margin; aRT = adjuvant radiotherapy; ENE = extraodal extension; LVSI = lymphovascular space invasion; NR = no recommendation made; N/A = not applicable.
* Update of guidelines in progress.
† 2009 update of original 2002 guideline.
‡ Micronodular, infiltrative, metatypical/basosquamous.

Table 3
Selected studies reporting outcomes for locally advanced squamous and basal cell carcinomas treated with definitive radiotherapy.

Study	Location	Inclusion	Staging	Number	Years	Dose/Fractionation	Technique	5 year LRC/LC	Notes
Kwan [29]	BC Cancer Agency, Vancouver, Canada	T2-4 BCC/SCC	AJCC 2nd	BCC- 61 SCC - 121	1994–1998	Variety; most common 35 Gy/5#; 40–45 Gy/10#; 50–55 Gy/15–20#; 60 Gy/25#; 60–70 Gy/30–35#	Orthovoltage, Electrons, Megavoltage	(4 year) BCC – 86%; SCC – 58%;	
Mendenhall [30]	University of Florida College of Medicine, Gainesville, USA	T2-4 BCC/SCC	UICC 1997	BCC - 42 SCC - 55 BSC - 3	1964–1983	NR	Orthovoltage, Cobalt, Electron, Megavoltage, Isotope	Previously untreated T2 – 93%; T3 – 83%; T4 – 54%; Recurrent T2 – 100%; T3 – 72%; T4 – 29%;	For T4 patients previously untreated 5 year control rates were BCC – 46% (N = 14) and SCC – 60% (n = 13)
Lee [32]	University of Florida College of Medicine, Gainesville, USA	T4 BCC/SCC	AJCC 3rd	BCC - 37 SCC/BSC - 31	1964–1989	60–75 Gy over 6–8 weeks most common	Orthovoltage, Cobalt, Electron, Megavoltage, Isotope	Previously untreated - 67%; Recurrent - 41%;	Lower control rates in recurrent setting; histology (BCC vs SCC) did not impact; Bone or nerve involvement reduced control rates
Locke [28]	Mallinckrodt Institute, St Louis, USA	All stages BCC/SCC	AJCC 5th	T3-4 cases* BCC - 34 SCC - 31	1966–1997	Range of doses	Superficial, Electron, Photons	BCC T3 – 84%; T4 – 87%; SCC T3 – 60%; T4 – 56%;	Higher daily fraction (4 Gy) improved LC in BCC 1–5 cm
van Hezewijk [34]	Leiden University Medical Center, Leiden, The Netherlands	T1-3 BCC/SCC	–	T3 cases* BCC - 6 SCC - 5	2001–2006	54 Gy/18# or 44 Gy/10#	Electron	BCC - 83%; SCC - 80%;	No difference between fractionations
Schulte [35]	Munster, Germany	T1-3 BCC/SCC	UICC 2002	T3 cases* BCC - 22 SCC - 14	1988–1992	Average dose BCC - 61 Gy; SCC 63.6 Gy (range 35->80 Gy)	Superficial	BCC - 11.4%; SCC - 25.9%;	1267 patients including all stages
PNI specific cases									
Lin [31]	Royal Brisbane and Women's Hospital, Brisbane, Queensland, Australia	Clinical PNI BCC/SCC	NR	BCC/SCC - 15†	1991–2004	Median 60 Gy (48–74Gy)	Photons, Electrons	Recurrence free survival – 59% (RT alone group)	No difference between RT alone and Surgery + aRT groups (59 v 45%; p = 0.46)
Balamucki [33]	University of Florida College of Medicine, Gainesville, USA	Clinical PNI cohort BCC/SCC	AJCC 1997	BCC/SCC - 36†	1965–2007	NR	Electrons, Photons (14% IMRT)	5 year LC 54% (RT: 42%; CRT: 62%);	RT alone - 36; CRT - 13; Similar outcomes for CRT/RT alone and Surgery + aRT groups (54% v 50%)

BCC = basal cell carcinoma; SCC = squamous cell carcinoma; BSC = basosquamous carcinoma; NR = not recorded; PNI = perineural invasion; aRT = adjuvant radiotherapy; IMRT = intensity-modulated radiotherapy.

* These studies include early-stage patients, however, only the selected LA-NMSC group are presented in this table.

† Subgroup of reported cohort treated definitively with radiotherapy or chemoradiotherapy.

chemotherapy would appear reasonable in selected cases. However, it is highly likely that future concurrent studies will focus on integrating immunotherapy into the treatment paradigm, given the 50% response rate seen in early clinical studies in the metastatic or locally recurrent setting [50].

Adjuvant radiotherapy (aRT)

There is a lack of consensus on the exact indications for aRT, hampered by a lack of high-level evidence. As a consequence, indications vary between national guidelines (Table 1). In general, however, aRT is usually recommended for patients with incomplete or close surgical margins, locally advanced disease (T3-4), lymph node involvement, extensive PNI or perineural tumor spread and immunosuppression.

SCC

Evidence and indications

The impact of aRT has not been assessed in randomised fashion, and justification rests with the identification of a number of adverse pathological features which are associated with recurrence. Such factors include larger diameter tumours (>2cm) [36], deep invasion [36,43], perineural [51] or lymphovascular space invasion [52,53], poor differentiation [36,54] and underlying immunosuppression [36,42]. Interpreting the literature can be challenging owing to pooled analyses of both BCC and SCC and inclusion of different treatment modalities (RT monotherapy, Mohs or surgery).

A systematic review by Jambusaria-Pahlajani et al. concluded that aRT was not beneficial where clear surgical margins were obtained (patients with positive margins were excluded from this study) [55]. In a subset of 74 patients with PNI, they drew the same conclusion. One notable finding in this study, however, was the higher incidence of

Table 4
Adjuvant radiation therapy studies reporting a survival benefit.

Author	Years	No.	Inclusion	Reported Five-Year Benefit (Surgery + aRT vs Surgery alone)	Notes
Harris [57]	2009–2016	349	Local or regional disease (37% regional disease)	OS (HR = 0.59, 95% CI, 0.38–0.90)	aRT also improved OS and DFS in patients with: (1) PNI: DFS HR = 0.47 (95% CI 0.23–0.93) OS HR = 0.44 (95% CI 0.24–0.86); and (2) Regional disease: DFS HR = 0.36 (95% CI 0.15–0.84) OS HR, = 0.30 (95% CI 0.15–0.61)
Veness [56]	1980–2000	167	Regional (parotid and/or cervical)	LRR 43% v 20% (*p* = NR) DFS 73 v 54% (*p* = 0.004)	
Wang [67]	1980–2008	122	Regional (cervical only)	LRR 23% v 55% (p = NR) DFS 74% v 34% (p = 0.001) OS 66% v 27% (p = 0.003)	
Hirshoren [68]	2003–2014	78	Parotid	RC 89% v 40% (*p* = NR) OS 50% v 22% (*p* = NR)	
Sapir [58]	2000–2013	102	Perineural involvement	*In patients with microscopic extensive PNI* RFS in nerves 94% vs. 25% (*p* = 0.01) DFS 73% vs. 40% (*p* = 0.05)	Entire cohort included patients with gross, microscopic extensive and microscopic focal PNI.

OS = Overall Survival; DFS = disease-free survival; LRR = locoregional recurrence; RC = regional control; PNI – perineural invasion; RFS = recurrence-free survival.

regional and distant relapse in the aRT cohort, suggesting a higher-risk population that was selected to receive aRT and thus an inherent selection bias underlying the selected studies. Only limited conclusions can be drawn from this review.

Other retrospective series have demonstrated an improvement in locoregional control and/or survival following aRT for either local or regional disease (Table 4) [56–61]. The data is conflicting, however, as other series show no benefit in either endpoint [62,63]. National guidelines on the use of aRT in the primary and nodal setting of NMSC are presented in Table 1.

The NCCN and Australian Cancer Council guidelines recommend the use of aRT in almost all cases of resected regional disease [19,23]. One exception is the low-risk group with a solitary node < 3 cm without extranodal extension. Ebrahimi et al. reported excellent rates of regional control with surgical monotherapy in this group [64]. This is not universally accepted as many older series included these patients and found benefits for aRT. The NCCN guidelines recommended either aRT or observation in this setting [19].

Adjuvant chemoradiotherapy

Although the NCCN recommend consideration of adding concurrent chemotherapy to aRT for selected high-risk cHNSCC patients, there is no evidence to support its benefit. Most but not all retrospective studies have failed to show a benefit from adding concurrent chemotherapy to aRT, although a high degree of selection bias in these studies is likely [16,65,66]. The Trans Tasman Radiation Oncology Group (TROG) performed a randomized study in high-risk resected cHNSCC (eligibility was based on primary tumor ≥ 5 cm or invading cartilage, skeletal muscle or bone; or presence of intransit-metastases or any intra-parotid node; or at least 2 cervical nodes or one ≥ 3 cm or with ENE) to either aRT or aRT with concomitant weekly carboplatin (AUC 2) [27]. The majority of cases (80%) had high-risk nodal disease. This study failed to show an improvement from the addition of carboplatin in freedom from locoregional failure, disease-free survival or overall survival. The rates of control in the aRT-alone arm were excellent and higher than generally expected at 88 and 83% at 2 and 5 years, compared to 89 and 87% for the concurrent arm, respectively. These outcomes compared favourably to retrospective series [16,56,59,60], with the caveat that patients enrolled were deemed fit to receive chemotherapy and were excluded if they had immunosuppression. There was no observed increase in acute radiation toxicity in the interventional arm, which does raise the question of whether carboplatin was an adequate radiosensitiser. Observed major protocol violations were low (11%) in the study, suggesting that high-quality aRT on its own provides excellent rates of locoregional control. It is unlikely that concurrent chemotherapy will be investigated further given the results of this study, as future efforts will likely focus on the integration of immunotherapy in the adjuvant setting.

Elective neck management in high-risk SCC

Existing guidelines do not generally discuss the role for elective management of the neck in high-risk cHNSCC. This should be considered in both the high-risk primary setting and also where there is metastatic involvement of the parotid gland. Although the vast majority of SCCs have a low metastatic potential, high-risk SCCs have a higher propensity for regional spread, based on factors such as primary tumor size (> 2 cm), depth of tumour invasion (≥ 6 mm) [38,69], poor differentiation [53,70] and the presence of lymphovascular and perineural invasion [53,58,70,71]. Recurrent tumours [53] and tumors occurring in the context of underlying immunosuppression [17] are also at increased risk. Clustering of high-risk features results in a striking increase in the risk of nodal relapse [71]. Carter et al. reported that in combination with PNI, the presence of two or three other risk factors (size > 2 cm, invasion beyond subcutaneous fat or moderate or poor tumour differentiation) resulted in a 4 and 14 fold increased risk of nodal metastases, respectively [71]. In the setting of cHNSCC with perineural disease, Sapir et al. reported an involved neck rate of 22.5% [58]. Where there is cHNSCC metastatic to parotid, the rate of subclinical disease by pathological assessment is as high as 44% [46,53,56,60,68,72–76].

Elective treatment of the neck may consist of either an elective neck dissection (END) or nodal irradiation (ENI). The decision will depend on a number of factors, including the location of the primary lesion, the morbidity of each treatment, and whether aRT can be avoided with further surgery.

In the largest and only series to date, Wray et al. reported on the efficacy of ENI in clinically node-negative patients treated with either definitive (25%) or aRT (75%) [77]. Half were staged T4 or had a primary lesion > 2 cm or a thickness > 5 mm and 76% had pathologically confirmed PNI. The estimated risk of nodal relapse in this cohort was >10%, based on historical comparisons. The actuarial rate of regional control at 4.5 years was 96% with no adverse grade 3 events. In their series, Sapir et al. reported no neck failures (0/35) in patients treated for gross PNI and ENI.

Although there have been no direct comparisons between END and ENI, both appear reasonable and will vary between institutions and clinicians. However, with such high rates of regional control following ENI in the setting of a clinically negative neck, an argument can be made for a non-surgical approach given the risk of potential complications, including shoulder dysfunction after END [78–80].

BCC

Similar to SCCs, there is little high-level research to guide the most appropriate use of aRT following excision of BCCs, and national guidelines vary or do not make any recommendations regarding the use of aRT (Table 1). Although BCCs only rarely metastasize [81], local recurrences can be troublesome, requiring progressively larger resections which may result in significant cosmetic and/or functional damage. Oncological clearance of at least 4–10 mm for high-risk BCCs has been recommended [21]. Incompletely excised lesions have a recurrence risk ≥30% [82], with the aggressive histological variants (micronodular, infiltrative, metatypical/basosquamous) at greater risk [83].

From the Princess Margaret Hospital, Liu et al. reported that immediate management of incompletely excised BCCs (99% with radiotherapy) resulted in a significantly lower rate of relapse at 5 years (91% v 61%, $p < 0.0001$) compared to those managed expectantly [84]. However, the ultimate local control at 10 years was the same (91 v 90%), due to high rates of successful surgical salvage.

Where clear margins are obtained, it is recommended that patients with large-calibre nerve infiltration (involvement of nerve ≥0.1 mm in diameter or nerve deep to dermis) undergo adjuvant radiation [20]. Patients with aggressive histological subtypes, including the micronodular, infiltrative, basosquamous and morpheaform types [83] or immunosuppression [85] are also at higher risk of recurrence, and aRT is often recommended. The incidence of nodal disease is exceedingly low in patients with primary typical BCC histology and elective nodal irradiation is not necessary. One exception to this is the more aggressive basosquamous subtype, where the metastatic potential is more in keeping with SCC than BCC [86].

Radiotherapy dose and volume considerations

Dose

No high-level data exist to inform the most appropriate dose or fractionation schedules for treating cHNSCC, and data are frequently extrapolated from the mucosal HNSCC setting. Recommended radical doses are presented in Table 5, but other fractionation schedules tailored to the specific institutional experience may be appropriate. Only small retrospective series have analysed dose response in NMSC. Kwan et al. from BC Cancer Agency investigated BCC and SCC and found no evidence of a dose response, despite including schedules ranging from 35 Gy in 5 fractions to 70 Gy in 35 fractions [29]. Locke et al. reported improved local control in BCCs measuring between 1.1 and 5 cm when a higher dose per fraction was used (compared to those treated at <2 Gy/fraction) [28]. A lower biologically effective dose was associated with poorer local control in a series combining SCC and BCC of the pinna [87]. In a parotid series by Chen et al., three of the four relapses occurred in patients treated with <60 Gy [88]. Although the data are not clear, recommended doses for cutaneous NMSC are similar to those used for SCC in the mucosal setting, and the NCCN recommendations are provided in Table 5 [19]. We agree in general with the doses, although in the adjuvant primary setting, for both BCC and SCC, our radical fractionation would typically be 60–66 Gy in 30–33 fractions in suitably fit patients.

Table 5
National comprehensive cancer guidelines recommended dose prescription for locally advanced non-melanomatous skin cancers [19,20].

Tumour and Setting	Recommended fractionation
Squamous cell carcinoma	
Definitive	
Primary ≥ 2 cm, T3-4, invasion of bone or soft tissue	60–70 Gy over 6–7 weeks; 45–55 Gy over 3–4 weeks
Clinically positive lymph node regions	60–70 Gy over 6–7 weeks
Clinically negative, at-risk lymph node regions	50 Gy over 5 weeks equivalent*
Clinically at-risk nerves	50–60 Gy over 5–6 weeks*
Adjuvant	
Primary	60–64 Gy over 6–7 weeks; 50 Gy over 4 weeks
After neck dissection, clear margins, no ENE	50–60 Gy over 5–6 weeks
After neck dissection, positive margin or ENE	60–66 Gy over 6–7 weeks
Basal Cell Carcinoma	
Definitive	
Primary ≥ 2 cm, T3-4, invasion of bone or soft tissue	60–70 Gy over 6–7 weeks; 45–55 Gy over 3–4 weeks
Adjuvant	
Primary	60–64 Gy over 6–7 weeks; 50 Gy over 4 weeks

ENE = extranodal extension.
* Simultaneous integrated boost techniques require consideration for increase in dose for overall treatment time (approximately 0.6 Gy/fraction).

Volumes

In the definitive setting, the gross disease, as determined by clinical and radiological means, should be covered with an adequate margin, usually 5 mm, to the clinical target volume (CTV) with a further 3–5 mm expansion to the planning target volume (PTV), depending on institutional practice. The areas at risk for microscopic involvement will depend on the clinical scenario. For example, for a case of gross disease involving the parotid, the entire parotid will be at risk of microscopic spread and should be included in the clinical target volume. Where there is high-risk pathologically identified PNI (large-calibre, extensive, involving a named nerve, or in a nerve involved at the surgical margin) the major nerve pathways at risk should be covered to the base of skull. Where there is clinical involvement of the nerve, this should be covered to the brainstem, as without pathological assessment it will be challenging to assess where PNI finishes.

In the adjuvant setting, volumes may be more challenging, as there are no consensus guidelines for postoperative contouring of cHNSCC. Any preoperative imaging, clinical photography and surgical description should be used to determine the regions at risk. The entire postoperative bed should be covered to a minimum dose of 60 Gy. The adjuvant dose should be increased to 66 Gy for positive margin status or the presence of ENE after resection of nodal disease. At-risk microscopic areas should be dosed according to location and risk.

Prophylactic nodal irradiation should be employed when the risk to the neck exceeds >15%. This includes the nodal basins draining high-risk primary tumors (based on location, size, depth of invasion, differentiation, recurrence) and the cervical neck following resection of cHNSCC metastatic to the parotid. In cases of BCC, nodal irradiation is only recommended to the draining regional basin in the rare setting of pathologically confirmed nodal disease.

Recent and emerging technologies

The last two decades have seen the rapid development and implementation of new and emerging radiotherapy technologies. Although there are no direct studies exploring the benefit in the cHNSCC cohort, intensity-modulated radiotherapy (IMRT) should be considered a standard of care for all patients with cancers located in the head and neck region, given the reductions in toxicity seen in the mucosal setting. Other emerging technologies include stereotactic radiotherapy (SRT), proton therapy and heavy particle therapy. The latter two will be discussed in more detail in a separate article in this special issue [99].

Recently there has been increasing interest in the use of SRT in the head and neck [89], and also in the setting of cHNSCC where reirradiation is being considered or for treatment of intracranial perineural disease. Although there are dosimetric advantages to using stereotactic treatment, either as a boost or as monotherapy where gross intracranial PNI exists [90], there are only few reports specifically in patients with cHNSCC [91–94]. Where reported, in-field control appears reasonable in the reirradiation setting, but out-of-field failure remains problematic [93,94]. For example, Tang et al. reported no infield failures in ten patients with recurrent gross PNI disease treated with SRS with recurrent disease [93]. Five of the eight nerve failures (one patient had 2 separate failures) occurred in previously uninvolved nerve segments. Two of the seven patients developed lung metastases. Progression-free and overall survival rates were 20% and 50% respectively. This is similar to the smaller series of Fowler et al. which reported a median survival of 24.2 months in five patients treated to areas of intracranial extension in either Meckels cave or the cavernous sinus. In this series all failures were outside the SRS-GTV field [94].

In summary, the application of stereotactic treatment may have utility in patients with macroscopic intracranial disease or in the setting of inoperable recurrence. Specialist expertise should be sought in these settings as evaluation of the combinatorial dose and fractionation schedules is important to avoid neurotoxicity.

Quality assurance

The quality of radiotherapy plans is critical to optimal outcomes in patients with head and neck cancer [95]. In the postoperative setting, it is likely that substantial heterogeneity exists between radiation oncologists' target volumes. Adequate postoperative contouring requires a complex synthesis of accurate preoperative information and cross-sectional imaging and a thorough understanding of the surgical techniques utilised, including the often-complex reconstructive procedures undertaken. There have been no trials to show the impact of RT-QA in the cHNSCC setting, although in the randomised TROG trial of aRT ± carboplatin, 11% of patients had a major protocol violation (6% in dose compliance; 5% in treatment verification violation) [27]. At a minimum, postoperative radiation therapy volumes should be subject to the same peer review process that is recommended for mucosal HNC in order to ensure patients receive optimal radiotherapy plans [96].

Conclusion

Although high-level data is lacking, radiotherapy plays an important role in the contemporary management of cutaneous NMSCs, either as (1) adjuvant therapy for high-risk resected lesions; (2) definitive treatment in surgically or medically inoperable patients, or in patients who refuse surgery; or (3) prophylactic treatment of areas at risk for microscopic spread along neural and lymphatic pathways.

Declaration of Competing Interest

None.

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