Abstract: Nonmelanoma skin cancers occur at an epidemic rate in Australia and are increasing in incidence worldwide. In most patients, local treatment is curative. However, a subset of patients will be diagnosed with a high-risk cutaneous squamous cell carcinoma (SCC) and are defined as patients at increased risk of developing metastases to regional lymph nodes. Patients with high-risk SCC may be identified based on primary lesion and patient factors. Most cutaneous SCC arises on the sun-exposed head and neck. The parotid and upper cervical nodes are common sites for the development of metastases arising from ear, anterior scalp, temple/forehead, or scalp SCC. The mortality and morbidity associated with high-risk cutaneous SCC is usually a consequence of uncontrolled metastatic nodal disease and, to a lesser extent, distant metastases. Patients with operable nodal disease have traditionally been recommended for surgery. The efficacy of adjuvant radiotherapy has previously been questioned based on weak evidence in the early literature. Recent evidence from larger studies has, however, strengthened the case for adjuvant radiotherapy as a means to improve locoregional control and survival. Despite this, many patients still experience relapse and die. Research aimed at improving outcome such as a randomized trial incorporating the addition of chemotherapy to adjuvant radiotherapy is currently in progress in Australia and New Zealand. Ongoing research also includes the development of a proposed new staging system and investigating the role of molecular factors such as the epidermal growth factor receptor.

Keywords: cutaneous squamous cell carcinoma; nodal metastases; radiotherapy; surgery

Nonmelanoma skin cancer (NMSC) is the most common malignancy worldwide and a consequence of chronic exposure to the mutagenic and immunosuppressive effects of solar ultraviolet radiation. Men are overrepresented secondary to occupational sun exposure. Most patients (75% to 80%) diagnosed with NMSC will have a small (<2 cm) basal cell carcinoma (BCC) that is easily treatable, with a high probability of local control (90% to 95%). Death from a BCC is rare, although local morbidity can be significant in advanced cases. The sun-exposed head and neck is the most common site (70% to 80%) for the development of a NMSC, and populations of fair-skin individuals living in countries close to the equator and tropics (eg, Australia and the southern United States) are particularly afflicted.

Since the 1960s, the worldwide incidence of NMSC has markedly increased and continues to
Possible reasons include depletion of the ozone layer, an aging population, increasing use of immunosuppression, and changing social trends. Australia has the highest incidence of NMSC in the world, with an annual incidence of almost 1300/100,000 population.4 All patients with cutaneous SCC are diagnosed with a cutaneous squamous cell carcinoma (SCC). In regions of northern Australia, the annual incidence of SCC in men exceeds 1300/100,000 population.4 All patients with cutaneous SCC are at risk of developing metastases, although outpatient-based studies suggest only a minority (2% to 3%)5,6 ever develop metastases, most often nodal. Despite this, hospital-referred patients with SCC often have a higher incidence of nodal metastases. The development of metastases places patients at risk of significant morbidity and death.7,8

The majority of immunocompetent patients with a nonrecurrent, small (<2 cm) and superficial (2–3 mm) SCC can be considered at low risk for developing nodal metastases. Conversely, many patients who develop nodal metastases will have a high-risk SCC,9,10 although a minority (20% to 30%) will not have an identifiable index lesion, and factors not well understood are involved in this subgroup of patients. The absolute number of patients diagnosed with cutaneous SCC worldwide makes this a major public health issue. In the United States, at least 2500 people die annually from the consequences of advanced SCC, usually as a result of developing metastatic nodal disease.11 Many Australians also die as a consequence of developing metastatic SCC, although accurate epidemiological data are lacking. In 1 study over a 5-year period, 120 NMSC deaths occurred in western Australia and accounted for approximately 1% of all cancer-related deaths.12 The morbidity of treating patients with metastatic SCC is considerable, with most requiring hospitalization for major surgery, followed by 6 to 7 weeks of daily outpatient adjuvant radiotherapy. Although the early literature suggested a very poor outcome with current best practice (surgery + radiotherapy), 5-year disease-free survival is around 70% to 75%.13,14

**PRIMARY CUTANEOUS SQUAMOUS CELL CARCINOMA**

**High-risk Patients and the TNM Staging System.** Most metastatic (60% to 70%) nodes from head and neck cutaneous SCC occur in the parotid gland (+/− cervical nodes). The parotid gland is considered the metastatic basin for cutaneous SCC of the head and neck, with high-risk sites draining via lymphatic vessels located on or around the ear, cheek, or temple/forehead.15 The current clinical TNM (tumor, nodes, metastases) staging system inadequately prognosticates for patients with cutaneous SCC because most patients developing nodal metastases have a T1 (<2 cm)/T2 (>2–5 cm) primary. Size alone is currently the only criterion for assigning T stage in patients without invasion of muscle or cartilage (T4).16 Important features such as tumor thickness/depth of invasion, histological grade, or the presence of perineural invasion or lymphovascular invasion are not considered. Despite this, patients with high-risk SCC can be identified, and clinicians should be aware so that appropriate management can be considered.

**Tumor Size.** Size alone is probably a weak predictor for metastases, although many studies document a threshold size of approximately 2 cm (T1 primary lesion) beyond which patients have an increasing propensity to have nodal metastasis develop. In a large review reporting outcome for patients with cutaneous SCC, the authors reported a metastatic rate of 30% for lesions >2 cm versus 9% for lesions <2 cm.17 In a series of 97 patients with lower lip SCC treated with local excision, 13% developed lymph node metastases with tumor size (T1 vs T2/3), a significant predictor of nodal metastases on multivariate analysis (HR: 13.5; p = .005).18 Moore et al19 reported median lesion size as highly significant (3 cm vs 2 cm; p = .0002) in a study of 40 patients with metastatic SCC when compared with 153 control patients without metastases. Veness et al20 reported a median lesion size of only 15 mm in a large series of 266 patients with metastatic cutaneous HNSCC, suggesting that even patients with small SCC have metastatic potential.

**Thickness/Depth of Invasion.** Tumor thickness/depth of invasion beyond 4 to 5 mm is an important predictor of nodal metastases. In a study of patients undergoing excision of a lower lip SCC, there was a significant difference in mean depth of invasion in node-negative patients when compared with those developing nodal metastases (4.2 mm vs 11.2 mm; p < .001).18 In another study of patients with metastatic SCC of the head and neck, only 17% with a lesion <4 mm deep metastasized when compared with 83% with lesions >4 mm.21 A large study of 550 patients with 594
SCC (including 149 lip SCC) documented 4% of patients developing nodal metastases with only 7 patients (2.9%) with a tumor <5 mm thick developing metastases when compared with 14 (17.5%) patients with a tumor >5 mm thick.22 Of note, this study had a median follow-up of 5.3 years (minimum 4 years), and importantly, no patient with a superficial SCC (<2 mm thick) developed metastases. Clark levels have also been analyzed, with 1 study identifying patients with metastatic SCC significantly ($p = .0001$) more likely to have lesions beyond Clark level III when compared with those without metastases.9 In a large review of prognostic factors in patients with SCC, those with a tumor <4 mm or Clark levels I–III had a metastatic rate of 6.7% when compared with 45.7% in those with a tumor >4 mm or Clark level IV–V.17

**Recurrent Squamous Cell Carcinoma.** Recurrent SCC is associated with a higher incidence of nodal metastases. In a study of patients with lip SCC, those with recurrent lip SCC experienced a significant difference in developing nodal metastases when compared with those not developing local recurrence (15% vs 2%; $p < .0001$).23 In a large review of the literature, patients experienced a 32% and 45% incidence of nodal metastases in the setting of recurrent lip SCC and ear SCC, respectively.17 Clayman et al7 reported recurrent SCC as larger (2.4 cm vs 1.5 cm; $p < .0001$) and significantly more likely to exhibit perineural invasion (24% vs 10%) or lymphovascular invasion (17% vs 8%), and invade beyond subcutaneous tissues (30% vs 10%) when compared with nonrecurrent lesions. These findings suggest recurrent SCC as biologically more aggressive.

**Tumor Grade.** Poorly differentiated SCCs are more likely to be associated with the development of regional metastases. A study of 571 patients reported a significant difference in the rate of metastases for high-grade SCC when compared with other grades (17% vs 4%; $p = .004$).24 The incidence of poorly differentiated lesions in 1 series of patients with metastatic SCC was significantly increased in patients developing metastases (44% vs 5%; $p < .01$).9 Similarly, there are also data that desmoplastic SCC, an aggressive histological variant of SCC, possess a high propensity to regional metastases, especially with increasing tumor thickness.22,25 Using Broder’s classification, 27% of patients in Breuninger et al’s22 study with a desmoplastic SCC were assigned a grade IV differentiation compared with only 11% with a nondesmoplastic SCC.

**Perineural Invasion.** Perineural invasion occurs in approximately 5% to 10% of patients, is usually an incidental finding, and is reported to be associated with a higher incidence of nodal metastases.9,26 In 1 study, there was a significant increase in both nodal (35% vs 15%; $p < .0005$) and distant metastases (15% vs 3.3%; $p < .0005$) for patients with perineural invasion when compared with those without.27 In a study of 135 patients treated with radiotherapy +/- surgery, half of all failures in patients with microscopic perineural invasion were nodal, prompting the authors to recommend elective nodal treatment.28 A study comparing prognostic features of patients with metastatic and nonmetastatic lip SCC also reported a highly significant difference in the presence of perineural invasion (41% vs 5%; $p < .0001$).26 Similarly, in another study of patients with HNSCC, the rate of perineural invasion differed between patients with nodal metastases and those without (40% vs 18%; $p = .005$).19

**Lymphovascular Invasion.** Recent evidence suggests that the presence of lymphovascular invasion may increase the risk of developing nodal metastases. Moore et al19 documented lymphovascular invasion as an independent predictor of nodal metastases on multivariate analysis (OR: 7.54; $p < .00001$). In this study, 40% of patients with nodal metastases had lymphovascular invasion when compared with only 8% of node negative patients. Other studies of high-risk SCC also report the presence of lymphovascular invasion although fail to find any significant impact on outcome.7,9,12

**Tumor Location.** Lesions located on or around the ear are considered to have a higher incidence of nodal metastases as a result of the close proximity and consequential lymphatic drainage to the parotid gland.15,29,30 Researchers from The University of Texas M. D. Anderson Cancer Center documented in 40 node-positive patients that most developed metastasis to the parotid +/- neck (70%) and that the majority (52%) had a primary located in the parotid drainage (periauricular or frontotemporal scalp).19 Lower lip SCC, at least in Australia and in some other countries, can also be considered a cutaneous SCC secondary to chronic sun exposure and usually seen in men with a history of chronic outdoor occupational sun exposure.31 Although most patients with a super-
ficial T1 lower lip SCC will not be at risk of developing metastatic nodal disease, those with larger more deeply invasive lesions may develop nodal metastases similar to other patients with high-risk SCC. Metastases from lower lip SCC usually involve level I nodes.

**Immunosuppression.** Immunosuppression, particularly in the setting of an organ transplantation recipient, often leads to significant morbidity from NMSC, usually SCC. Patients develop SCC at a much younger age and experience recurrent new SCC. Unlike immunocompetent patients, SCC in organ transplant recipients occurs at a much higher incidence than BCC. One Australasian study reported a 66% probability of developing a cutaneous malignancy by 24 years post–renal transplant. A subset of SCC in immunosuppressed patients is aggressive in nature, with rapid growth and the development of regional and distant metastases. In an Australian study of 619 cardiothoracic transplant recipients, 26 developed an aggressive NMSC, with most diagnosed with a poorly differentiated SCC. Death occurred in 13 of the 26, with 10 patients dying from systemic disease. Martinez et al reported the outcome of 60 organ transplant recipients all with metastatic skin cancer (85% SCC), noting that 27% of patients had an unknown index lesion. In this study, median primary lesion size was 12 mm and median depth of invasion was 3.2 mm. Three-year disease-specific survival was only 56%. This would suggest a smaller lesion size and depth of invasion threshold for the development of metastatic cutaneous SCC and a significantly worse outcome when compared with immunocompetent patients. In another study comparing immunocompetent and organ transplant recipient patients, a significant proportion of organ transplant recipients had thick (>5 mm) tumors and exhibited early dermal invasion when compared with immunocompetent patients. Of note, patients immunosuppressed as a consequence of chronic lymphocytic leukemia also have a similar increased risk of cutaneous SCC and poor outcome from developing metastases.

**Sentinel Node Biopsy.** Despite evidence documenting factors that place a patient at risk of developing nodal metastases, accurately predicting an individual’s risk is difficult. Routine investigations usually contribute little to a thorough clinical examination in the setting of a clinically N0 neck. The concept of sentinel node biopsy (SNB) has evolved in malignancies such as melanoma and breast cancer to identify patients with subclinical spread to first echelon lymph nodes. There are emerging data that SNB may also have a role in identifying patients with high-risk SCC. In a series of 9 patients with high-risk SCC, 4 of 9 (44%) were positive on SNB, with 2 subsequently dying of metastatic disease. All node-positive patients had SCC >3 cm in diameter and >8 mm in depth. The 5 with a negative SNB remained disease free, although the median follow-up of 8 months was short. In another series of 24 patients with high-risk NMSC (n = 17 SCC) undergoing SNB, 7 (29%) had a positive sentinel node, with only 1 false positive. This included 5 SCC positive on SNB, although only 2 involved head and neck nodes. A recent study documented the lymphatic drainage pattern of the ear (high-risk site) in healthy patients utilizing lymphoscintigraphy. The findings from this study suggest a more predictable pattern of spread than previously thought. Despite this, and other studies, the role of SNB in patients with high-risk cutaneous HNSCC is evolving and still requires further validation. Similarly, the role and benefits of positron emission tomography in highlighting subclinical disease is unproven but with emerging data in the setting of mucosal HNSCC, and with further research, this investigation may also be of benefit in cutaneous HNSCC.

**Elective Nodal Treatment.** The option of electively treating at-risk nodes to prevent regional relapse may be considered. Radiotherapy or surgery is an option, and the recommendation of one over another is based on multiple factors. Yoon et al reported on 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 +/- radiotherapy in patients with poor prognostic features such as cartilage invasion, deep invasion, or poor differentiation. Similarly, Afzelius et al recommended elective nodal dissection in patients with unfavorable ear SCC: >4 cm, cartilage invasion, or deep invasion. 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. Zitsch et al recommended elective nodal dissection in the setting of lip SCC that are undifferentiated or locally recurrent (if initial lesion > 2 cm).
Electively irradiating nodes is also an option, although high-level supportive evidence is lacking. Kwan et al. reported a higher locoregional failure (30% vs 20%) in 37 patients with advanced SCC who did not receive nodal irradiation when compared with 5 patients undergoing elective nodal treatment. Other proponents also recommend elective nodal treatment (surgery or radiotherapy) in the presence of adverse or high-risk features.

Accurately predicting patients who may develop nodal relapse is difficult; however, clinicians should consider patients with recurrent SCC that is >4 to 5 mm thick and in the vicinity of the parotid gland (ear, lateral scalp, forehead, temple, cheek) at higher risk of developing parotid nodal metastases. It is these patients who should be considered as candidates for the elective treatment of parotid nodes. Depending on the type of treatment to the primary cutaneous lesion, elective nodal treatment may entail either a superficial parotidectomy or alternatively radiotherapy to the parotid gland.

**METASTATIC NODAL SQUAMOUS CELL CARCINOMA**

**Background.** In Australia, metastatic cutaneous SCC is overwhelmingly the most frequent parotid malignancy. The lateral/anterior head and neck sites (ear, anterior scalp, forehead, temple, cheek) are the most frequent sites for a primary index SCC. Most patients (70% to 80%) who have an identifiable index lesion and subsequently develop nodal metastases do so after treatment for this lesion rather than present with a concomitant primary and nodal disease. Median time for the development of nodal metastases following treatment of an index SCC is approximately 12 months, although late relapse (2–3 years) is well documented and justifies ongoing regular follow-up of patients following treatment of a high-risk SCC. The pattern of distribution of nodal metastases is approximately equally divided between the parotid alone, the parotid and neck, and the neck alone (levels I–V).

**Evidence-Based Management.** The optimal management of a patient with cutaneous metastatic nodal HNSCC has evolved. Early evidence usually consisted of small case series often reflecting selection and treatment bias. The paucity of evidence meant clinicians were often unclear of the benefit of recommending combined treatment incorporating adjuvant radiotherapy given the extended treatment time (5–7 weeks) and the perceived side effects. Because of this uncertainty, many patients who may have benefited from adjuvant radiotherapy were not offered further treatment.

In patients that have relapse develop, most (70% to 80%) experience locoregional relapse as the first site of relapse. This finding would strongly suggest that any treatment to improve disease control in the head and neck is likely to also impact on survival. Patients suffering locoregional relapse are often incurable either secondary to untreated regional disease or the subsequent development of distant disease.

**Early Evidence.** Early studies suggested that patients might achieve a better outcome (improved locoregional control and survival) following surgery and adjuvant radiotherapy when compared with either surgery or radiotherapy alone (Tables 1 and 2; refs. 21 and 47–54). Of note, the University of Florida Group published updates of their series of patients, concluding that a better outcome was achieved with combined treatment. In 1978, Cassisi et al. reviewed 20 patients with parotid lymph node metastases from SCC. Following surgery and adjuvant radiotherapy, they reported a locoregional recurrence rate of 10% and an absolute survival rate of 80%. The outcomes of these patients with further accrual were updated in 1985, 1991, and 1998, again demonstrating improved absolute and disease-free survival following combined-modality treatment, when compared with patients treated with a single modality.

However, many early studies were small and heterogeneous with regard to the site and stage of disease and treatment approach (extent of sur-

<table>
<thead>
<tr>
<th>Author/year</th>
<th>Surgery/radiotherapy, %</th>
<th>Surgery, %</th>
<th>Radiotherapy, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>delCharco et al, 1998</td>
<td>10</td>
<td>20</td>
<td>47</td>
</tr>
<tr>
<td>Khurana et al, 1995</td>
<td>38</td>
<td>24</td>
<td>NR</td>
</tr>
<tr>
<td>Taylor et al, 1991</td>
<td>11</td>
<td>37</td>
<td>54</td>
</tr>
<tr>
<td>Shimm and Wilder, 1991</td>
<td>27</td>
<td>–</td>
<td>63</td>
</tr>
<tr>
<td>Shimm, 1988</td>
<td>36</td>
<td>–</td>
<td>29</td>
</tr>
<tr>
<td>Mendenhall et al, 1985</td>
<td>12</td>
<td>85</td>
<td>50</td>
</tr>
<tr>
<td>Cassisi et al, 1978</td>
<td>20</td>
<td>75</td>
<td>50</td>
</tr>
</tbody>
</table>

Abbreviation: NR, not reported.
gery, radiotherapy technique/doses). The potentially biased selection of patients for treatment may have resulted in patients with unfavorable features being recommended combined treatment, perhaps explaining the wide variation in reported locoregional relapse rates. The percentage of patients receiving adjuvant radiotherapy varied markedly in most series almost certainly reflecting the uncertain benefit and the doubt of many clinicians. No studies were controlled, and most were retrospective and descriptive in analysis and lacked the number of patients and events to perform multivariate analysis. Earlier studies were often criticized as weak and inconclusive, with authors concluding the need for larger, multi-institutional, prospectively randomized trials to identify the best approach, or even discounting the role of adjuvant radiotherapy because of a lack of a statistically significant proven benefit.

**Recent Evidence.** Recent publications support surgery and adjuvant radiotherapy as best practice in operable patients (see Tables 3 and 4; refs. 13, 14, 19, and 55–66). Taking into consideration the heterogeneity of patient, tumor, and treatment factors across multiple studies, a patient treated with a combined approach can probably expect a 20% to 25% chance of locoregional relapse. Those treated with a single modality (surgery or radiotherapy) can expect a less than 50% likelihood of achieving freedom from locoregional relapse. Many publications, particularly from Australia, present the results from large single institutional series. Publications from the Westmead Group,13,58,61,62,64 Sydney, have documented the outcome of a large number of prospectively analyzed patients treated with curative intent within the context of a tertiary referral multidisciplinary head and neck cancer service. A consistent treatment approach since the 1980s has been followed, with operable patients undergoing surgery followed by adjuvant radiotherapy. The most recent analysis from this group confirmed a marked decrease in locoregional relapse (20% vs 43%) and improved disease-free survival (73% vs 54%; p = .004) with the addition of adjuvant radiotherapy when compared with surgery alone.13 Other authors have also reported results for patients treated with metastatic cutaneous nodal HNSCC, although many studies remain small and heterogeneous.

**Adjuvant Radiotherapy.** Bron et al163 reported adjuvant radiotherapy as the only factor that significantly improved local control in the parotid and recommended it as standard treatment. In concordance, O’Brien et al165 also reported adjuvant radiotherapy as significantly improving parotid control on multivariate analysis. Similarly, del-Charco et al47 documented treatment (surgery/
radiotherapy vs radiotherapy) as the only factor to predict parotid disease control on multivariate analysis ($p = .004$). In another series, 5-year disease-free survival was significantly improved in patients undergoing surgery and adjuvant radiotherapy when compared with surgery alone (73% vs 18%; $p = .001$), as was loco-regional control improved (77% vs 15%). Barzilai et al$^{57}$ documented improved 5-year survival in patients receiving adjuvant radiotherapy, although this failed to reach statistical significance (73% vs 38%; $p = .26$). Jol et al$^{60}$ also reported decreased loco-regional failure in patients undergoing surgery and adjuvant radiotherapy when compared with surgery alone (17% vs 44%). Most recent studies suggest 60 Gy in 2 Gy daily fractions as an acceptable dose of adjuvant radiotherapy to a dissected involved nodal region and 50 Gy to the undissected at-risk neck.

**Prognostic Variables.** In 74 patients with SCC to nonparotid head and neck nodes, increasing nodal size ($\geq 3$ cm), multiple nodes, extranodal spread, and single-modality treatment independently predicted survival. Barzilai et al$^{57}$ reported positive surgical margins associated with poor local disease control ($p = .02$), as did O’Brien et al.$^{65}$ who identified margin positivity as an independent predictor for parotid relapse. Veness et al$^{13}$ identified extranodal spread as a predictor for survival on univariate analysis, although on multivariate analysis, only number of nodes and treatment remained significant. Immunosuppression strongly predicts a very poor outcome.$^{37,62,67}$ Southwell et al$^{67}$ reported no immunosuppressed patients alive at 2 years when compared with 87% of immunocompetent patients alive in a study of 49 patients. Palme et al$^{62}$ also identified immunosuppression as an independent predictor of survival on multivariate analysis. In a recent consensus survey, leading transplant physicians recommended a severe reduction in the level of immunosuppression in patients with metastatic cutaneous SCC.$^{68}$

### Table 4. Selected recent studies reporting outcome relapse after surgery and adjuvant radiotherapy.

<table>
<thead>
<tr>
<th>Author/year/number</th>
<th>Patients treated with surgery/ adjuvant radiotherapy, %</th>
<th>Locoregional relapse, %</th>
<th>Survival*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ying et al$^{55}$ 2006 (n = 41)</td>
<td>61</td>
<td>36</td>
<td>64% AS-cured</td>
</tr>
<tr>
<td>Moore et al$^{19}$ 2005 (n = 40)</td>
<td>93</td>
<td>18</td>
<td>NR</td>
</tr>
<tr>
<td>Hong et al$^{66}$ 2005 (n = 20)</td>
<td>70</td>
<td>7</td>
<td>NR</td>
</tr>
<tr>
<td>Barzilai et al$^{57}$ 2005 (n = 22)</td>
<td>55</td>
<td>0</td>
<td>5 y 73% OS</td>
</tr>
<tr>
<td>Veness et al$^{13}$ 2005 (n = 167)</td>
<td>87</td>
<td>20</td>
<td>5 y 73% DFS</td>
</tr>
<tr>
<td>Audet et al$^{14}$ 2004 (n = 56)</td>
<td>79</td>
<td>27</td>
<td>3 y 72% DSS</td>
</tr>
<tr>
<td>Veness et al$^{58}$ 2003 (n = 74)</td>
<td>70</td>
<td>15</td>
<td>5 y 61% DSS</td>
</tr>
<tr>
<td>Dona et al$^{51}$ 2003 (n = 74)</td>
<td>100</td>
<td>24</td>
<td>5 y 72% CSS</td>
</tr>
<tr>
<td>Martinez et al$^{56}$ 2003 (n = 68)$^\dagger$</td>
<td>37</td>
<td>29</td>
<td>3 y 56% DSS</td>
</tr>
<tr>
<td>Palme et al$^{62}$ 2003 (n = 126)</td>
<td>89</td>
<td>28</td>
<td>5 y 68% DSS</td>
</tr>
<tr>
<td>Bron et al$^{63}$ 2003 (n = 101)</td>
<td>85</td>
<td>25</td>
<td>5 y 65% DSS</td>
</tr>
<tr>
<td>Gooris et al$^{59}$ 2002 (n = 44)</td>
<td>73</td>
<td>13</td>
<td>NR</td>
</tr>
<tr>
<td>Jol et al$^{50}$ 2002 (n = 41)</td>
<td>59</td>
<td>17</td>
<td>5 y 46% OS</td>
</tr>
<tr>
<td>Chua et al$^{54}$ 2002 (n = 52)</td>
<td>100</td>
<td>31</td>
<td>5 y 65% CSS</td>
</tr>
<tr>
<td>O’Brien et al$^{65}$ 2002 (n = 87)</td>
<td>86</td>
<td>24</td>
<td>5 y 63% DSS</td>
</tr>
<tr>
<td>Baker et al$^{66}$ 2001 (n = 12)</td>
<td>100</td>
<td>50</td>
<td>NR</td>
</tr>
</tbody>
</table>

Abbreviations: AS, adjusted survival; NR, not reported; CSS, cause-specific survival; DSS, disease-specific survival; DFS, disease-free survival; OS, overall survival.

$^\dagger$In some studies, only results for patients treated with surgery and radiotherapy are presented.

$^\dagger$Organ transplant recipients.

**Treatment of the Parotid.** In the setting of a functioning facial nerve, there is a little convincing evidence that more aggressive surgery in the form of a total parotidectomy, as opposed to a facial nerve-sparing superficial parotidectomy followed by adjuvant radiotherapy, will improve locore-
gional control. The incidence of facial nerve sacrifice (partial or complete) varies across series (5% to 43%) and possibly reflects differences in disease location and stage in conjunction with clinician preference. Patients with involvement of the facial nerve often have a worse outcome. However, the facial nerve should only be sacrificed if the patient has malignant facial nerve palsy or is found to have nerve involvement at the time of operation. Surgery rarely achieves oncological excision margins (>5 mm) especially in the deep plane in proximity to the facial nerve. Studies have documented high rates of close or incomplete excision (40% to 65%) following parotidectomy. Extranodal spread is also a common pathologic finding (30% to 75%) and in combination with a close or positive margin adds weight to the importance of adjuvant radiotherapy to improve locoregional control and may explain the high recurrence rate following surgery alone.

Neck Treatment. Treatment to clinically uninvolved cervical nodes is important. One study documented a 35% rate of subclinical metastases in dissected clinically negative neck nodes. Similarly, O’Brien et al reported a 35% incidence of subclinical spread in 37 patients with metastatic parotid nodes following elective neck dissection. This compares with a lower incidence (16%) of occult spread in neck nodes in another Australian series and a 16% occult rate in a Canadian study by Audet et al. Researchers from The University of Texas M. D. Anderson Cancer Center documented a 42% incidence of occult cervical metastases in a study of patients with metastatic parotid SCC. Ying et al similarly documented 44% of patients with parotid metastases as having pathologically positive cervical nodes. Therefore, all patients with parotid metastases and a clinically negative neck should undergo a selective neck (levels I/II or levels I/II/III) dissection in conjunction with a parotidectomy. In a recent article reporting the patterns of nodal metastases in cutaneous SCC of the head and neck, 79% of pathologically involved cervical nodes were located at level II. The authors recommended that the external jugular node, which is not assigned to a specific level although often included as a level node II, be excised in any dissection. Involvement of this node can be considered pathognomonic for spread from a cutaneous malignancy. Level IV/V nodes were usually only involved in the setting of extensive nodal disease.

Patients with nasal/cheek/lip SCC are more likely to benefit from the addition of a level I dissection when compared with lesions located on the forehead/scalp.

Deleting a neck dissection in the setting of parotid disease and a N0 neck is an option. However, this will commit all patients to receive elective radiotherapy (50 Gy) directed to the hemineck. Although it is well accepted that neck control is equivalent in a clinically N0 neck with either surgery or radiotherapy, the finding of pathologically negative upper level neck nodes may result in a patient not requiring adjuvant radiotherapy to the lower neck.

Patients with clinical involvement of cervical nodes should undergo an appropriate neck dissection. Radiotherapy is delivered to the ipsilateral neck if disease is identified in multiple nodes (>2) or extranodal spread is present in a single node. An undissected neck should be irradiated in the presence of parotid nodal disease even if clinically negative.

Radiotherapy Alone. Disease in patients with skull base or carotid vessel involvement can be considered inoperable. Skin involvement does not preclude surgery but will necessitate excision of skin and soft tissue and appropriate reconstruction. In patients with operable disease that are treated with high-dose (66–70 Gy) radiotherapy (medically unfit/patient refusal), there is a chance of cure although patients with advanced and inoperable disease are unlikely to obtain durable locoregional control. The addition of chemotherapy to these patients is experimental but may be considered in suitable good performance patients.

FUTURE RESEARCH

Adjuvant Radiochemotherapy. There are emerging data in postoperative mucosal HNSCC that combination concurrent platinum chemotherapy and adjuvant radiotherapy may improve locoregional control and disease-free survival in high-risk patients (extranodal spread, multiple nodes). High-risk pathologic features, such as multiple nodes, extranodal spread, positive margins, and perineural or vascular invasion, are often present in metastatic cutaneous HNSCC patients. Patients with these pathologic features may benefit from means to improve locoregional control. Data from a Peter MacCallum Cancer Institute, Melbourne, pilot study using weekly
concomitant platinum-based chemotherapy and adjuvant radiotherapy suggests a possible role for combined treatment to improve locoregional control in high-risk cutaneous (extracapsular spread, close/positive margins) SCC patients, although randomized data in this setting are needed to confirm any hypothesis. A trial testing this has been activated in Australian and New Zealand patients under the auspices of the Trans Tasman Radiation Oncology Group (TROG), with the aim to accrue 265 patients randomized to receive adjuvant radiotherapy (60 Gy) or adjuvant radiotherapy and weekly carboplatin (Post-Operative Skin Trial; POST 05.01). Carboplatin was chosen on the basis that the patient cohorts in this study are unlikely to tolerate cisplatin, as many are older with preexisting comorbidities. Patients with T3/T4 N0 SCC are also included in this study to test the improvement in local control and where possible to also electively treat first echelon nodes.

Molecular Prognostic Factors. There are limited data investigating prognostic molecular factors that could provide valuable data to guide novel treatment. Differences at a molecular level may, in part, also explain the metastatic potential of SCC lacking established high-risk features such as size and thickness and explain why patients with relatively small, thin SCC have metastasis develop. The overexpression of epidermal growth factor receptor (EGFR) is postulated as 1 possible factor.74,75 The authors of 1 study suggest the potential use of tyrosine kinase inhibitors in patients with EGFR-positive tumors.74 The association of human papillomavirus (HPV) and NMSC is also an area of potential research, with some evidence to implicate oncogenic HPV subtypes and the development of NMSC.76 However, further research is required in this area so that a clearer understanding of the biology of metastatic SCC can be elucidated.

Proposed Staging System. The TNM staging system currently assigns all patients with metastatic cutaneous SCC as stage N1. Collaborative research must be undertaken with a staging system that takes into account important and proven prognostic variables such as nodal location and size, number of metastatic nodes, and facial nerve involvement (perineural invasion). Using a modified P (Parotid; P0-3) and N (Nodes; N0-2) clinical staging system, O’Brien et al,66 Palme et al,62 and Audet et al14 have validated the benefit of such a system in identifying patients who have a worse outcome based on PN criteria. A recent large collaborative retrospective series of 325 patients from 3 Australian institutions (Royal Prince Alfred, Westmead, Queensland Radium Institute) and 3 North American institutions (Memorial Sloan-Kettering, Toronto General, University of Florida) analyzed outcome for patients with metastatic cutaneous HNSCC using the proposed PN staging system of O’Brien et al65 (Table 5). The findings from this large study confirm the utility of separate parotid and neck stages in predicting outcome.77 Patients with pathologic involvement of both the parotid and neck did worse when compared with those having only parotid disease.

**CONCLUSIONS**

The rising worldwide incidence of cutaneous SCC implies that clinicians are increasingly likely to encounter patients with a high-risk primary HNSCC or metastatic nodal HNSCC. Patients at risk of developing nodal metastases often have features that may predict an increased risk beyond the often-quoted 2% to 3% in the literature. However, accurately predicting a patient’s risk is difficult. The parotid nodes represent a frequent site of metastatic nodes, and electively treating first echelon nodes may prevent the consequences of nodal disease, although high-level evidence to support this approach is lacking. Patients with operable metastatic nodal disease should be offered surgery and adjuvant radiotherapy. Single-modality treatment is less likely to cure a patient. Patients with parotid metastases should also have the neck treated. Using a proposed new staging system may allow the identification of patients at higher risk of relapse and justify more intensive treatment such as the addition of chemotherapy to adjuvant radiotherapy. Con-

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<th>Table 5. Proposed staging system of O’Brien et al.65</th>
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Cutaneous HNSCC
exclusive evidence for this latter approach is pending the mature results of the TROG study.

REFERENCES


47. deCharco JO, Mendenhall WM, Parsons JT, Stringer SP, Cassisi NJ, Mendenhall NP. Carcinoma of the skin metastatic to the parotid area lymph nodes. Head Neck 1998;20:369–373.