Objective: To characterize clinical presentation and prognostic factors in patients with histologically proven regional lymph node metastasis from cutaneous squamous cell carcinoma of head and neck origin.

Design: Retrospective, nonrandomized case series.

Setting: Tertiary referral center.


Intervention: Forty-one patients underwent neck dissection (20 with parotidectomy) and 4 patients underwent parotidectomy alone. Thirty-six patients (80%) received postoperative radiation therapy with a mean dose of 60 Gy (range, 34-71 Gy).

Main Outcome Measures: Recurrences and survival by univariate analysis using the Kaplan-Meier product-limit method. The log-rank test was used to evaluate prognostic significance of clinical variables.

Results: Follow-up ranged from 2 months to 10 years (mean, 21 months). Compared with historical controls, a greater percentage of patients in our population with regional lymph node metastasis had primary lesions greater than 2 cm in diameter and 4 mm deep. Overall 2- and 5-year survival rates were 33% and 22%, respectively, while 5-year disease-free survival rate was 34%. Clinical staging of the neck proved to be the only factor of prognostic value ($P < .01$). Treatment failures occurred in 22 patients.

Conclusions: For the small subset of patients with regional metastasis from cutaneous squamous cell carcinoma, survival remains poor despite multimodality treatment. Clinical stage of the neck was the only factor that predicted outcome.


Skin cancer is currently the most common malignancy found in the United States, with cutaneous squamous cell carcinoma (SCC) accounting for 20% of these cases. The development of cutaneous SCC has been increasing in recent decades and is related to increasing actinic damage, specifically from UV-B radiation (290-320 nm), possibly related to the thinning ozone layer. The head and neck region, which experiences a significant amount of solar exposure, accounts for the site of origin of more than 95% of cutaneous SCCs.

In contrast to mucosal SCC of the upper aerodigestive tract, cutaneous SCC rarely metastasizes. The reported rates of regional metastasis from cutaneous SCC vary from 0.5% to 10%. The purpose of this study was to characterize the clinical presentation and prognostic factors in patients with regional lymph node metastasis from cutaneous SCC of head and neck origin. Defining the factors that influence development of regional lymph node metastasis, disease control, and survival may enable improvement in our treatment of this subset of patients who have a known poor prognosis.

Results

Treatment failures occurred in 22 patients, with some at multiple sites. Eight patients failed at the primary site, 11 regionally, and 8 distantly. Failure at the primary was defined as a cutaneous recurrence in the location of the index primary. Recurrences in the parotid gland were considered regional failures. Overall 2- and 5-year determinant survival rates were 33% and 22%, respectively, while 5-year disease-free survival was 34% (Figure 1).

Follow-up ranged from 2 months to 10 years (mean, 21 months). Follow-up was
PATIENTS, MATERIALS, AND METHODS

A retrospective review was undertaken of 45 patients with histologically proven regional lymph node metastasis of cutaneous head and neck origin treated between 1984 and 1995 at Memorial Sloan-Kettering Cancer Center (MSKCC), New York, NY. The database at MSKCC was initially searched to determine the total number of patients treated for cutaneous SCC of the head and neck region during this period. However, the vast majority of patients were treated with local excision in an outpatient setting and only the patients who required surgical excision in the main operating room were retrievable. Nevertheless, 179 patients were treated during this period with wide local excision, without evidence of regional lymph node metastasis. It is suspected that an even larger number of patients were treated with local excision in the outpatient clinic during this same time.

In the 45 patients with histologically proven regional lymph node metastasis of cutaneous head and neck origin, information regarding sex, age, immune system status, prior skin cancer, primary tumor (location, depth, diameter, and pathologic conditions), status of the neck at time of neck dissection (stage or levels involved), number of previous operations, time from treatment of primary tumor to treatment of the neck, neck dissection (type or histological findings), adjuvant treatment (radiation therapy [RT] or chemotherapy), and follow-up was recorded. For those who received their RT at institutions other than MSKCC, we reviewed the treatment summary recorded. For those who received their RT at institutions other than MSKCC, we reviewed the treatment summary because portal films were not available for review. If follow-up within the past year could not be retrieved from the chart, the patient was contacted by telephone to assess status.

The impact of histological grade and status of primary tumor at the time of nodal dissection, clinical stage of the involved nodal basin, and postoperative RT on survival of patients was assessed by univariate analysis using the Kaplan-Meier product-limit method. The log-rank test was used to evaluate prognostic significance of these variables. Statistical significance was determined at the 95% level (P < .05).

PATIENT CHARACTERISTICS

The population of 45 patients was composed of 7 women and 38 men with a mean age of 67 years (range, 37-85 years). Forty-one patients underwent neck dissection (20 with parotidectomy) and 4 patients underwent parotidectomy alone. Five patients (11%) had disorders of the immune system, with the most common being lymphoma (3 [7%]). Four patients were receiving immunosuppressive medications, most commonly oral steroids. Previous skin cancers at other sites had been excised in 18 patients (40%) with the most common being basal cell carcinoma. The mean depth of the index primary was 2.9 cm (range, 0.4-6.0 cm). The index primary tumor was greater than 4 mm deep in 83% of patients and greater than 2 cm in diameter in 81% of patients. The characteristics of the patients with regional lymph node metastasis in this study were compared with those cited in the literature in all patients with cutaneous SCC (Table 1). Data for the historical controls were derived from a calculation of the weighted means of these reports.3-6 Primary site distribution is shown below.

<table>
<thead>
<tr>
<th>Primary Site</th>
<th>Population Distribution, No. (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anterior scalp</td>
<td>12 (26.7)</td>
</tr>
<tr>
<td>Posterior scalp</td>
<td>1 (2.2)</td>
</tr>
<tr>
<td>Eyelid</td>
<td>2 (4.4)</td>
</tr>
<tr>
<td>Cheek</td>
<td>2 (4.4)</td>
</tr>
<tr>
<td>Nose</td>
<td>8 (17.8)</td>
</tr>
<tr>
<td>Lip</td>
<td>3 (6.7)</td>
</tr>
<tr>
<td>Ear or preauricular area</td>
<td>16 (35.6)</td>
</tr>
<tr>
<td>Anterior aspect of the neck</td>
<td>1 (2.2)</td>
</tr>
</tbody>
</table>

The most common sites were the ear or preauricular region, anterior scalp, and nose. Regional metastases were staged according to the American Joint Committee on Cancer staging system.12 It should be noted that patients with single parotid metastasis less than 3 cm were staged as N1 while patients with ipsilateral neck and parotid metastasis less than 6 cm were staged as N2B. Twenty-two patients (49%) had necks staged as N1, 9 (20%) were staged as N2A, 9 (20%) were staged as N2B, 2 (4%) were staged as N2C, and 3 (7%) were staged as N3. Total or subtotal parotidectomy (13 of 24) was performed more often than superficial parotidectomy (11 of 24 patients). Twenty-eight comprehensive neck dissections (68%), 10 selective neck dissections (24%), and 3 extended neck dissections (7%) were performed. Neck dissections were therapeutic in 36 and elective in 5 patients. Elective neck dissections were performed for bulky primaries (3) or electively for the management of parotid metastasis (2).

Forty-two of the 45 patients had undergone prior treatment of their primary site. Patients had a mean of 2.0 (range, 1-6) previous resections of their primaries before presentation for neck dissection, with only 3 patients undergoing nodal dissection concurrent with the treatment of their primary. The mean time between treatment of the primary and the development of clinically apparent regional metastasis was 13 months (range, 0-36 months). A total of 19 patients (42.2%) had recurrence at their primary site.

All patients included in this study had histologically proven disease involving the parotid gland, cervical lymph nodes, or soft tissues (ie, skeletal muscle, adipose, or neural tissue) of the neck. The overall pattern of regionally metastatic disease is presented in Table 2. Parotid gland involvement, either intraparotid (9) or periparotid (9), occurred in 16 (67%) of 24 patients undergoing parotidectomy. Periparotid lymph nodes are defined as those nodes that lie superficial to the parotid fascia. Anterior scalp, face (eyelid, cheek, and nose), and ear or preauricular primary sites accounted for 15 (94%) of 16 positive parotid specimens while posterior scalp and neck accounted for only 1 (6%) of 16 positive parotid specimens.

RADIATION THERAPY

Thirty-six patients (80%) received postoperative external beam RT and 5 patients received brachytherapy. A mean of 60 Gy was given as external beam RT (range, 34-71 Gy). The most common indication for postoperative RT was multiple histologically positive lymph nodes. Only 1 patient received less than 30 Gy and this patient was excluded when...
determining the effects of RT on survival. Of patients receiving RT, 16 (44%) received their postoperative RT at MSKCC (mean dose, 64 Gy) and 20 (56%) received their RT at other institutions (mean dose, 59 Gy). Records of treatment were available only for patients treated at MSKCC. Patients usually received a combination of 6-mV photons in 1.8-Gy fractions and electrons to the ipsilateral neck. If the primary had recurrent disease or the parotid gland was involved, these too were treated with RT.

Nine patients did not receive postoperative RT. Six of these 9 patients had received prior RT and therefore could not undergo RT after surgery. The other 3 of these 9 patients had limited disease and therefore did not receive adjuvant postoperative RT. Two of the 3 had regional lymph node metastasis proved by a lymph node biopsy specimen, but subsequent neck dissection findings were histologically negative, and 1 patient underwent a subtotal parotidectomy that revealed metastasis in 2 periparotid lymph nodes.

primarily limited by the poor prognosis of these patients, with most dying within 2 years. Results of univariate analysis using the Kaplan-Meier product-limit method with the log-rank test of Mantel of the factors affecting survival are shown in Figure 2. Clinical stage of the neck was the only factor that proved to be of prognostic value in predicting disease-free survival (P<.01). Patients with N1 necks had a 2-year survival rate of 53%, while patients with N2 or N3 necks had a 2-year survival rate of 18%.

Kaplan-Meier survival curves comparing patients who received postoperative RT with those who did not are shown in Figure 3. Patients receiving RT had a 2-year survival rate of 33% while those not receiving RT had a 2-year survival rate of 34%. There was no statistically significant difference between survival in these groups. It should be noted, however, that within the group of patients not receiving postoperative RT there were 2 subsets of patients with significantly different disease characteristics. One subset of patients had received prior RT that precluded them from receiving postoperative RT. The other subset had limited disease, either with positive lymph node biopsy specimens but histologically negative neck dissection specimens or an isolated parotid lymph node metastasis. It was elected to forgo postoperative RT in this subset with limited disease. Survival curves were then plotted by subdividing the patients who did not receive postoperative RT into these 2 subsets—those who had received prior RT and those with limited disease (Figure 4). Although there was a limited number of patients within these 2 subgroups, a statistically significant difference was found between patients with limited disease not receiving postoperative RT, patients receiving RT, and patients who had received prior RT and therefore could not receive postoperative RT (P<.05).

Many studies have attempted to identify factors that predict aggressive tumor behavior and regional lymph node metastasis in cutaneous SCC. Identifying patients at greatest risk for metastasis and detecting these patients at earlier stages would facilitate early intervention and potentially improve survival in this group. Kwa and colleagues1 stated that the frequency of metastasis in cutaneous SCC depended mainly on anatomical site, histological features, origin, immunosuppression, lesion diameter, and prior treatment. In a review of studies published in the last 50 years, Rowe and coworkers11 found that the risk factors for metastasis from cutaneous SCC included location, size, depth, histological differentiation, histological evidence of perineural invasion, and host immunosuppression.

Although this study was not designed to determine risk factors associated with regional lymph node metastasis in cutaneous SCC, characteristics of this select group with histologically proven regional metastasis can be compared with those of previous studies2-6,11 of nonselected patients with cutaneous SCC (Table 1). The mean age in both groups is nearly equal. Men represent a greater proportion of patients in our study group compared with the literature of nonselected patients. Five patients (11%) in our group had an impaired immune system, most commonly due to lymphoma. Although human immunodeficiency virus–related disease is currently a common cause of immunodeficiency, there were no patients in our series with this disorder. Immunosurveillance has been related to the development and biological behavior of cutaneous SCC.1 When size of the index primary is examined, a higher percentage of tumors greater than 4 mm deep (83%) and 2 cm in diameter (81%) was found in our patient population relative to those reported in nonselected patients (Table 1).11 The initial tumor depth and diameter for the majority of our patients, however, was not available since most patients were referred to our cancer center after their primary lesion had been excised and they subsequently developed regional metastasis. In 1 series of 22 patients with metastatic SCC, the average

Table 1. Comparison of Patients*

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<tr>
<td>Mean age, y</td>
<td>67</td>
<td>71</td>
</tr>
<tr>
<td>Sex, male-female</td>
<td>5:2:1</td>
<td>2:1</td>
</tr>
<tr>
<td>Impaired immune system</td>
<td>5/45 (11)</td>
<td>Not stated</td>
</tr>
<tr>
<td>Tumor depth, mm</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt;4</td>
<td>5/6 (83)</td>
<td>227/697 (33)</td>
</tr>
<tr>
<td>&lt;4</td>
<td>1/6 (17)</td>
<td>470/697 (67)</td>
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<tr>
<td>Tumor diameter, cm</td>
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<td></td>
</tr>
<tr>
<td>&gt;2</td>
<td>13/16 (81)</td>
<td>705/2939 (24)</td>
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<td>&lt;2</td>
<td>3/16 (19)</td>
<td>2234/2939 (76)</td>
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<tr>
<td>Poorly differentiated</td>
<td>2/19 (8.5)</td>
<td>54/637 (8.5)</td>
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*All values are number (percentage), except where otherwise indicated. †Patients described in the literature with cutaneous squamous cell carcinoma (not selected for regional lymph node metastasis).

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tumor thickness was found to be 6.6 mm, further supporting a higher rate of metastasis in thicker lesions.\textsuperscript{13} Approximately equal numbers of patients in our study and the historical control group had poorly differentiated index primary tumors. Although comparing the characteristics in the selected group of patients with regional metastasis with those of past studies of nonselected patients with cutaneous SCC is a method with limited statistical power, it confirms the observation that tumor size, depth, and immune status are related to the development of regional metastasis from cutaneous SCC. A high index of suspicion in these risk groups necessitates careful examination of the neck to detect cervical lymph node metastasis at an early stage.

In this study, the mean time between treatment of the primary and development of clinically detectable regional lymph node metastasis was 13 months (range, 0-36 months). In previous studies,\textsuperscript{11} 69% of regional lymph node metastases became clinically apparent in 1 year and more than 90% became apparent within 3 years. Late regional metastases, however, have been reported up to 5 years after the primary.\textsuperscript{11} Physicians treating patients with cutaneous SCC must establish continued long-term follow-up, including a thorough examination of the regional lymph nodes.

Several studies have concentrated on the subset of patients with parotid gland metastasis from cutaneous SCC. Conley and Arena\textsuperscript{14} presented 30 patients with cutaneous SCC metastasizing to the parotid gland. They found that cutaneous SCC most commonly metastasized to the intraglandular parotid lymph nodes.\textsuperscript{14} According to Graham,\textsuperscript{15} the intraglandular lymph nodes are located lateral to the posterior facial vein and can be superficial or deep to the facial nerve. In a study of cadaver dissections, McKean et al\textsuperscript{16} found 2 to 22 nodes superficial to the facial nerve, while only 0 to 4 nodes were deep to the facial nerve. The extent of parotidectomy for metastatic cutaneous SCC remains controversial. Most authors\textsuperscript{15,17,18} believe that superficial parotidectomy is inadequate to address the intraglandular lymph nodes that may be deep to the facial nerve and have found a high rate of recurrence with superficial parotidectomy alone. Others\textsuperscript{18} claim that the lymphatic tissue deep to the facial nerve is of limited clinical significance in the case of metastatic disease to the parotid gland. Previous studies\textsuperscript{17,18} have shown that superficial parotidectomy alone

\begin{table}
\centering
\caption{Prevalence of Nodal Metastasis by Site in 45 Patients With Regional Metastasis}
\begin{tabular}{llllllllll}
\hline
Primary Site & Neck Nodes, Positive Levels & & & & & & & & & Parotid Gland \\
& & I & II & III & IV & V & ST & Intraparotid & Periparotid \\
\hline
Anterior scalp & 12 & 0 & 5 & 2 & 2 & 2 & 3 & 10 & 6 & 4 \\
Posterior scalp & 1 & 0 & 0 & 0 & 0 & 0 & 0 & 1 & 1 & 1 \\
Eyelid & 2 & 0 & 1 & 0 & 0 & 0 & 1 & 2 & 1 & 1 \\
Cheek & 2 & 1 & 1 & 0 & 0 & 0 & 0 & 2 & 0 & 1 \\
Nose & 8 & 6 & 3 & 4 & 0 & 0 & 1 & 1 & 0 & 0 \\
Lip & 3 & 3 & 2 & 2 & 0 & 0 & 0 & 0 & 0 & 0 \\
Ear or preauricular area & 16 & 3 & 8 & 4 & 0 & 2 & 7 & 8 & 2 & 2 \\
Anterior aspect of the neck & 1 & 0 & 0 & 0 & 0 & 0 & 1 & 0 & 0 & 0 \\
Total & 45 & 13 & 20 & 12 & 2 & 4 & 13 & 24 & 9 & 9 \\
\hline
\end{tabular}
\end{table}

\textsuperscript{*}ST indicates soft tissue invasion (ie, skeletal muscle or fibroadipose tissue of the neck).
has significantly worse locoregional control rates (25%-63%) compared with superficial parotidectomy followed by postoperative RT (80%-89%). In our series, just more than half (54%) of the patients underwent total or subtotal parotidectomy and the vast majority received postoperative RT. Intraparotid (n = 9) and periparotid (n = 9) metastasis occurred with equal frequency. The small number of patients undergoing parotidectomy precluded any meaningful statistical analysis with regard to the extent of surgery.

While several studies have characterized the treatment outcome of patients with parotid metastasis from cutaneous SCC, few have documented the results following neck dissection for regional lymph node metastasis. Tavin and Persky\(^7\) retrospectively reviewed 37 patients with regional metastasis from cutaneous SCC. Patients with neck metastases made up 62% of their population and 31 patients were treated for cure. The 5-year disease-free survival rate was 36% and patients were treated with either surgery alone (n = 13), RT alone (n = 2), or a combination of surgery and RT (n = 16). Because of the limited study size, a statistically significant difference in survival could not be demonstrated between the treatment groups. Joseph et al\(^9\) retrospectively reviewed 34 patients with metastatic cutaneous SCC of the trunk and extremities, with 21 patients treated for cure. An overall survival rate of 29% was found and adverse histological findings, such as multiple node metastasis, extracapsular spread, vascular invasion, and perineural invasion, were associated with regional recurrence and poor survival. Regional failures without evidence of distant metastasis occurred in 42% of patients. In the largest series, Khurana and colleagues\(^20\) performed a combined retrospective and prospective study of 75 patients with parotid and neck metastasis from cutaneous SCC of the head and neck. Neck dissections were performed in 59 of these patients. They found that positive surgical margins of the parotidectomy or neck dissection specimens were associated with a poor local control. Recurrences occurred in 43% of their patients at 1 year. Although they did not find any benefit in disease control from postoperative RT, their study was limited by its retrospective design, with patients with more advanced disease more likely to receive RT, and the limited number in the nonirradiated arm. In our study of 45 patients, 5-year disease-free survival (34%) was similar to previous reports (29%-36%).\(^7,19\) The only factor that predicted improved survival was clinical stage of the regional metastasis. Patients with N1 disease did significantly better (P<.01), with a 5-year disease-free survival rate of 53%.

Several studies\(^11,17,18\) have reported improved survival and locoregional control with postoperative RT in treating patients with parotid metastasis and have advocated its use in patients with regional metastasis from cutaneous SCC. Most of these studies, however, only look at parotid metastasis and were retrospective, which limits their ability to detect a benefit from RT because a higher percentage of patients with advanced disease and poor prognostic signs would receive postoperative RT. The few studies\(^7,20\) that have examined regional metastasis from cutaneous SCC, including the parotid gland and neck, have failed to show any significant difference in survival based on postoperative RT. These studies have also been limited by their retrospective design. In determining the efficacy of postoperative RT as an adjunct in the treatment of regional metastasis from cutaneous SCC, our study was limited by the small number of patients (n = 9) who did not receive postoperative RT as well as its retrospective design. However, within this group of patients not receiving postoperative RT there were 2 subsets. The first was those patients with limited disease and the second was those who had received previous RT and therefore could not receive postoperative RT. Despite the small number of patients in each subgroup, the patients with limited disease forgoing postoperative RT had better survival than the patients who received previous RT and could not receive additional postoperative RT (P<.05). Although conclusive data in the form of a prospective randomized study establishing the role of combination therapy for metastatic SCC of the skin do not
Results from our study concur with previous findings that patients with impaired immune systems and deeply invading (>4 mm), large (>2 cm in diameter), and locally recurrent tumors are at the greatest risk for developing regional lymph node metastasis from cutaneous SCC. Survival in patients with regional lymph node metastasis from cutaneous SCC remains poor. Clinical stage of the regional metastasis is the only factor predicting survival. Future directions include identification of regional lymph node metastasis at an earlier stage (N1) in patients at greatest risk. The use of multimodal therapy (surgery and RT) is the standard of care for this cohort with poor prognosis.

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REFERENCES