Review Article

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Treatment recommendations in patients diagnosed with high-risk cutaneous squamous cell carcinoma

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SUMMARY

Non-melanoma cutaneous cancers occur at an epidemic rate in Australia. With an ageing population, more Australians will develop these cancers and at an increasing rate. In the majority of cases local treatment is highly curative. However, a subset of the population will be diagnosed with a high-risk cutaneous squamous cell carcinoma. These can be defined as patients at risk of having subclinical metastases to regional lymph nodes based on unfavourable primary lesion features (including inadequately excised and recurrent lesions), patients with metastatic squamous cell carcinoma to regional lymph nodes, and squamous cell carcinoma in immunosuppressed patients. The mortality and morbidity associated with high-risk cutaneous squamous cell carcinoma is usually as a consequence of uncontrolled metastatic nodal disease and, to a lesser extent, distant metastases. Radiotherapy has an essential role in treating these patients and in many cases the addition of adjuvant radiotherapy may be life saving. It is therefore important that all clinicians treating skin cancers have an understanding and awareness of the optimal approach to these patients. The aim of this article is to present treatment recommendations based on an overview of the current published literature.

Key words: *immunosuppression; perineural invasion; radiotherapy; skin cancer.*

INTRODUCTION

As the Australian population ages, skin cancer will become an even greater public health issue. Australians experience the highest annual incidence of non-melanoma skin cancer (NMSC) in the world, occurring in approximately 1000/100 000 of the population[1] and rising.[2] As a consequence, NMSC is the most common malignancy in Australia. The majority of lesions (80–90%) arise on the sun-exposed head and neck in middle-aged to elderly patients, often male, with basal cell carcinoma (BCC) occurring more often than squamous cell carcinoma (SCC) in a ratio of approximately 4:1.[3]

Most patients with NMSC are cured, although a small number of patients will die as a direct result of an aggressive NMSC, most often SCC, and usually in the setting of uncontrolled nodal metastases.[4] The role of radiotherapy in treating early skin cancers (BCC, SCC) is well established as a treatment option when patient and tumour factors favour a better outcome (cosmesis, function), especially when compared to surgery.[5] However, in the setting of high-risk cutaneous SCC the correct management decision, in particular the addition of adjuvant radiotherapy, may be life saving.

Patients with high-risk cutaneous SCC can be defined as those at risk of having subclinical metastases to regional lymph nodes based on unfavourable primary lesion features (including inadequately excised and recurrent lesions), patients with metastatic SCC to regional lymph nodes, and SCC in immunosuppressed patients (usually solid organ transplant patients).

The aim of this article is to discuss the treatment of patients with high-risk cutaneous SCC and, where applicable, also present the current role of radiotherapy in the management of these patients. Of note, the evidence base to support many recommendations is often weak and limited to single institution case series. There are no data from randomised controlled trials. It is not the aim of this article to present the technical aspects of delivering radiotherapy, although often a recommendation on a radiotherapy dose is relevant and therefore

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discussed. This article, therefore, is not meant to be prescriptive in nature, but a guide to clinicians, including radiation oncologists, who may treat patients with high-risk cutaneous SCC.

ELECTIVE TREATMENT OF LYMPH NODES

All patients treated with invasive cutaneous SCC are at risk of experiencing a fatal outcome, usually as a result of developing metastatic spread to regional lymph nodes. In the general population, only a minority (<5%)[6,7] of patients with cutaneous SCC will develop metastatic spread to lymph nodes, although in selected populations, such as hospital-referred patients with unfavourable tumour characteristics, the incidence may be greater than 10–15%.[8,9] When metastases occur, most cases will involve spread to the lymph nodes of the head and neck (Fig. 1), although truncal/extremity SCC with spread to the groin/axilla are also reported (Figs 2,3).[10,11] Survival following the development of metastatic nodal disease is markedly decreased compared to patients that remain node negative. Patients with metastatic lymph nodes are still curable but remain at risk of regional relapse, which is usually incurable and increases the risk of developing distant metastases (bone, lung), despite treatment.

There are limited data to guide clinicians in accurately predicting those at risk of having subclinical nodal metastases, although there are published risk factors[12,13] that include primary lesion factors such as size, site, depth of invasion, tumour thickness, grade and the presence of perineural invasion. Patients with recurrent lesions and those that are immunosuppressed are also at risk. No one single variable can be considered as a strong enough independent predictor on which to base a recommendation. As with many clinical scenarios, it is usually a combination of risk factors, in conjunction with patient factors and preferences, that clinicians use in decision-making. As such, it is imperative that pathologists report important histological factors such as size, grade, thickness, extent of excision margins and the presence or absence of perineural invasion, so as to aid clinicians in decision-making.

Studies suggest increasing depth of invasion and tumour thickness as important predictors of subclinical nodal spread (Fig. 4). Using depth of invasion as a predictor, some report a threshold depth of >4–5 mm beyond which risk significantly

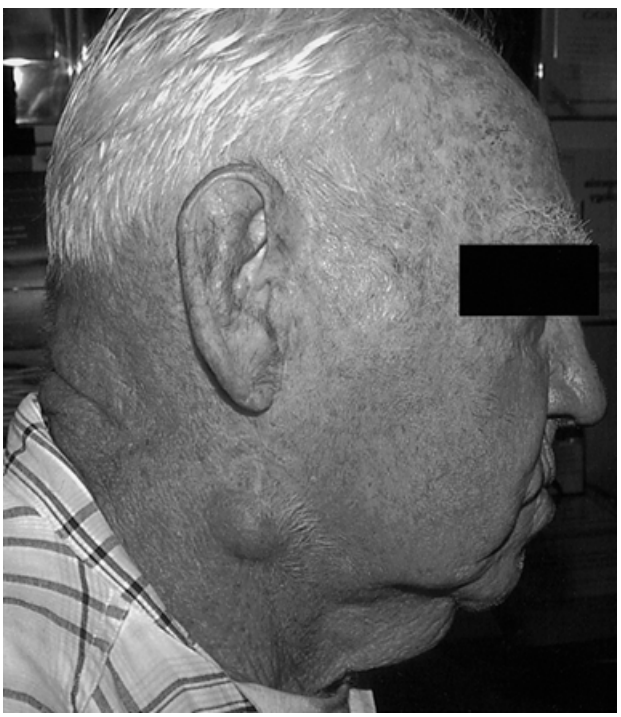

Fig. 1. A 75-year-old man with metastatic cutaneous squamous cell carcinoma to lymph nodes in his right mid neck. An obvious index lesion was not identified although the patient had a long past history of multiple cutaneous cancers treated in the head and neck.

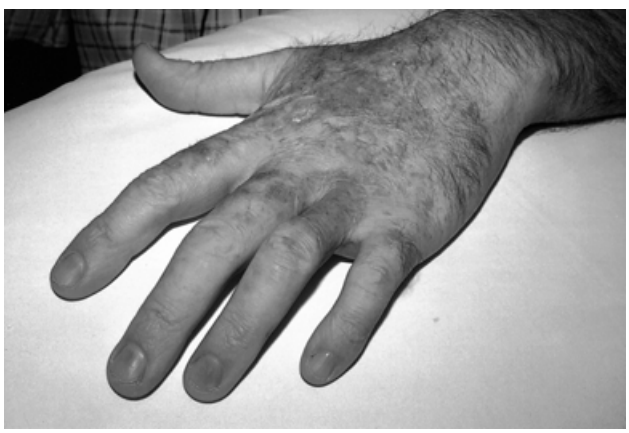

Fig. 2. A 35-year-old man with a previously excised poorly differentiated cutaneous squamous cell carcinoma from the dorsum of his left hand.

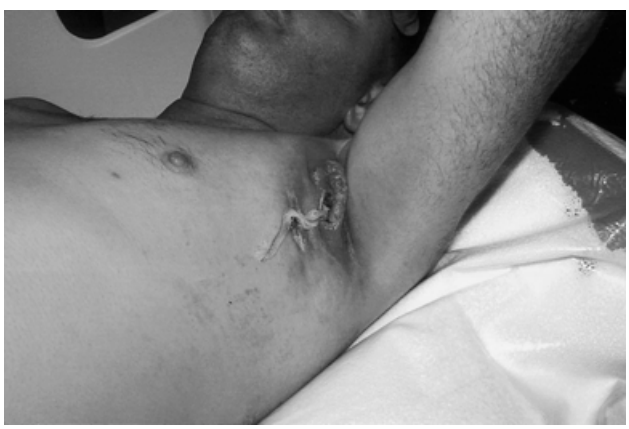

Fig. 3. Extensive left axillary nodal metastases from a previously treated cutaneous squamous cell carcinoma (see Fig. 2) causing fungation. The patient was treated with initial radiotherapy followed by surgery. He died from widespread recurrent disease.

increases.[14–17] Rodolico *et al*. reported a significant difference in mean depth of invasion in patients with lower lip SCC that were node negative compared with those developing nodal metastases (4.2 vs 11.2 mm; $P < 0.001$).[16] In another study of patients with metastatic cutaneous SCC of the head and neck, only 17% with a lesion <4 mm metastasized compared with 83% with lesions >4 mm.[15] Similarly, lesions <3–4 mm thick have a low incidence of nodal spread.[18–20] Clark levels have also been analysed, with one study identifying patients with tumours beyond Clark level III significantly more likely to develop nodal metastases.[8] Similar to a threshold depth of invasion/tumour thickness, lesions beyond a threshold size of 2 cm have a greater propensity to metastasize to nodes.[8,15,16,20,21] Cherpelis *et al*. reported a significant difference in the rate of nodal metastases from various primary sites of the head and neck using a 2 cm threshold in size (13 vs 68%; $P = 0.004$).[8] Kraus *et al*. also reported a difference of 19 versus 81%, using a 2-cm cut-off in size, for the development of nodal metastases.[15] Recurrent SCC are also reported to be associated with a higher incidence of nodal metastases compared to the initial presentation with spread in 25–45% of cases, depending on the site of the recurrence (Fig. 5).[8,14,21] In one study of metastatic cutaneous SCC to head and neck nodes, 51% of patients had a recurrent primary lesion prior to developing nodal metastases.[22] There is evidence that particular sites, such as the ear and lip (Fig. 6), may be associated with a higher incidence of metastases.[9,21,23] Poorly differentiated lesions are also more likely to be associated with the development of regional metastases.[24,25] In a study of 571 patients with cutaneous SCC, there was a significant difference in the rate of metastases for high-grade lesions compared to others (17 vs 4%; $P = 0.004$).[24] Similarly, there are also data which indicate that desmoplastic SCC, although rarely reported, is an aggressive histological variant of SCC that possesses a high propensity to develop regional metastases, especially with increasing tumour thickness.[25,26] Breuninger *et al*. recommend prophylactic nodal dissection in desmoplastic SCC >5 mm in thickness.[26] The prognostic implications of lymph vessel or vascular invasion are unclear, although there are data that these features may be associated with an increased risk of nodal metastases;[17,27] however, this finding is usually reported in conjunction with other unfavourable features.

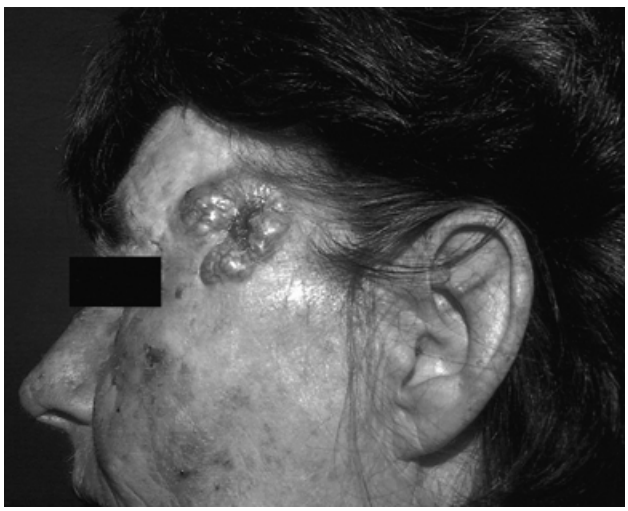

Fig. 4. A 47-year-old woman with a neglected 3-cm poorly differentiated squamous cell carcinoma on her left temple. This lesion was excised and reported as 10 mm in thickness and incompletely excised at the deep margin. The patient subsequently received loco-regional adjuvant radiotherapy (50 Gy in 20 fractions using 9 MeV electrons and bolus) to the excision site and preauricular lymph nodes.

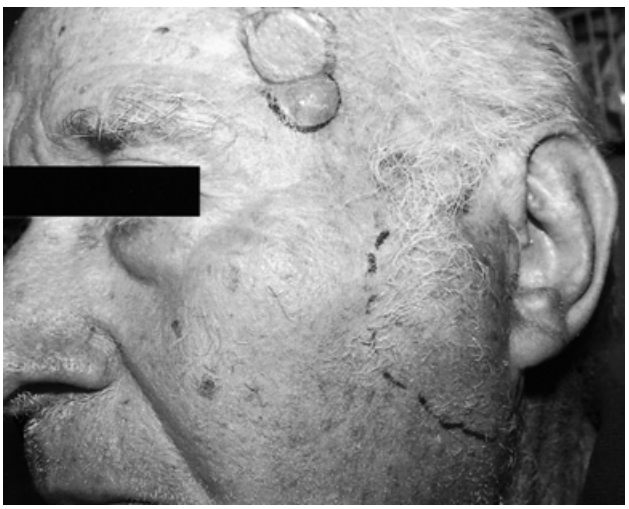

Fig. 5. A 65-year-old man with a recurrent left temple squamous cell carcinoma on the periphery of a recent skin graft with concomitant bulky nodal metastases to the left parotid region.

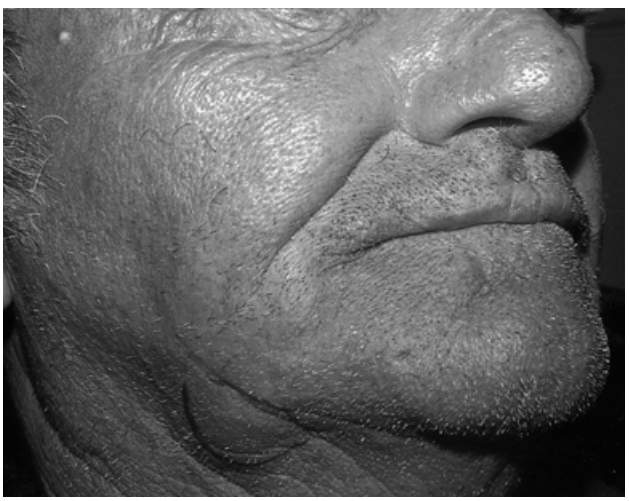

Fig. 6. A 54-year-old male with nodal metastases to his right upper neck (as marked) from a previously excised right lower lip squamous cell carcinoma.

The presence of perineural invasion, or immunosuppression, are relatively uncommon scenarios. However, there are data that patients identified with perineural invasion have a higher incidence of nodal metastases compared to patients without perineural invasion.[8,19] In a large study from the MD Anderson Cancer Center, Texas, there was a significant increase in both regional (35 vs 15%; $P < 0.0005$) and distant metastases (15 vs 3.3%; $P < 0.0005$) for patients diagnosed with perineural invasion compared to those without this finding.[28] Perineural invasion may also portend to significant morbidity and mortality in its own right.[28] Similarly, immunosupressed patients are also at a higher risk of developing recurrent and metastatic SCC.[29]

There are advocates of elective nodal dissection in selected high-risk patients with lesions located on the ear/preauricualr region[9,22,30,31] and lip.[32] Yoon *et al*. reported 38 patients with external ear SCC treated predominantly with surgery. The authors reported a 53% recurrence rate with almost half metastasizing to regional lymph nodes, and recommended prophylactic parotidectomy and neck dissection and/or radiotherapy in patients with poor prognostic features such as cartilage invasion, deep invasion or poor differentiation.[30] Vartanian *et al*. suggest patients with T3/T4 lip SCC are at >20% risk of having occult spread to upper cervical lymph nodes and should undergo an elective supraomohyoid neck dissection.[32] The alternative of elective radiotherapy to nodes at risk (50 Gy) is an option with similar control rates expected to that of surgery if a decision is made to treat nodes electively. Whether surgery or radiotherapy is recommended needs to be individualized, and balanced against the advantages and disadvantages of both treatments.

Some would argue close observation and expectant treatment as an appropriate option in high-risk patients. However, there are analogous data from patients with high-risk mucosal head and neck SCC suggesting that even with close follow up most patients experiencing nodal relapse usually present with advanced (often incurable) nodal disease.[33,34] There are currently no randomised data to support a survival benefit from the elective treatment of cutaneous high-risk lymph nodes. However, using this as an argument against treatment in selected high-risk patients fails to consider the available evidence and especially the associated morbidity of treating patients with nodal relapse.

Identifying patients with subclinical spread to lymph nodes may allow appropriate regional treatment and prevent nodal relapse. Imaging techniques, such as CT/MRI scans, usually add very little to the clinical examination of a node-negative region. However, the concept of sentinel lymph node biopsy (SNB) has evolved in other malignancies, such as melanoma and breast cancer, to identify patients with spread to first echelon lymph nodes. There are emerging data that SNB may also have a role in similarly identifying high-risk patients with cutaneous SCC that have spread to regional lymph nodes.[35–37] Wagner *et al*. reported on 24 patients with high-risk NMSC ($n = 17$ with SCC) undergoing SNB. Seven (29%) had a positive sentinel node with only one false positive. The negative predictive value was 0.94.[36] In another series of 9 patients with high-risk cutaneous SCC, 4/9 (44%) were positive on SNB with, subsequently, two dying of metastatic disease. The five with a negative SNB remained disease free although the median follow up of 8 months is short.[35] The role of SNB in cutaneous SCC is evolving and complicated by patient (age, comorbidity), lesion (location, size, invasiveness, grade) and treatment (incorporation of radiotherapy) factors. Identifying which patients would benefit from SNB in view of the extra surgery and cost is unclear. Currently, SNB is an option in select patients treated by experienced operators but, in general, should not be considered standard and requires further validation.

Recommendation

The majority of patients with cutaneous SCC will not develop nodal metastatases. Therefore, the elective treatment of lymph nodes in all patients is inappropriate. Patients with adequately excised (discussed further on) and previously untreated lesions are usually not candidates for further treatment. Accurately predicting patients at high risk and therefore justifying the elective treatment of first echelon lymph nodes is difficult. However, patients with more than one high-risk factor (deeply invasive >4–5 mm, >2 cm in diameter), especially in the recurrent setting, should be considered at risk of developing nodal metastases. In such cases, elective treatment to first echelon nodes may be of benefit. At a minimum, patients should be followed closely (2–3 months) for at least 2–3 years. If radiotherapy is used to treat a primary high-risk lesion (definitive or adjuvant), consideration should be given to encompassing first echelon nodes in the treatment field.

METASTATIC SCC TO LYMPH NODES

Patients with biopsy-proven metastatic cutaneous SCC should be considered at the highest risk of a poor outcome. Patients are typically older Caucasian males, and the majority of metastases will be to head and neck lymph nodes and can be broadly separated into parotid and cervical (levels I–V) lymph nodes (Figs 7,8). It is rare for patients to present concomitantly with both nodal and distant metastases. Both the parotid and cervical lymph nodes (levels I–V) represent the first echelon of lymphatic drainage from primary cutaneous sites on the scalp, forehead, face, lip, ear and neck.

The most frequent parotid malignancy in Australia is metastatic cutaneous SCC. Although patients invariably have a past history of skin cancers, in approximately 20% an obvious index lesion cannot be identified.[23,38,39] Chu and Osguthorpe documented 22/28 (79%) high-risk NMSC (majority SCC)

developing regional metastases in a median time of 9 months following treatment of the primary lesion.[40] Despite a median time to develop metastatic nodal disease following treatment of a primary SCC of approximately 12 months, there are at least two studies suggesting that late relapse beyond 2–3 years is not uncommon.[41,42] Despite treatment, 20–25% of patients will develop loco-regional (usually infield) recurrence or, less often, distant metastases.[38,39,43–45] There is evidence that patients treated with a combined approach, incorporating surgery and adjuvant radiotherapy, achieve a marked improvement in loco-regional control and outcome.[43–52] In a study of 74 Australian patients with metastatic SCC to cervical nodes (non-parotid), those undergoing surgery and adjuvant radiotherapy had a lower recurrence rate (15 vs 77%) and significantly better 5-year disease-free survival compared to those treated with surgery alone (75 vs 18%; $P = 0.001$).[52] Jol *et al*. also reported improved regional control in patients undergoing surgery and adjuvant radiotherapy compared with surgery alone (83 vs 56%).[45] Bron *et al*. reported adjuvant radiotherapy as the only factor that significantly improved local control in patients with metastatic SCC to the parotid, and consequently recommended adjuvant radiotherapy as standard practice.[51]

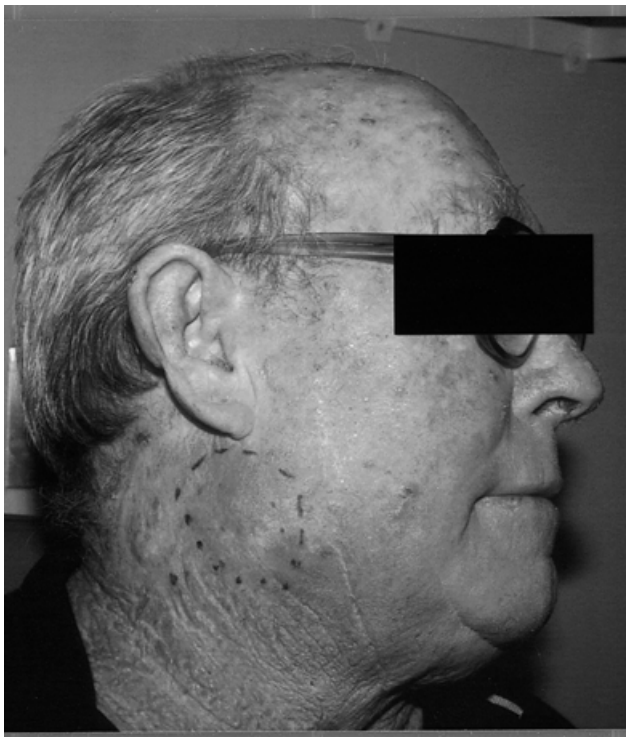

Fig. 7. Metastatic cutaneous squamous cell carcinoma (SCC) to the tail of the right parotid following previous excision of a right cheek SCC.

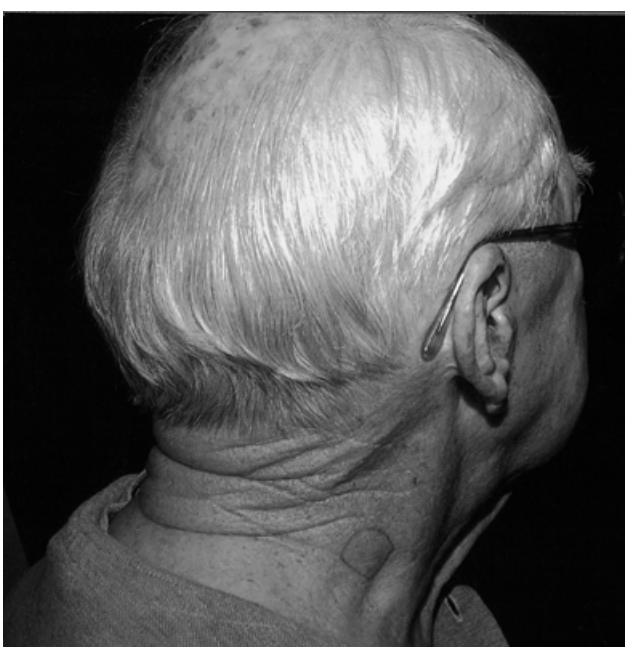

Fig. 8. Metastatic cutaneous squamous cell carcinoma (SCC) to a lymph node in the right posterior triangle in an elderly man following previous treatment for a post-auricular groove SCC.

There are limited data to suggest a better outcome in patients treated with metastatic SCC to cervical nodes only (level I–V) compared to those with metastatic parotid nodes.[52] A reason for this may be the high rate of close or positive margins following a facial nerve sparing parotidectomy and the difficulty in obtaining oncological excision margins. At least one study reported most parotidectomy specimens (70%) to have close/positive surgical margins.[39] Khurana *et al*. reported that positive surgical margins were significantly associated with poor loco-regional control ($P = 0.02$),[53] as did Chua *et al*. ($P = 0.02$).[39] The presence of multiple involved lymph nodes and extracapsular spread are frequently reported and associated with a worse outcome.[39,42] Similarly, the extent of metastatic parotid disease influences the likelihood of achieving loco-regional control and cure.[50] There is no evidence that more aggressive surgery in the form of a total parotidectomy, as opposed to a facial nerve-sparing superficial parotidectomy, when followed by adjuvant radiotherapy will improve loco-regional control. The facial nerve should only be sacrificed if the patient has malignant facial nerve palsy (Fig. 9) or is identified to be grossly involved by tumour at the time of operation. An attempt is usually made at facial re-animation using either nerve grafts or static slings since hemi-facial paresis may significantly impact on a patient's quality of life.

The treatment of the clinically negative neck in patients with metastatic parotid SCC is unresolved. Jackson and Ballantyne reported 24% of clinically negative patients treated with elective neck dissection as having occult metastases.[54] O'Brien *et al*. reported a 35% incidence of occult spread in 37 clinically negative necks treated at the Royal Prince Alfred Hospital, Australia.[55] However, Dona *et al*. reported a lower incidence (16%) of occult neck metastases in the Westmead Hospital, Australia, series.[43] Taylor *et al*. advocate radiotherapy alone to treat a clinically negative neck.[48] Others, however, propose

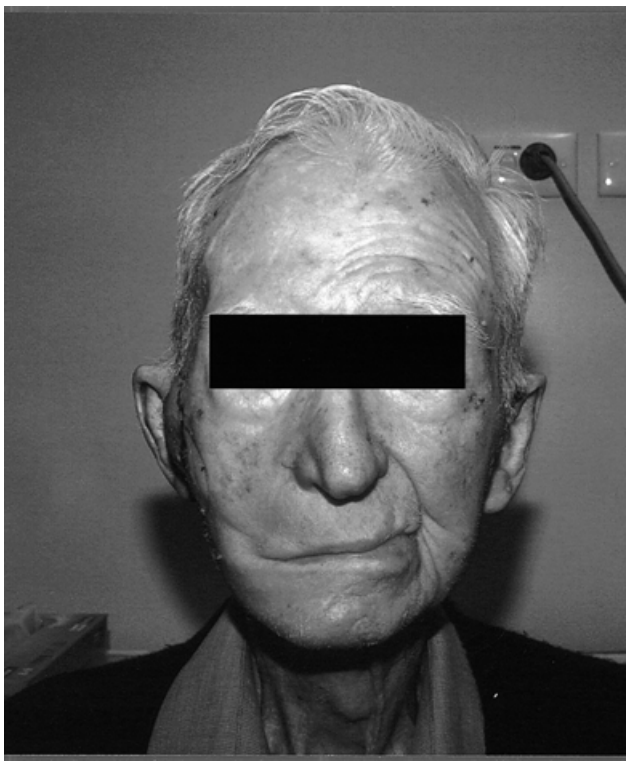

Fig. 9. An elderly man with right facial nerve palsy secondary to extensive nodal metastases to the right parotid gland. The patient underwent a total parotidectomy with static hemi-facial re-animation followed by adjuvant radiotherapy (66 Gy to the parotid using a wedge pair and 50 Gy to the ipsilateral hemi-neck).

neck dissection to determine pathological involvement, or not, of cervical nodes.[53,55] In the setting of metastatic parotid SCC, patients with a clinically negative neck should undergo a selective upper neck (levels II/III) dissection in conjunction with a parotidectomy. A finding of negative upper cervical lymph nodes may negate the need for adjuvant radiotherapy to the lower neck. However, patients with clinical involvement of cervical nodes should have a comprehensive neck dissection. Adjuvant radiotherapy is nearly always recommended to the entire ipsilateral neck if disease is identified in multiple nodes or extracapsular spread is present. An undissected neck should be irradiated in the presence of parotid nodal disease, even if clinically negative, as the risk of subclinical disease is high. The risk of contralateral subclinical nodal metastases is exceptionally low and does not justify treatment to the contralateral neck.[39,43,52] There can be few cases where adjuvant radiotherapy should not be strongly recommended following surgery.

There are limited dose-response data to guide clinicians in the adjuvant setting. The poor loco-regional control rate would suggest an inability to eradicate residual microscopic disease in many patients. Despite this, a dose of approximately 60 Gy has been delivered in many series and is an appropriate dose in the adjuvant setting with an acceptable side-effect profile. At least one author suggests 70 Gy as the recommended adjuvant dose although he presents no strong data to support this recommendation.[56] Hyperfractionation, as practised by the University of Florida since 1978 for various head and neck cancers (including cutaneous SCC), has the ability to deliver a higher biological dose (70–75 Gy) using twice-daily fractions of 1.2 Gy.[57] Whether dose escalation using standard dose (2 Gy) fractionation or, alternatively, hyperfractionation will improve loco-regional control rates is unclear.

Chemotherapy has been investigated as a form of adjuvant therapy. There are emerging data in postoperative mucosal head and neck SCC patients that a combination of concurrent platinum-based chemotherapy and adjuvant radiotherapy may improve loco-regional control and disease-free survival in high-risk patients (extranodal spread, multiple nodes).[58] In respect to cutaneous SCC, there are data from a Peter MacCallum Cancer Institute, Australia, pilot study using weekly concomitant platinum chemotherapy and radiotherapy to suggest a possible role for combined treatment to improve loco-regional control.[59] Randomised data are needed to confirm any hypothesis. Eligible patients for any trial comparing adjuvant radiotherapy versus adjuvant chemoradiotherapy in high-risk cutaneous SCC would be similar to those in the mucosal setting, that is, patients with one or more unfavourable features, such as multiple involved nodes, extranodal spread or incomplete excision. The presence of perineural invasion should also warrant inclusion into this unfavourable group. Some authors also suggest that neoadjuvant cisplatin-based chemotherapy may have a role in downstaging advanced cutaneous SCC prior to surgery or radiotherapy.[60,61] However, the addition of neoadjuvant chemotherapy should be considered investigational. In most cases of inoperable disease (skull base involvement), the patient is usually not a candidate for any radical intent treatment (Fig. 10). The presence of dermal involvement or facial nerve palsy is not always a contraindication to radical surgery but does portend to a poor outcome.

Recommendation

Patients with metastases to parotid lymph nodes should undergo a parotidectomy and neck dissection. The extent of both the parotidectomy and neck dissection depends on the extent of clinical disease. Essentially, all patients should also be recommended adjuvant radiotherapy (60 Gy) to the parotid bed, and in many cases, to the lower neck. Similarly, patients with operable metastases to cervical lymph nodes should undergo a comprehensive neck dissection followed by adjuvant radiotherapy. Single modality treatment alone, either surgery or radiotherapy, is associated with a worse outcome. Close follow up for at least 3–4 years is imperative if early loco-regional recurrence is to be potentially salvaged. The benefits from the addition of chemotherapy, altered fractionation or routine radical parotidectomy are currently unproven and not recommended.

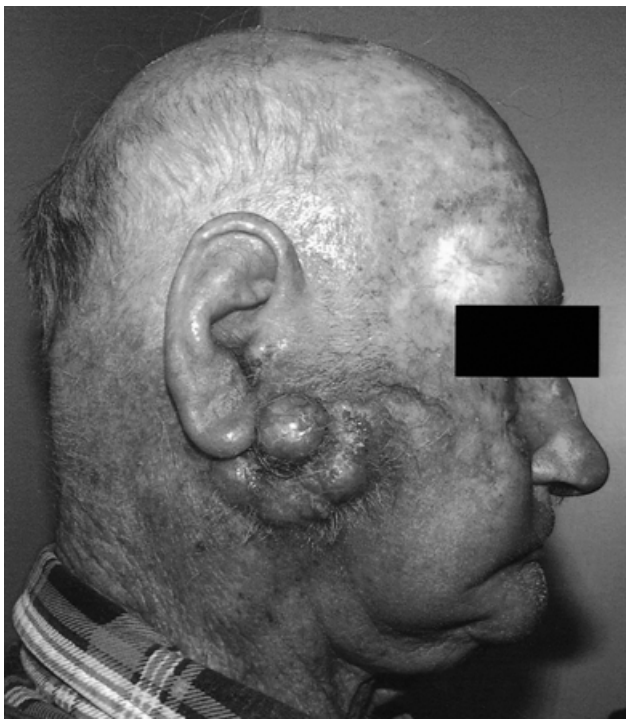

Fig. 10. A 73-year-old man with very advanced metastatic nodal disease to his right parotid. The patient had dermal involvement and facial nerve palsy. He had significant medical comorbidity and consequently underwent high-dose palliative radiotherapy (55 Gy in 20 fractions using 12 MeV electrons and bolus).

INCOMPLETELY EXCISED SCC

It is imperative that any pathology report document and quantify margin status. The comment that 'excision margins are clear' is meaningless. A patient with an incompletely excised (positive or close margin) SCC remains at risk of local recurrence. Patients with local recurrence are subsequently at risk of developing regional metastases. However, there is no consensus in regards to the definition of an acceptable surgical margin. Published recommendations, in the setting of lip and other cutaneous SCC, range from 3–10 mm.[62–65] In a surgical series of 72 patients using intraoperative frozen section analysis to achieve a minimum of a 3-mm surgical margin, only 3% recurred with a median follow up of 5.1 years.[62] In one study on lip SCC, local recurrence was significantly more likely with close (≤2 mm) or positive margins ($P = 0.05$).[64] Another study of patients with cutaneous SCC <2 cm in diameter found that with a 4-mm excision margin 95% had negative excision margins. With lesions >2 cm, a 6-mm margin would achieve a 95% rate of negative excision margins.[65] There was also a significant association between tumour invasiveness and increasing grade and high-risk sites such as the scalp, ears, nose, eyelids and lips. The authors subsequently recommended 6-mm margins with high-grade tumours or those located in high-risk areas.[65] In concordance with these findings, Thomas *et al*. reported that in cutaneous SCC a 4-mm surgical margin would obtain clearance in 97% of cases and that a 2-mm margin would do so only in 78% of cases.[66] The significance of recurrence has previously been documented. Zitsch *et al*. reported a worse survival in patients with involved margins compared to patients with clear margins ($P < 0.024$).[67] Rowe *et al*. documented a 32% incidence of nodal metastases in the setting of recurrent lip cancer.[21] Adjuvant radiotherapy is an effective option when excision is incomplete and re-excision is not considered possible.[68] In the setting of lip SCC, several studies have suggested improved local control with the addition of adjuvant radiotherapy.[64,69,70] Babington *et al*. documented a 37% local recurrence rate in surgery-only patients (27% close/positive margins) versus a 6% local recurrence rate in patients treated with surgery and adjuvant radiotherapy (94% close/positive margins). In this particular study, the most commonly prescribed dose was 51 Gy in 17 once-daily 3 Gy fractions.[64] This fractionation schedule is equivalent to approximately 55 Gy using 2 Gy fractions in regard to tumour response. Despite limited data on an optimal adjuvant radiotherapy dose in the setting of incomplete excision margins, a minimum dose of 55–60 Gy (or equivalent) is recommended. In another study, patients with locally recurrent lip SCC experienced a significant difference in nodal metastases compared with those not developing local recurrence (15 vs 2%; $P < 0.0001$).[70]

Recommendation

Ideally, 4–5 mm excision margins are desirable. Margins <2 mm should be considered inadequate and warrant further treatment. It is not recommended to wait and watch 'expectantly' as a minority of patients will recur and increase a patient's risk of developing nodal metastases. If function is not compromised, re-excision should be considered. If re-excision is not appropriate, a course of adjuvant radiotherapy (55–60 Gy) is likely to provide excellent local control without compromising function. All patients should be followed up regularly for at least 4–5 years to monitor for recurrence.

PERINEURAL INVASION

Perineural invasion from skin cancer is a form of metastatic spread and a manifestation of cancer aggressiveness. Although uncommon, it represents a serious consequence of cutaneous SCC.[71] Approximately 5–10% of excised skin cancers are reported to show pathological confirmation of perineural invasion.[72,73] Of these, only a minority (30–40%) will actually present with, or develop, neurological signs or symptoms. Formication (sensation of ants crawling) may herald the diagnosis of perineural invasion. However, dysaesthesia, paraesthesia, numbness and pain are all suggestive symptoms. Diagnosis is often delayed, as perineural invasion is

usually not suspected. Treatment following diagnosis is controversial, with consensus lacking. Prognosis once established signs or symptoms develop is poor with long-term survival reported at approximately 20–30%.[74,75] It is also reported, although less frequently, in BCC; however, the less aggressive nature of BCC and the limited data make recommendations difficult.[76] Nevertheless, if perineural invasion is identified in a periorbital BCC, further treatment may be warranted similar to SCC.

The finding of incidental perineural invasion following excision of a periorbital SCC, especially in the supraorbital area, warrants the consideration of further treatment to prevent orbital spread, which is often fatal (Fig. 11).[77–80] The phenomenon of skip lesions along a nerve has been reported. Spread is usually antegrade (centripetal) towards the central nervous system, but may become retrograde (centrifugal) once spread reaches a junction point (e.g. trigeminal ganglion). The retrograde spread of SCC along the first division of the trigeminal nerve towards the orbital apex portends a grave prognosis. The second division of this nerve and the facial nerve are also potential conduits for spread back to the central nervous system.

In some circumstances surgery, often extensive, is undertaken to explore and dissect out potentially involved nerves. However, disease spread beyond the orbital apex and/or involving the skull base/cavernous sinus is essentially incurable. Radiotherapy, often requiring multifield megavoltage photons, treating back to the brainstem, may be recommended with doses of approximately 50–60 Gy.[74,80,81] Radiotherapy has the advantage of avoiding surgery but with a small risk of serious late radiation damage to orbital contents, visual pathways and central nervous system structures. Data from the University of Florida suggest late complications may occur in over 30% of patients if doses of approximately 70 Gy are delivered.[71] Hyperfractionation (74 Gy in 1.2 Gy twice-daily fractions) has also been used by the University of Florida group to decrease the risk of late effects and improve outcome.[74] Any recommendations need to be considered carefully by both the patient and the clinician weighing up the potential risks and benefits of such treatment. There are limited data to suggest a benefit to the addition of adjuvant radiotherapy.[71,73–75] There is also evidence that the elective treatment of regional nodes may be of benefit,[71] especially in view of the increased risk of regional spread associated with perineural invasion.[28] Therefore, in patients considered at high risk, adjuvant radiotherapy may be life saving.

The natural history of patients with advanced perineural invasion may extend over many years. Magnetic resonance imaging is considered the imaging modality of choice because of its multiplanar capabilities and better soft tissue definition. Computed tomography scanning complements MRI by better defining skull base foraminal destruction and enlargement. Nemzek *et al.* reported a sensitivity of 95% for the MRI detection of perineural invasion but 63% sensitivity for mapping the entire extent of perineural invasion.[82] Typical radiological findings include nerve enlargement/enhancement (Fig. 12), foraminal enlargement/destruction, obliteration of fat planes and convexity of the lateral cavernous sinus wall. Clinicians should be aware that despite a high index of clinical suspicion, patients still might have normal imaging in the early phase of disease progression. Jungehuelsing *et al.* reported on eight patients with malignant unilateral facial paralysis, with all having initial MRI scans that failed to detect an abnormality.[83] In certain circumstances, open biopsy may be required to confirm a diagnosis.

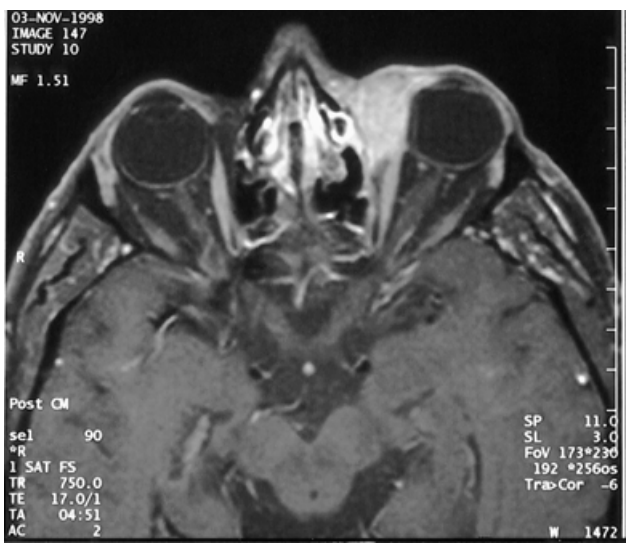

Fig. 11. Magnetic resonance imaging scan showing an extensive deposit of metastatic cutaneous squamous cell carcinoma (SCC) displacing the left globe. This occurred secondary to perineural invasion from a previously treated forehead SCC. The patient underwent orbital exenteration and adjuvant radiotherapy.

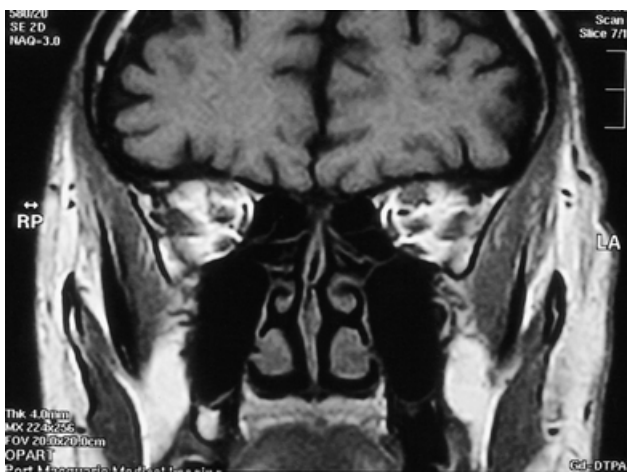

Fig. 12. Magnetic resonance imaging scan highlighting thickening of the left supraorbital nerve secondary to perineural invasion.

Recommendation

Patients with established palsies and/or involvement of the cavernous sinus or skull base are incurable. However, radiotherapy may palliate debilitating neuropathic-type symptoms. Following the reporting of perineural invasion of a cranial nerve, or branch of a cranial nerve, patients should be considered candidates for wide-field radiotherapy to encompass the potential neural pathway which often extends back to the brainstem.

IMMUNOSUPPRESSION

Immunosuppression, particularly in the setting of solid organ transplantation (renal, cardiothoracic), often leads to significant ongoing morbidity from skin cancer.[84,85] There is also evidence that patients infected with the human immunodeficiency virus (HIV) can develop aggressive cutaneous SCC characterized by rapid growth and a high rate of loco-regional relapse similar to transplant patients.[86] Patients with chronic haematological malignancies may also develop aggressive cutaneous SCC. An Australasian study of 6596 renal transplant patients reported a 27% probability of developing a non-cutaneous malignancy and a 66% probability of developing a cutaneous malignancy by 24 years post-transplant.[87] In the normal population, the ratio of BCC to SCC is approximately 4–5:1. This ratio is reversed in the transplant population, with studies reporting ratios of SCC : BCC from 1.2:1 up to 15:1.[87–90] Patients therefore require regular review and treatment for new and recurrent skin cancers. A subset of SCC in immunosuppressed patients is aggressive in nature, resulting in rapid growth and the development of regional and distant metastatic disease. In an Australian study of 619 cardiothoracic transplant recipients, 26 developed an aggressive skin cancer with most being diagnosed with poorly differentiated SCC. Death occurred in 13/26 with 10 patients dying from systemic disease. All of the 18/26 patients diagnosed with non-melanomas received radiotherapy, either as part of initial treatment or on relapse; eight subsequently suffered an infield relapse.[91] Martinez *et al*. documented a cumulative relapse rate of 29% at 1 year after treatment for metastatic cutaneous SCC, although patients treated aggressively with an approach that involved surgery did better.[92] In-transit metastases, although not commonly reported in cutaneous SCC, are documented to occur in both immunosuppressed and immunocompetent patients. In 15 organ transplant patients treated for in-transit metastases, most either died or subsequently developed regional or distant metastases (Fig. 13). In contrast, non-transplant patients had a markedly better outcome. Subsequently, the authors strongly recommended wide-field radiotherapy as an important component of any treatment recommendation.[93]

It is imperative that lesions are treated early and patients are followed closely. Patients who are immunosuppressed represent a difficult problem and should be treated by clinicians and teams experienced in their care. In many cases the level of immunosuppression cannot be markedly reduced. Recently published guidelines representing the best available evidence may aid clinicians treating an immunosuppressed patient with a cutaneous SCC.[94]

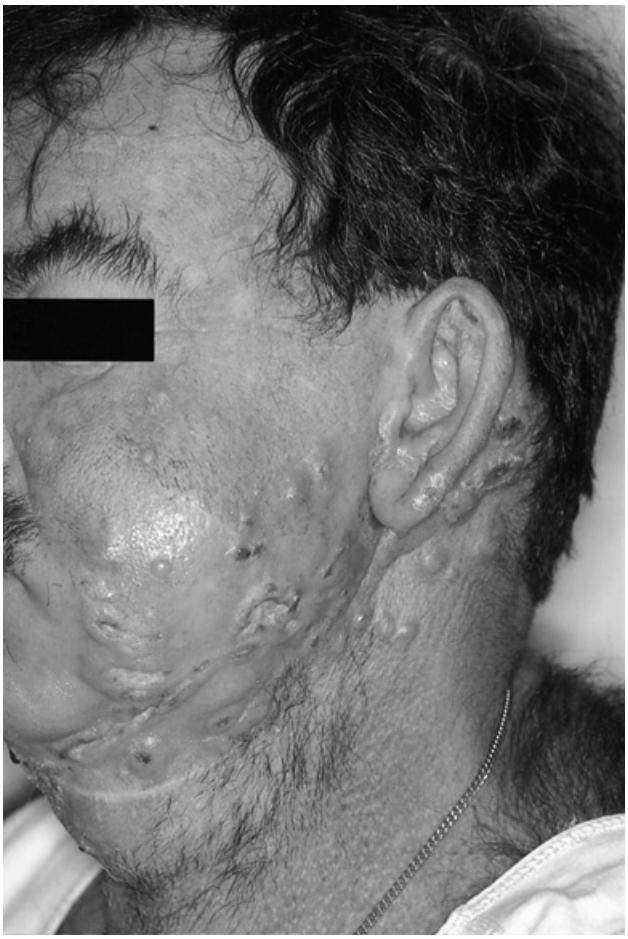

Fig. 13. A 47-year-old cardiothoracic transplant patient with widespread and rapidly progressing dermal metastases arising from a previously treated left cheek squamous cell carcinoma (SCC). Such aggressive behaviour of cutaneous SCC is rarely encountered in immunocompetent patients.

Recommendations

The basic tenets of obtaining adequate surgical margins and examining for perineural invasion are especially applicable to this group of patients. Although routine prophylactic treatment to regional lymph nodes cannot be recommended, adjuvant radiotherapy to incompletely excised SCC, or those with perineural invasion, should be strongly considered. Close liaison with a transplant physician is important.

CONCLUSIONS

Clinicians who treat patients with skin cancer should be aware of a small subset of patients with cutaneous SCC that may potentially benefit from a more intensive treatment approach

that often incorporates adjuvant radiotherapy. Current guidelines exist to aid clinicians in making evidence-based decisions for their patients, although some fail to adequately highlight the role of radiotherapy and the potential benefits it may provide in securing improved loco-regional control.[95–97]

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