

Metastatic Cutaneous Squamous Cell Carcinoma Involving the Parotid Gland: Experience Outside of the Sun Belt

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Abstract

Objective. To characterize a subset of patients with metastatic head and neck cutaneous squamous cell carcinoma in a tertiary North American center and describe oncologic outcomes following definitive treatment.

Study Design. Retrospective chart review.

Setting. National Cancer Institute–designated Comprehensive Cancer Center.

Methods. We conducted a retrospective chart review of patients with cutaneous squamous cell carcinoma with metastases to intraparotid lymph nodes who underwent parotidectomy between 1993 and 2020. Baseline patient and tumor characteristics were assessed. Regional control, disease-specific survival, and overall survival were estimated using Kaplan-Meier method. Multivariate analysis was used to determine the relationship between adverse pathological features and survival.

Results. A total of 122 patients were included. The median age was 76, 84.4% of patients were male, and 17.2% were immunosuppressed. Regional control, disease-specific survival, and overall survival were 68.5%, 70.7%, and 59.4% at 5 years, respectively. Perineural and lymphovascular invasion were predictive of worse disease-specific survival. Extracapsular spread was observed in 90.2% of patients and was not a significant predictor of outcome.

Conclusions. We found the demographics and oncologic outcomes of our cohort in the Northeast United States to be comparable with those previously reported in Australia and the Sun Belt of the United States. We noted a high rate of extracapsular spread but did not find it to be a significant predictor of recurrence or survival. Future efforts should address the impact of extracapsular spread on prognosis and adjuvant treatment decisions.

Keywords

parotid, cutaneous squamous cell carcinoma, prognostic indicators, outcomes

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Nonmelanoma skin cancer is the most prevalent cancer worldwide.¹ Although the precise incidence is difficult to ascertain, it is estimated that 5.4 million new cases in 3.3 million patients are diagnosed each year in the United States alone.^{2,3} Cutaneous squamous cell carcinomas (cSCCs) account for 20% of these cases,^{3,4} of which 70% to 80% arise in the head and neck region.^{5,6} Nodal metastases occur in up to 5% of patients^{7,8} and are more commonly associated with lesions arising on the temple or ear regions of the head and neck.^{9,10} These lesions typically metastasize to the parotid gland.¹¹

The incidence, risk factors, and natural history of intraparotid metastatic cSCC are well documented in Australia and New Zealand, where it accounts for the majority of malignant parotid lesions.¹² Comparable data for the North American population are sparsely reported, particularly from centers outside the “Sun Belt” region, due to a lower incidence of disease. An understanding of the similarities and differences in disease profiles across different geographical regions is vital to identifying those at risk of poor outcomes.

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The primary objective of this study was to describe the demographic profile of patients presenting to Memorial Sloan Kettering Cancer Center (MSK) with metastatic cSCC to the parotid gland and to report outcomes in this cohort. The secondary objective was to determine factors predictive of recurrence and survival.

Methods

Patient Selection

Following Memorial Sloan Kettering Institutional Review Board approval, a retrospective cohort study was conducted of all patients with a diagnosis of cSCC who underwent parotidectomy at MSK from January 1993 to January 2020. Cases were identified using *International Classification of Disease* diagnostic codes and *Current Procedural Terminology* codes. Clinical records, operative notes, imaging, and pathology reports were reviewed.

Patients were included if they had a history of primary cSCC of the head and neck and pathological confirmation of cSCC metastatic to the parotid gland. Patients were excluded if the parotid tumor was not truly a metastatic cSCC. This occurred in 3 instances, and patients were excluded if there was a primary cutaneous lesion overlying the gland with direct invasion into the parotid gland without obvious intraparotid nodal metastases, there was a primary mucosal lesion invading the gland, or if the patient had a history of mucosal SCC that was thought to be the primary site of their intraparotid metastasis (eg, advanced buccal SCC).

Treatment Details

All patients underwent surgical parotidectomy. The type of parotidectomy was determined by the extent of disease and surgeon preference. Concurrent therapeutic neck dissection was performed in all patients with clinical cervical nodal involvement, and elective neck dissection was performed at the discretion of the operating surgeon.

Cases were discussed in a multidisciplinary tumor board to identify patients who would benefit from adjuvant treatment. All patients with intraparotid metastases met the criteria for postoperative radiotherapy. Adjuvant platinum-based chemoradiotherapy was offered at the discretion of the multidisciplinary team to patients with involved margins, extracapsular spread (ECS), parotid or cervical lymph nodes, or other high-risk features as determined by the multidisciplinary team.

Outcomes

The primary outcome was regional control rate (including both the parotid bed and neck). Secondary outcomes were overall survival (OS) and disease-specific survival (DSS). Outcomes were measured starting at the time of surgery to the time of an event (recurrence or death) or to the last follow-up (whichever was later).

Table 1. Patient and Treatment Characteristics of Patients With Metastatic Cutaneous Squamous Cell Carcinoma Involving the Parotid Gland.

| Characteristic | No. of Patients (n = 122) | % |
|---|------------------------------|-------|
| Age, median (range), y | 76 (35-93) | |
| Sex | | |
| Male | 103 | 84.4 |
| Female | 19 | 15.6 |
| Immunosuppression | | |
| Yes | 21 | 17.2 |
| No | 101 | 82.8 |
| Location of primary | | |
| Cheek | 20 | 16.4 |
| Temple | 18 | 14.8 |
| External ear | 17 | 13.9 |
| Forehead | 13 | 10.7 |
| Preauricular | 12 | 9.8 |
| Periorbital | 10 | 8.2 |
| Scalp | 4 | 3.3 |
| Postauricular | 4 | 3.3 |
| Nose | 1 | 0.8 |
| Lower lip | 1 | 0.8 |
| Multiple sites or unknown | 22 | 18.0 |
| Treatment | | |
| Surgery | 122 | 100.0 |
| Surgery + adjuvant radiotherapy only | 94 | 77.0 |
| Surgery + adjuvant platinum-based chemoradiotherapy | 20 | 16.4 |

Statistical Analysis

Survival analyses were performed using Kaplan-Meier curves starting at the date of surgery. The log-rank test was used to compare survival outcomes. Cox regression analysis was used for multivariate comparison for all variables with $P < .05$ on univariate analysis. All analyses were performed using SPSS Statistics v.25 (Windows) software (SPSS, Inc). Statistical significance was set at an α level of $<.05$.

Results

Patient Characteristics

A total of 122 patients met inclusion criteria. The median age was 76 years, and the male to female ratio was 5:1 (Table 1). Immunosuppression was identified in 21 patients and was secondary to lymphoproliferative disorder (n = 15), solid organ transplant (n = 4), immunosuppressive medications (n = 1), or HIV/AIDS (n = 1). The median duration of follow up was 2.6 years (range, 2 months to 25 years).

The primary lesion site was in the upper or midface in 74 patients (60.7%). Seventeen patients (13.9%) had a

Table 2. Pathological Characteristics of Patients With Metastatic Cutaneous Squamous Cell Carcinoma Involving the Parotid Gland.

| Characteristic | No. of Patients (n = 122) | % |
|--------------------------------------|------------------------------|------|
| Number of intraparotid metastases | | |
| 1 | 61 | 50.0 |
| ≥2 | 61 | 50.0 |
| Histological grade ^a | | |
| Well differentiated | 4 | 3.3 |
| Moderately differentiated | 62 | 50.8 |
| Poorly differentiated | 48 | 39.3 |
| Unknown | 8 | 6.6 |
| Extracapsular spread ^a | | |
| No | 12 | 9.8 |
| Yes | 110 | 90.2 |
| Perineural invasion ^a | | |
| No | 47 | 38.5 |
| Yes | 61 | 50.0 |
| Unknown | 14 | 11.5 |
| Lymphovascular invasion ^a | | |
| No | 83 | 68.0 |
| Yes | 25 | 20.5 |
| Unknown | 14 | 11.5 |
| Margin ^a | | |
| Clear | 40 | 32.8 |
| Close ≥0-1 mm | 24 | 19.7 |
| Involved | 36 | 29.5 |
| Unknown | 22 | 18.0 |
| Cervical nodal metastases | | |
| N0 | 64 | 52.5 |
| N+ | 50 | 41.0 |
| Unknown | 8 | 6.6 |

^aHistological features relating to the parotid metastasis only.

primary lesion of the external ear. The primary site was unknown in 22 patients (18.0%), some of whom had multiple documented lesions removed from the head and neck region (**Table 1**). The median time from identification of the primary lesion to diagnosis of parotid metastases was 10 months (range, 0-72 months).

Pathology

The pathological features of the parotidectomy specimen are detailed in **Table 2**. On histological examination, a single focus of cSCC was found within the parotid gland in 61 patients (50%), and multiple foci were found in the remaining 61 (50%). An overwhelming majority of the intraparotid nodal deposits displayed evidence of ECS (90.2%). Surgical margins of the parotid specimen were involved in 36 cases (29.5%), of which 32 were R1 and 4 were R2 resections.

Neck dissections were performed in 114 patients (93.4%), of whom 50 had cervical nodal metastases upon pathological examination (43.9%). Of the 76 patients who were clinically N0 preoperatively (based on a combination

of clinical and radiological examination), 12 patients (15.8%) were found to have occult cervical metastases.

Survival Outcomes

Parotid recurrence occurred in 23 patients (18.9%), and cervical recurrence occurred in 13 patients (10.7%). Both parotid and cervical recurrence occurred in 4 patients (3.3%). Median time to parotid recurrence was 7 months (range, 1-62 months), and cervical recurrence was 9 months (range, 5-45 months). Regional control at 2 and 5 years was 73.3% and 68.5%, respectively. Distant metastases occurred in 58 patients (47.5%) within a median time of 20 months (range, 0-71 months). Outcomes are illustrated in **Figure 1**.

Median OS was 79 months (95% CI, 63-95 months). OS and DSS at 2 years were 72.9% and 80.1%, respectively. Five-year OS and DSS were 59.4% and 70.7%, respectively.

Factors Predictive of Recurrence and Survival

After adjustment for relevant covariates, we found that none of the histological features of the parotid disease were predictive of regional control outcomes (**Table 3**). Furthermore, the extent and location of regional metastases (including multifocal parotid metastases and/or cervical nodal involvement) also failed to predict regional control (**Table 3**). Perineural and lymphovascular invasion were predictive of worse DSS ($P = .032$ and $P = .024$, respectively). Patients with ECS trended toward worse DSS, but this did not reach significance ($P = .091$). Other patient factors (including immunosuppression), histological findings, and adjuvant treatment were not predictive of survival outcomes. Specifically, the addition of adjuvant chemotherapy to postoperative radiotherapy did not improve parotid recurrence-free survival, DSS, or OS in our cohort (**Figure 2**).

Discussion

This study represents one of the largest series in North America of patients with metastatic cSCC to the parotid gland. Our results provide an updated, comprehensive survey of the demographic profiles of this disease and the factors that may affect recurrence and survival for these patients. The median age in our patient cohort was 76 years, and males accounted for 84.4% of patients. These findings are similar to those reported in other single and multi-institution studies originating from North America,¹³⁻²⁰ Australia,²¹⁻²⁸ and New Zealand.²⁹⁻³¹

We noted an overall immunosuppression rate of 17.2%, secondary to organ transplants, lymphoproliferative disorders, HIV/AIDS, and immunosuppressive medication. Our findings are similar to the 11% to 25% immunosuppression rates described in other studies.²⁹⁻³² Prior studies have also reported a high prevalence of immunosuppression among patients with metastatic cSCC of the head and neck.^{27,31-34} The link between immunosuppression and worse survival outcomes is well established.^{6,16} In line with prior publications, we did not include conditions such as end-stage renal disease or uncontrolled diabetes in our criteria for

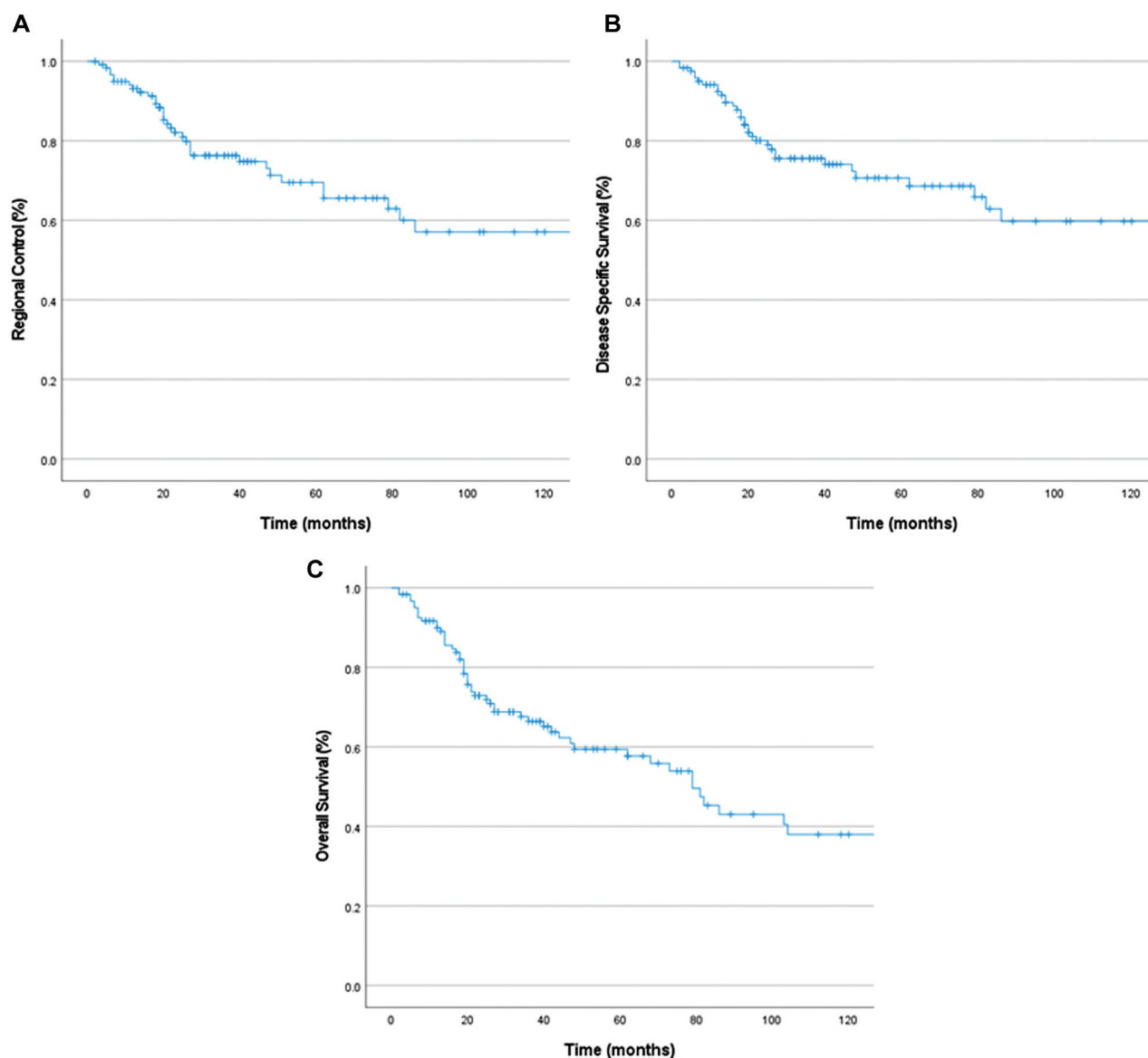


Figure 1. Survival outcomes in patients with metastatic cutaneous squamous cell carcinoma involving the parotid gland treated with surgery. (A) Regional control. (B) Disease-specific survival. (C) Overall survival.

Table 3. Prognostic Factors for Regional Control in Patients With Metastatic Cutaneous Squamous Cell Carcinoma Involving the Parotid Gland.^a

| Characteristic | Univariable analysis | Multivariable analysis HR (95% CI), P value |
|--------------------------------|----------------------|---|
| Age (<70 vs >70 years) | 0.642 | |
| Sex | 0.126 | |
| Immunosuppression | 0.947 | |
| Multiple intraparotid deposits | 0.602 | |
| Cervical nodal involvement | 0.928 | |
| Histological grade | 0.087 | |
| Extracapsular spread | 0.105 | |
| Perineural invasion | 0.004 | 2.327 (0.976-5.532), P = .056 |
| Lymphovascular invasion | 0.216 | |
| Positive margins | 0.037 | 1.684 (0.801-3.540), P = .169 |
| Adjuvant radiotherapy | 0.685 | |
| Adjuvant chemoradiotherapy | 0.794 | |

^aThe histological features refer to those of the intraparotid metastasis. Bold values indicate statistical significance.

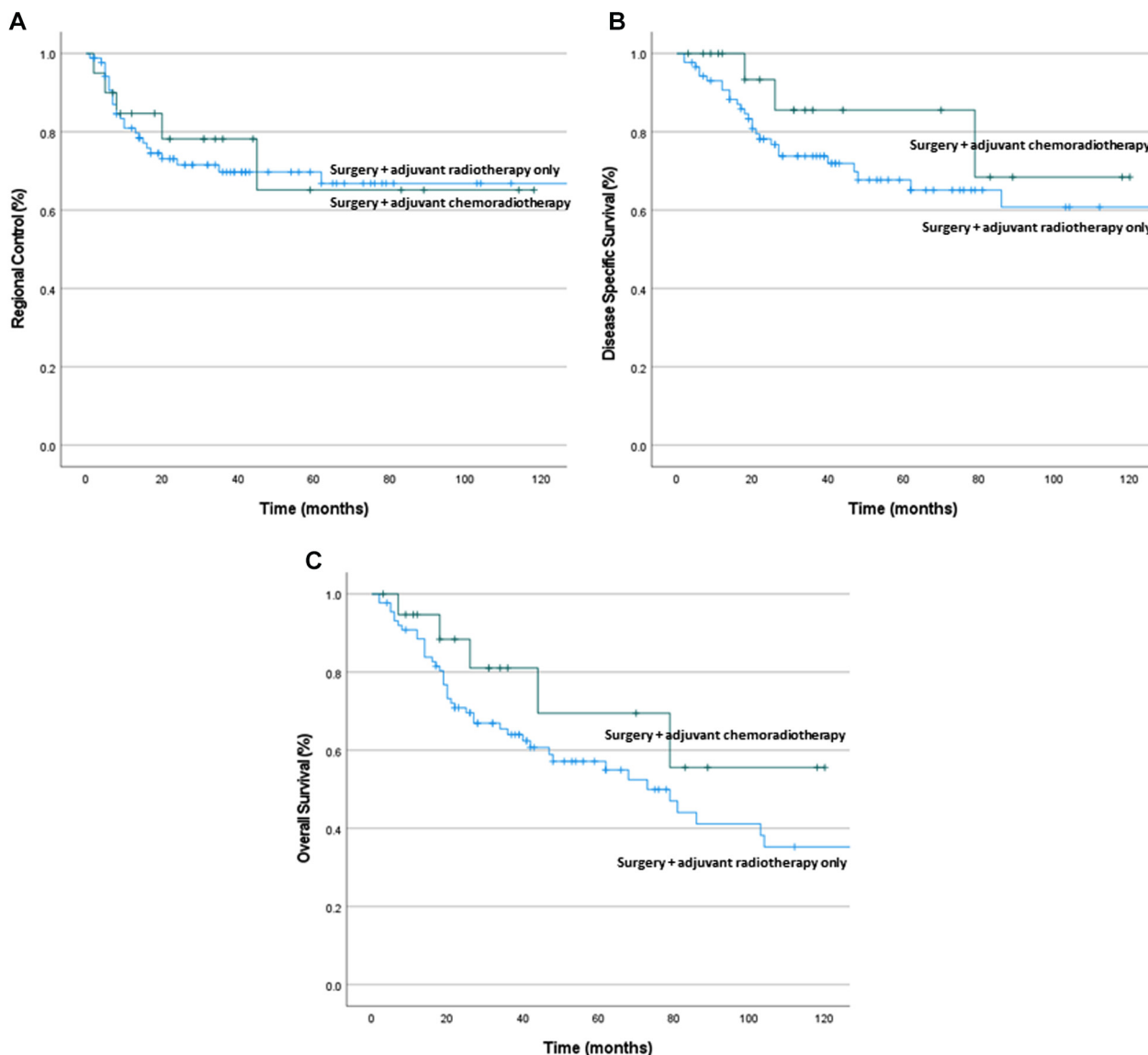


Figure 2. Survival outcomes in patients with metastatic cutaneous squamous cell carcinoma involving the parotid gland treated with surgery. (A) Regional control. (B) Disease-specific survival. (C) Overall survival.

immunosuppression, although these too have been shown to be associated with a higher rate of nonmelanoma skin cancer.^{35,36}

Our results did not show significantly worse outcomes among immunosuppressed patients, which is in contrast to prior findings.^{27,29-32} The reason for this discrepancy is unclear; however, the overwhelming evidence points to the importance of immune status on oncologic outcomes and deserves further evaluation. It is important to note that estimating rates of immunosuppression among patients with cSCC may be difficult due to the lack of standardized criteria for defining immunosuppression.

We noted a relatively high rate of involved surgical margins, likely due to the proximity of the metastatic nodal deposits to the facial nerve. It is our institutional practice to preserve a functioning facial nerve whenever possible.

Consequently, it is sometimes necessary to peel tumor off the nerve, resulting in a microscopically positive tumor margin. Our results showed a trend toward worse regional control in patients with positive margins, although this did not reach significance. Margin status was also not prognostic for survival outcomes. This is in contrast to other studies in which close and positive margins were associated with worse survival.^{23,27} The potential for recurrence should be carefully balanced against the morbidity of facial nerve sacrifice. It is our opinion that the preservation of facial nerve function justifies the slightly increased risk of recurrence in many cases. The benefit of adjuvant chemotherapy in addition to radiotherapy in the setting of involved margins in cSCC remains uncertain.³⁷ Our data failed to show an improvement in local control or survival outcomes with the addition of adjuvant chemotherapy.

Neck nodes were pathologically positive in 43.9% of patients with parotid metastases who underwent neck dissection. This rate of nodal positivity is similar to that observed in other studies.^{21,38} The rate of occult cervical metastasis in patients with clinically N0 necks was 15.8%. This is consistent with the findings of other authors who have reported occult nodal positivity in 15% to 24% of elective neck dissections.^{24,25,39} Given the high incidence of positive nodes and concern for occult metastases, we recommend elective neck dissection in all patients with intraparotid metastatic cSCC. The levels required depend on the location of the primary tumor.^{40,41}

Our rates of parotid and cervical recurrence and survival outcomes approximated those previously reported in the literature.⁶ There was a roughly 10% difference between the DSS and OS in our cohort, which is likely attributable to the fact that this disease predominately affects elderly patients, and therefore, the incidence of death from other causes is expected to be relatively high.

We evaluated pathological features that are predictive of local or regional recurrence. ECS, perineural invasion, and involved or positive margins have been shown in other series to be predictive of regional recurrence.⁶ However, none of these features predicted regional recurrence in our cohort. Despite this, we found both perineural and lymphovascular invasion to be prognostic for DSS.

The lack of prognostic significance of ECS in patients with intraparotid metastatic cSCC is surprising. One possible explanation for this finding may be the high overall rate of ECS among our patient cohort (90.2%). The high prevalence of this finding reduces its usefulness as a risk-stratifying feature. Other series report ECS in 78% to 88% of patients, which is similar to our observed rate.^{11,27,30} The presence of ECS is recognized as a high-risk feature in metastatic head and neck mucosal SCC⁴² and has thus been added to the American Joint Committee on Cancer (AJCC) eighth edition staging for all head and neck cancers, including cSCC.⁴³ Patients with ECS are classified as pN2a (if single ipsilateral lymph node <3 cm in size) or pN3b (if >3 cm or multiple nodes), both of which correlate with stage IV disease. Consequently, most of our patients were classified as having stage IV disease based on the presence of ECS alone.

An effective clinical staging system should demonstrate homogeneity (similar outcomes for patients within the same group), discriminatory ability (difference in survival between patient groups), and monotonicity (decreasing survival with increasing stage group). To this end, a retrospective review of 382 patients undertaken by the Sydney Head and Neck Cancer Institute sought to evaluate the prognostic efficacy of the eighth edition AJCC pathologic nodal staging system for cSCC.⁴⁴ They found that 27.7% of patients were upstaged from stage III to IV disease only on the basis of ECS and that the seventh edition AJCC system marginally outperformed the eighth edition AJCC system in terms of DSS and OS. The AJCC eighth edition did not demonstrate any risk stratification between any of the nodal

groups (including pN3), and it grouped together patients with wide variance in the size and number of involved lymph nodes.

Similarly, we found that the upstaging of our patients to pN2 and pN3 disease (and both groups to stage IV disease) was primarily driven by the presence of ECS. Given the findings of the above study and the high reported rates of ECS (in up to 88% of patients), the integration of ECS into the staging system does not appear to adequately or appropriately prognosticate up to 90% of patients with metastatic cSCC. This finding highlights the need for further research focusing on the impact of ECS in cSCC.

In addition to prognosis, the importance of defining the risk of ECS in cSCC also extends to treatment recommendations. The addition of adjuvant chemotherapy to standard postoperative radiotherapy has been shown to result in better survival outcomes in patients with head and neck mucosal SCC.^{42,45,46} This finding has been extrapolated to support the use of adjuvant chemoradiotherapy in high-risk cSCC, including for patients with ECS. A recently published large randomized controlled trial from Australia comparing postoperative radiation alone with chemoradiotherapy in this setting showed no difference in survival outcomes between treatment groups.³⁷ Similarly, we found no improvement in locoregional control or survival from the addition of adjuvant chemotherapy to the standard treatment. Further subclassification of ECS in this cohort may help identify patients who will benefit from trimodality therapy and spare others from overtreatment.

In general, our treatment paradigm involves recommendation for adjuvant therapy for all patients with parotid metastases who undergo surgical intervention. In our cohort, 6.5% of patients did not undergo adjuvant radiation or chemoradiation. These patients belonged to 1 of 2 groups: those who refused radiation treatment or those who had a history of radiation to the head and neck. The decision on choice of radiation vs chemoradiation is challenging to definitively characterize in this retrospective study. Certainly, prior to the completion of the trial by Porceddu et al,³⁷ those patients who seemed to have the highest risk pathology (and were healthy enough to undergo chemoradiation) were offered this intervention after discussion in a multidisciplinary conference. Since publication of these important data, patients are now seldom offered chemotherapy.

Our study has several important limitations. First, this was a retrospective review, which is subject to missing or inaccurate data, as well as selection bias. Similarly, some outcomes (such as local recurrence) may be related to intraoperative decision making that is difficult to elucidate on retrospective review. The management of metastatic head and neck cSCC has evolved over the study period, which introduces an element of variability in treatment approaches. Within this retrospective study, it is challenging, if not impossible, to accurately explain why certain choices were made with respect to treatment (ie, postoperative radiation vs chemoradiation). Finally, while this was one of the larger patient series, the cohort size was still

relatively small and did not allow for further comparisons and analyses of risk factors, such as ECS.

Conclusion

We have reported our experience in the management of cSCC metastatic to the parotid gland at our North American institution that lies outside of the “Sun Belt” region. Within our cohort, we have found that intraparotid metastatic cSCC is primarily a disease of elderly men with OS at 5 years approximating 60%. We also observed ECS to be widely prevalent in our cohort. Based on our findings and those of other studies, we suggest that ECS is not a major discriminating factor of risk among patients with cSCC metastatic to the parotid gland. Further research into its importance in influencing both prognosis and management is needed.

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Author Contributions

Stephanie Flukes, concept, design, data collection, data analysis, data interpretation, manuscript preparation, approval of final version of manuscript; **Sallie Long**, concept, design, data collection, data analysis, data interpretation, manuscript preparation, approval of final version of manuscript; **Shivangi Lohia**, data interpretation, manuscript preparation, approval of final version of manuscript; **Christopher A. Barker**, data interpretation, manuscript preparation, approval of final version of manuscript; **Lara A. Dunn**, data interpretation, manuscript preparation, approval of final version of manuscript; **Jennifer Cracchiolo**, data interpretation, manuscript preparation, approval of final version of manuscript; **Ian Ganly**, data interpretation, manuscript preparation, approval of final version of manuscript; **Snehal Patel**, data interpretation, manuscript preparation, approval of final version of manuscript; **Marc A. Cohen**, concept, design, data analysis, data interpretation, manuscript preparation, approval of final version of manuscript.

Disclosures

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