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Prognostic Factors in Intraoral Squamous Cell Carcinoma: The Influence of Histologic Grade

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Purpose: The purpose of this retrospective study was to review the outcome of patients with oral cavity squamous cell carcinoma treated at a single institution by primary surgical resection with or without adjuvant radiotherapy or chemoradiotherapy and to identify factors affecting survival and locoregional control.

Patients and Methods: The records of 233 patients with oral cavity squamous cell carcinoma treated at a single institution from 1993 to 2003 were identified from the Legacy Emanuel Hospital and Health Center's cancer registry (Portland, OR). All patients undergoing surgical resection as a primary treatment modality were included in the study. Patients with nonresectable disease, distant metastasis, and those with inadequate follow-up data were excluded from the study. Patients with positive surgical margins, high-grade histology, aggressive biologic behavior, or advanced staged disease underwent adjuvant radiotherapy or chemoradiotherapy. The data collected included age, gender, race, tumor site, margin status, grade, TNM stage, cancer therapies, and cancer status. Data were statistically analyzed in an attempt to identify predictors of locoregional control and disease-free survival. Descriptive statistics were calculated for each variable and survival was calculated using the Kaplan-Meier method. Prognostic factors were analyzed using the Cox proportional hazard model.

Results: Two hundred fifteen patients consisting of 119 men (55%) and 123 females (52%), with an average age at diagnosis of 66 years (SD ± 14), met the criteria for inclusion in the study. Average tumor size was 23.5 mm (SD ± 14.1). Overall 5-year survival was 56% and disease-free survival at 5 years was 58%. Stage and grade were identified as having a statistically significant effect on survival ($P = .014$; likelihood ratio chi-square = 10.7, 3 degrees of freedom; and $P = .026$; likelihood ratio chi-square = 5, 1 degree of freedom, respectively). Neither age, gender, race, tumor site, nor positive margins showed a statistically significant effect on survival ($P > .05$).

Conclusion: This study highlights the importance of grade and stage as independent factors in predicting survival in patients with oral squamous cell carcinoma.

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Oral cavity squamous cell carcinoma (OCSCC) is the eighth leading cause of cancer-related death, accounting for 35,000 newly diagnosed cases in the United States per year, with approximately 8,000 deaths annually.[1,2] OCSCC continues to portend a poor prognosis, with an estimated 5-year overall survival of 56%. In the United States and Western Europe, OCSCC is treated with primary surgical excision or radiotherapy alone or in combination for advanced stage disease. Supplemental adjuvant chemotherapy is occasionally used to improve locoregional and distant disease control. Improved prognostic markers would be clinically useful in delineating the biologic aggressiveness of these tumors, and enable specific tailored therapies to be applied to each tumor.

The TNM classification of OCSCC provides a reliable basis for patient prognosis and therapeutic planning. There are a number of clinically small or undetectable primary tumors that display biologic aggressiveness with early regional metastases and death (Fig 1). Conversely, some large tumors may be slow to metastasize regionally and distantly and such patients display a disease-free posttreatment course (Fig 2). It is well recognized that the presence of cervical metastasis is the most important prognostic factor in OCSCC, accounting for a 50% reduction in patient survival for those who present with or develop cervical lymph node disease.[3,4] The TNM classification has proved to be a reliable indicator of patient prognosis with primary tumor size and cervical lymph node status being 2 of the most significant factors affecting patient survival. Typically, T1-T2 lesions are associated with a risk of regional metastasis of 10% to 30%, respectively, whereas T3-T4 lesions have a significantly higher risk of regional neck disease.[5,6] There are several attributes of the primary tumor site, in particular depth of invasion that is well recognized as having prognostic implications.[7] A greater than 15% to 20% risk of nodal disease based on primary tumor site characteristics has been the traditional level at which therapy of the N_0 neck is undertaken.

The prognostic value of the histologic grading remains controversial.[8] The most commonly used grading system for OCSCC is the Anneroth[9] classification that was further modified by Woolgar and Scott in 1995.[10] The use of histologic grade from a tissue biopsy may provide additional information regarding the biologic activity of a tumor, potentially allowing for a more comprehensive treatment approach than would be otherwise implemented using conventional therapeutic guidelines.

The purpose of this retrospective review was to analyze the outcome of patients with OCSCC treated by primary surgical resection at a single institution with or without the use of adjuvant radiotherapy or chemoradiotherapy and to identify factors, particularly in relation to histologic grade, that may affect overall 5-year and disease-free survival.

Materials and Methods

Data were retrospectively collected on all patients from the Cancer Data Registry at Legacy

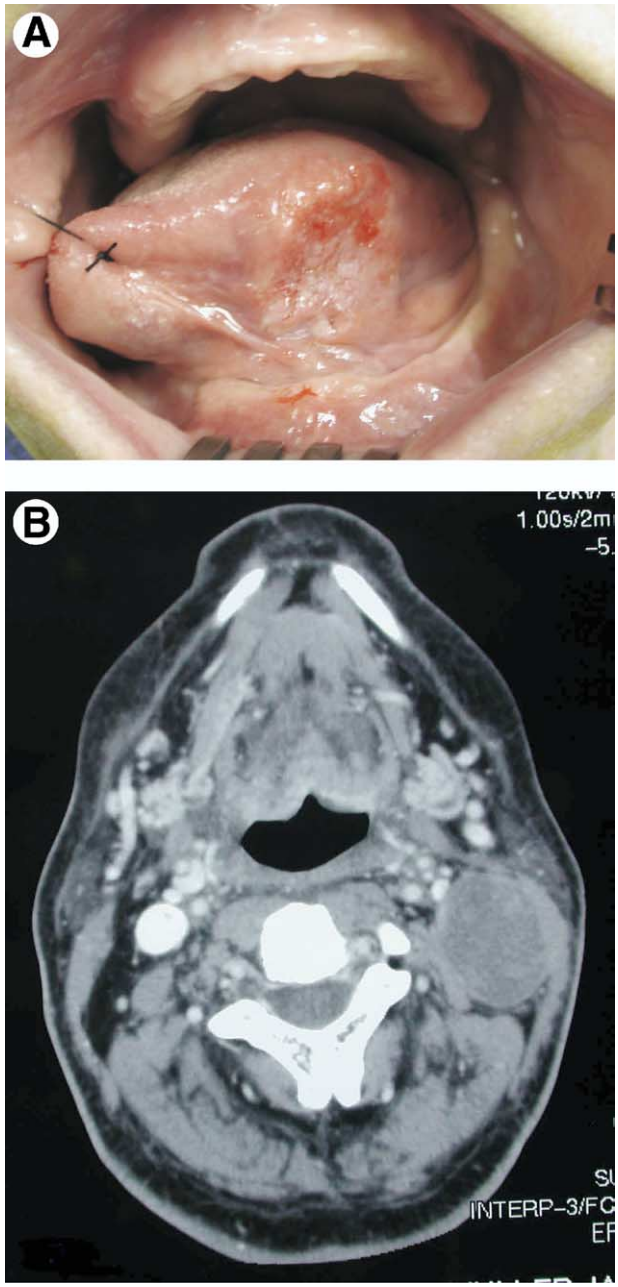

FIGURE 1. *A*, A 91-year-old woman with a T1 squamous cell carcinoma of the left lateral border of the tongue presenting with clinically cervical metastases (N_+). *B*, CT scan of a patient with an unidentified primary head and neck squamous cell carcinoma with massive jugulodigastric node metastases.

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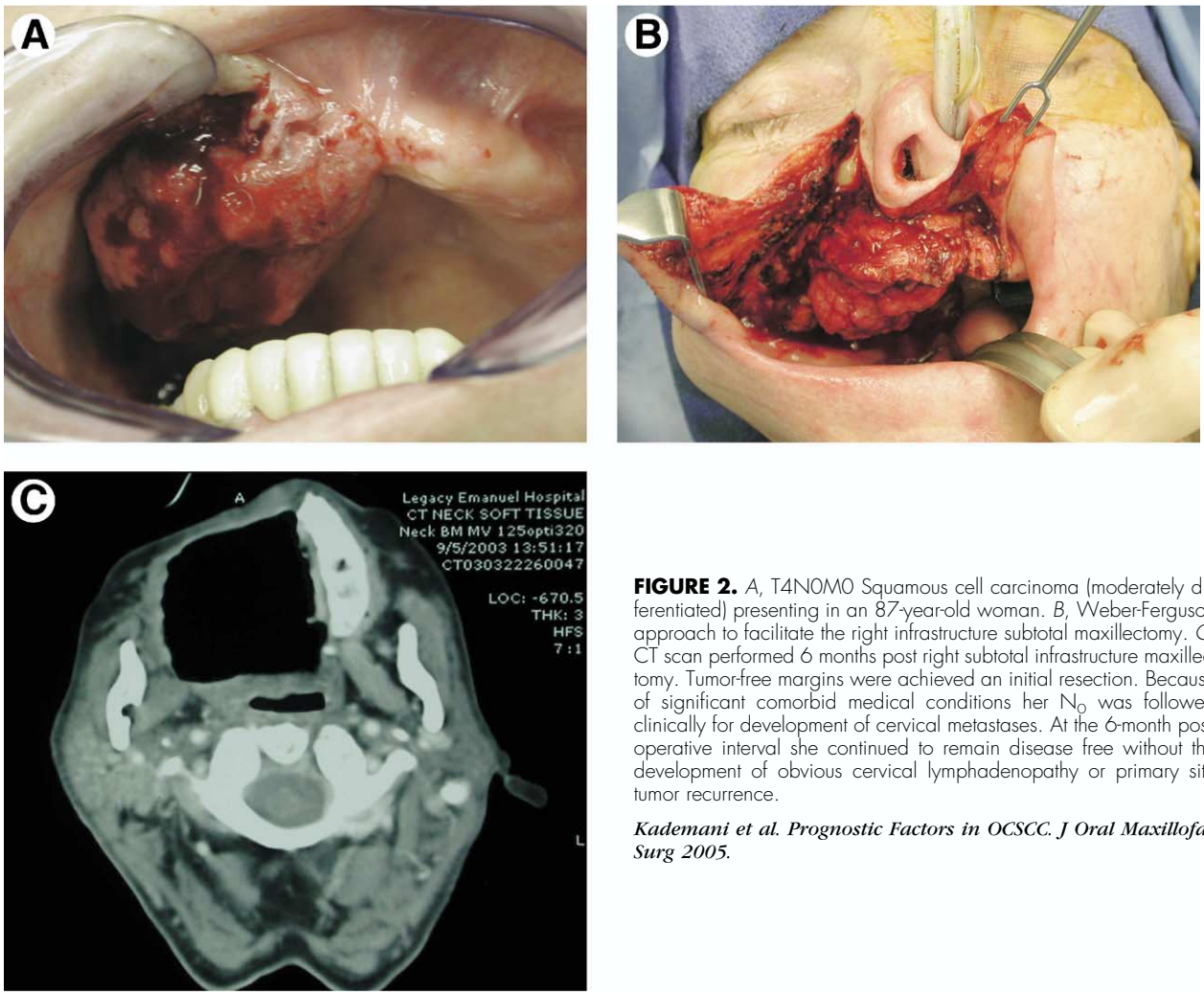

FIGURE 2. *A*, T4N0M0 Squamous cell carcinoma (moderately differentiated) presenting in an 87-year-old woman. *B*, Weber-Ferguson approach to facilitate the right infrastructure subtotal maxillectomy. *C*, CT scan performed 6 months post right subtotal infrastructure maxillectomy. Tumor-free margins were achieved an initial resection. Because of significant comorbid medical conditions her N_0 was followed clinically for development of cervical metastases. At the 6-month postoperative interval she continued to remain disease free without the development of obvious cervical lymphadenopathy or primary site tumor recurrence.

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Emanuel Hospital (Portland, OR) who presented with a primary diagnosis of OCSCC over a 10-year period from January 1, 1993 to January 1, 2003. Data collected included demographic information, site, size, TNM stage at diagnosis, histologic grade, presence of neck disease at presentation, treatment, presence or absence of positive margins, recurrence, and whether adjuvant radiotherapy or chemoradiotherapy was used for disease control. Histologic grading of tumors was based on the degree of keratinization, nuclear pleomorphism, degree of mitosis, and squamous differentiation, and was classified as either well, moderate, or poorly differentiated (Table 1). Tumors were required to display 3 out of 4 histologic criteria to be classified into a specific grade. When mixed histologic features were encountered, the predominant features were used for classification. If tumors had balanced histologic features between 2 groups the highest applicable grade was assigned to the tumor.

Inclusion criteria in the study included those patients with OCSCC that were primarily managed with ablative surgery at Legacy Emanuel Hospital and whose records and follow-up were available for review. Typical follow-up schedule was 1, 3, 6, and 12 months postoperatively in the first year, followed by every 6 months thereafter until the fifth year. Thereafter, the patient was seen on an annual basis. Tumor surveillance was completed with clinical examination and diagnostic testing using computed tomography (CT) and/or positron emission tomography scanning when tumor recurrence was suspected. Those patients treated by the authors at other hospitals and those with unresectable disease and/or inadequate follow-up were excluded from the study. Patients with squamous cell cancers arising in the lip, pharynx, or other head and neck sites were excluded. The outcome measures used as endpoints in our study included overall 5-year and disease-free survival. Descriptive statistics were cal-

TABLE 1. HISTOLOGIC GRADING SYSTEM

Degree of Keratinization	Well	Moderate	Poor
Nuclear polymorphism	Minimal	Moderate	Numerous
Mitotic activity (N0/HPF)	0–15	16–35	36–55
Invasion pattern	Pushing	Bands	Cords or islands
Stage of invasion	Borderline	Into lamina propria	Into submucosa

Data from Woolgar & Scott.[10]

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culated for each prognostic variable using the Cox proportional hazard model and survival data was calculated using the Kaplan-Meier method.

Results

Two hundred forty-two records on 233 patients were collected and reviewed. Of these, 9 patients did not undergo their primary surgery at Legacy Emanuel Hospital and were excluded. Eight patients were excluded because of incomplete medical records, leaving 225, or 93% of the patient records, that meet criteria for inclusion into the study.

The two hundred twenty-five patients consisted of 119 males (48%) and 123 females (52%), with an average age at diagnosis of 66 years (SD ± 14). Average tumor size was 23.5 mm (SD ± 14.1). All patients were treated with ablative surgical resection as the primary modality of treatment, with the aim of traditional 1 cm tumor-free margins. Intraoperative frozen section analysis to determine margin status was used among the majority of patients to ensure oncologic safety; however, the final pathology report identified the presence of close (< 2 mm) or positive margins among 32 patients or 14% of the study population. Based on the TNM classification, high-risk primary tumors with greater than a 15% to 20% risk of nodal metastases and patients who presented with node positive neck disease underwent elective neck dissection. Adjuvant radiotherapy with local dose fields of 50 to 70 Gy was used in all patients with high risk factors for locoregional disease recurrence, including close or positive margins, high-grade histology, vascular or perineural invasion, and extracapsular spread.

Follow-up ranged from 6 months to 9 years in our study population. One hundred thirteen patients (64%) were alive and free of tumor recurrence at their last follow-up. Twenty-nine patients (16%) presented with locoregional disease recurrence, with a median time of 19 months and 5 patients (3%) were never free of disease. Thirty-five patient deaths were reported because of unrelated causes in patients without the presence of tumor recurrence. Overall 5-year survival was 56% (95% confidence interval, 48% to 64%) (Fig 3) with 58% disease-free survival (95% confidence interval, 49% to 68%) (Fig 4).

Site distribution was as follows: 73 tongue (33.5%), 40 floor of mouth (18.3%), 13 palate (6.0%), 19 cheek (8.7%), 27 retromolar trigone (12.4%), 31 upper gingiva (14.2%), 12 lower gingival (5.5%), and 3 tumor of unspecified location (1%) (Fig 5). There was no evidence that primary tumor site affected survival (Cox proportional hazards, $P = .8$).

Seventy patients were identified with grade 1 histology (33%), 117 grade 2 (54%), and 28 grade 3 (13%). Using the Cox proportional hazard model, we attempted to distinguish different survival curves depending on the histopathologic grade of the primary tumor. By treating grade as a continuous variable we were able to distinguish an overall effect of grade on patient survival ($P = .026$). Mean 5-year survival with a 95% confidence interval for grade 1 ranges from 54% to 80%; grade 2, 41% to 62%; and 29% to 70% for grade 3 disease. There is clear overlap of these regions; therefore we cannot be precise about the daily survival between grades except that it correlates to a

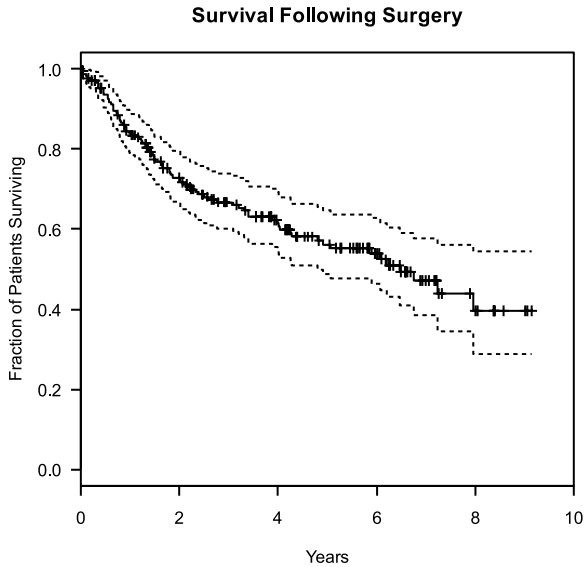

FIGURE 3. Overall 5-year survival (56%) of patients with OCSCC.

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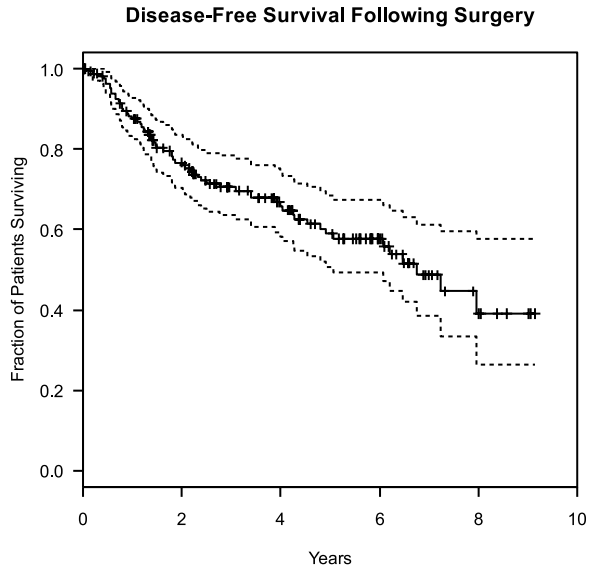

FIGURE 4. Disease-free survival (58%) in patients with OCSCC.

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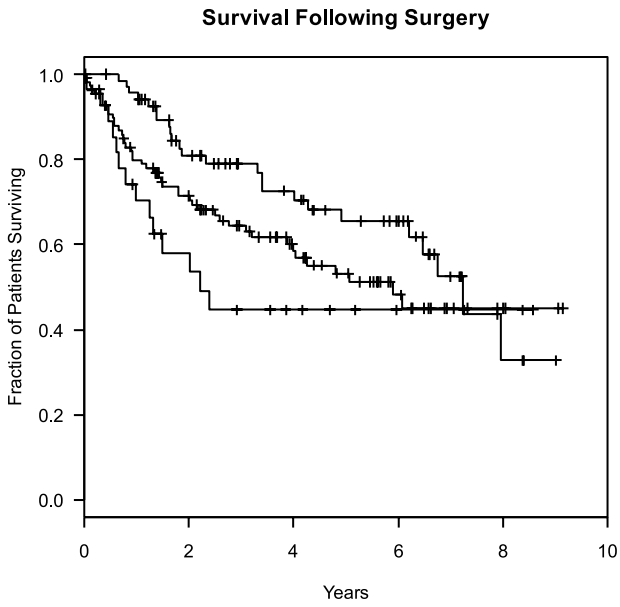

FIGURE 6. Disease-free survival following treatment correlated with histologic grade of tumor. Grade 1 is the upper curve, grade 2 the middle, and grade 3 the lower curve. There is an average decrease in patient survival of 44% per grade of tumor ($P = .026$).

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44% decrease in survival per grade with a confidence interval from 5% to 95% (Fig 6). The number (percentage) of patients in our study population presenting with neck disease according to histologic grade at diagnosis was as follows: grade 1, 6 patients (8.5%); grade 2, 30 patients (25%); and grade 3, 12 patients (48.5%) (Fig 7).

There were 106 patients presenting with stage 1 disease (49%), 40 with stage 2 (18%), 17 with stage 3 (8%), and 52 with stage 4 (24%) The Cox proportional hazard model was successful in rejecting the null hypothesis that survival curves for all stages were alike ($P = .014$). Survival differences between stage 4 and stage 1 are clearly distinguishable (Fig 8).

Close or positive margins were found in 32 patients (15%). The presence of positive margins had no influence on survival ($P = .09$). The Cox proportional hazard model gave an estimated 95% confidence interval for the daily survival ratio of clear margins to positive margins of 0.96 to 2.8. In patients with grade 1 histology, the presence of close or positive margins was seen in 4%; grade 2, 18%; and grade 3, 25% of the study group.

The most important prognostic factors influencing patient survival in our study group included stage ($P = .014$) and histopathologic grade ($P = .026$) at the time of diagnosis.

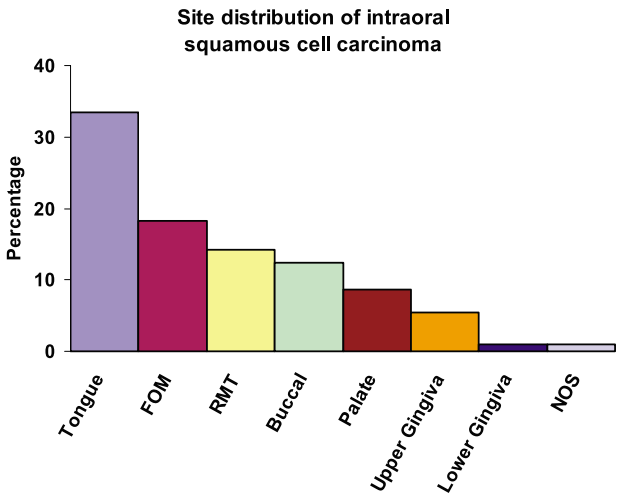

FIGURE 5. Site distribution of OCSCC.

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Discussion

OCSCC continues to have a poor overall prognosis with a strong tendency to recur both at the primary site and regionally in the cervical lymph nodes.[2,6] It is well known that OCSCC displays varying biologic behavior patterns, dependent on several host and primary tumor factors. In particular, grade was found to be a significant predictor of locoregional failure and tumor recurrence in our study population. The presence of lymph node metastasis as a marker of overall patient prognosis is valuable in predicting patient survival. The TNM staging system has been shown to be a useful prognostic tool; however, the

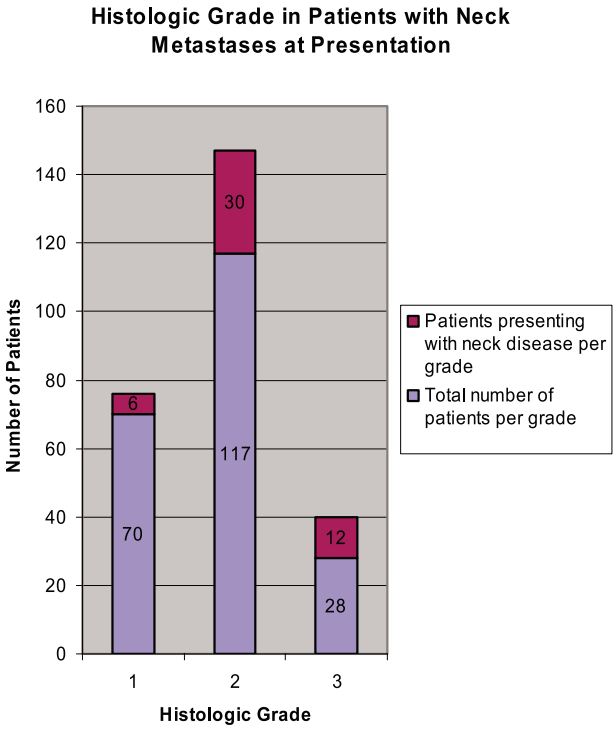

FIGURE 7. Histologic grade in patients with neck metastases at presentation.

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biologic behavior of individual tumors remains unpredictable. It is unclear why some patients with locally advanced stage disease (stage 3 and 4) are slow to develop regional metastasis, whereas some lower stage lesions (stage 1 and 2) show early and aggressive involvement of the regional lymph nodes. The ability to predict which primary lesions are capable of early metastasis would enable more individualized and aggressive therapy to be delivered to patients at higher risk of locoregional disease recurrence and death.

The treatment of OCSCC remains primarily surgical, with the addition of adjuvant radiotherapy or chemoradiotherapy for advanced stage disease or in patients at high risk of locoregional failure. All patients who presented with a diagnosis of OCSCC underwent surgical resection as a primary method of treatment. Gross tumor removal was undertaken in an attempt to obtain 1 cm tumor-free margins. Despite the use of intraoperative frozen section analysis, 15% of patients had close or positive margins on final histologic sections, which compared favorably with several large series in the literature.[11,12] Oncologic neck dissection was performed on all patients in which the risk of nodal metastases was greater than 15% to 20%.[3,13] This accounts for all primary sites of the oral cavity with tumors that are T2 (greater than 2 cm) and greater as well as patients who present with node positive neck disease at the time of diagnosis, regardless of primary tumor size, site, or histology. Patients were reconstructed with the simplest technique that would offer optimal long-term functional outcome with the least donor site morbidity. These included primary closure, locoregional rotational flaps, or composite microvascular free tissue transfer. Free tissue transfer was commonly used to reconstruct major ablative defects. Composite defects involving bone were reconstructed with a free fibula osteocutaneous flap. The radial forearm fasciocutaneous free flap was our "workhouse" flap for reconstruction of soft tissue defects.

The presence of high-grade histology, close or positive margins, multiple metastatic lymph node, extracapsular extension, and perineural or angiolymphatic invasion are indications for postoperative radiotherapy.[14,15] Using 3-dimensional conformal field techniques or intensity modulated radiotherapy, therapeutic doses of 63 Gy were delivered to the primary tumor site and cervical lymph nodes bilaterally for regional disease control.[15] Concomitant chemotherapeutic regimes were reserved for patients with locoregional recurrence, distant metastases, or as a neoadjuvant preoperative treatment with chemoradiotherapy in patients with gross T4 disease to improve resectability. We did not attempt to evaluate the effects of postoperative radiotherapy or chemoradiotherapy on survival. Patients with close or positive margins all received postoperative radiotherapy for local disease control. Despite the presence of positive margins, adjuvant therapy was able to control locoregional

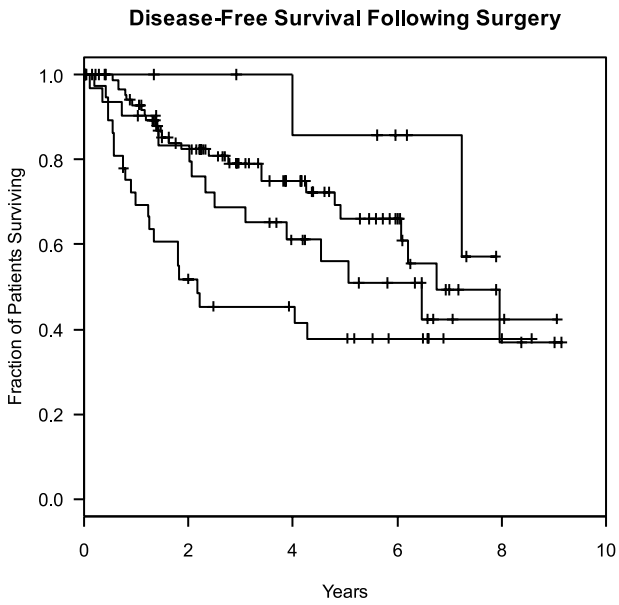

FIGURE 8. Disease-free survival correlated with stage at diagnosis. The upper curve represents stage 1 and the lower curve stage 4. There is a clear survival difference between stages 1 and 4 ($P = .014$).

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disease. No difference in survival was identified in patients with tumor-free margins versus patients with positive margins that received postoperative radiotherapy ($P = .09$).

The role of postoperative chemotherapy in the treatment of oral cavity squamous cell carcinoma is continuing to evolve. Recently, the Radiation Oncology Treatment Group and the European Radiation Oncology Treatment Group trials have shown a clear survival benefit of 11% improvement with the use of concurrent single agent chemoradiotherapy (cisplatin) in the postoperative high risk advanced stage oropharyngeal tumor patient.[16,17]

In our study population, the overall 5-year and disease-free survival compared favorably with other reports in the literature.[2,18] The unfavorable impact of stage and histologic grade as independent factors on patient survival is confirmed in this study. Tumors with high-grade (grade 3) histology, regardless of T stage and use of adjunctive treatments, were found to present with regional metastasis more frequently.[19] There was also significantly more difficulty in achieving tumor-free margins in patients with poorly differentiated carcinomas (grade 3) versus other tumor grades.

There are several limitations of our study. First, this was a retrospective chart review of patients through the Tumor Registry. Only complete medical records for patients that were treated surgically at Legacy Emanuel Hospital by the 2 senior authors (E.D. and B.P.) were included. There was a minimum follow-up period of 6 months and all recalls were performed by the 2 senior authors. The accuracy of the database is validated by the overall and disease-free survival rates that are consistent with national averages.[2,18] Second, improvements in the adjuvant treatments of OCSCC have evolved over the study period, with newer chemotherapeutic agents and more refined radiation oncology techniques such as intensity-modulated radiotherapy being used. The effects of chemoradiotherapy were not addressed because various treatment regimes have been used over the study period, resulting in few patients receiving any 1 protocol. In patients with high risk factors, adjuvant therapy was used to attempt to control for locoregional and distant disease. Despite this, we still see patients with high-grade histology doing poorly, suggesting that regardless of stage, high-grade tumors have a worse prognosis. We did not attempt to correlate stage and histology as a single variable because it is well established that patients with higher TNM stage generally have a worse prognosis.

There continues to be considerable variation in the biologic behavior of oral squamous cell carcinoma. It is imperative for the surgeon and pathologist communicate effectively regarding the histologic "impression" of the tumor using grading systems as a tool to aid in standardizing histologic diagnosis of squamous cell carcinoma. In the future, reliable biologic markers that can predict tumor behavior and aggressiveness at the biopsy stage would enable surgeons to tailor multimodal therapy to individual patients and hopefully improve patient survival. Our study clearly shows that poorly differentiated carcinoma (grade 3) is more likely to present with cervical metastases at diagnosis, has a higher likelihood of close or positive margins at time of resection, and is associated with a decrease in patient survival as compared with other tumor grades.

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