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HIGH RATES OF REGIONAL FAILURE IN SQUAMOUS CELL CARCINOMA OF THE HARD PALATE AND MAXILLARY ALVEOLUS

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Abstract

Background—The purpose of this study was to determine the incidence of neck metastasis in hard palate and maxillary alveolus squamous cell carcinoma (SCC) and to identify factors predictive of regional failure.

Methods—In 139 patients treated for SCC of the hard palate and maxillary alveolus (from 1985–2006), the incidence rates of regional metastasis at presentation and at recurrence were calculated. Factors predictive of regional recurrence-free survival were identified on Cox multivariable regression analysis.

Results—Regional failure occurred in 28.4% of patients and was significantly associated with pathologic T classification, ranging from 18.7% (pT1) to 37.3% (pT4). T classification was an independent predictor of regional recurrence-free survival (RRFS) on multivariable analysis. Most patients (65.6%) with regional recurrence were not able to be salvaged.

Conclusion—Patients with T2 to T4 primary tumors of the hard palate and maxillary alveolus exhibited high rates of regional failure. In most cases, successful salvage was not achieved. Elective treatment of the neck with surgery or radiation is therefore recommended.

Keywords

cervical; regional; neck; metastases; hard palate; alveolus; gingiva

The risk of neck metastasis in squamous cell carcinoma (SCC) of the hard palate and upper (maxillary) alveolus has not been well defined but has traditionally been believed to be low. Therefore, the node-negative neck is usually observed, rather than electively treated. Historical studies have reported variable outcomes but are difficult to interpret because hard and soft palate tumors were often grouped together, as were maxillary and mandibular alveolus tumors.^{1–9} Because of the relative rarity of these cancers, the contemporary literature consists entirely of small case series lacking survival or other outcome analyses.^{10–14} The rate of clinical and occult neck metastases arising from these primary sites has not been systematically studied, and prognostic factors have yet to be defined. Our objectives were to determine the incidence and characteristics of regional failure in these patients and to identify patient or tumor-related characteristics which are predictive of regional recurrence.

PATIENTS AND METHODS

One hundred thirty-nine patients with SCC of the hard palate, maxillary gingiva, and maxillary alveolar ridge were identified from a pre-existing database of oral cavity SCC cases treated at Memorial Sloan–Kettering Cancer Center between the years 1985 and 2006. Patient, tumor, and treatment characteristics were recorded for each patient in a clinical database and were individually validated in primary hospital medical records for this study. Patients with tumors from adjacent subsites, such as the maxillary sinus, buccal mucosa, or oropharynx, extending to the hard palate or alveolar ridge, were not included. Institutional Review Board approval was obtained in advance of the study.

The rate of regional nodal metastasis at presentation and rates of regional failure were calculated. Two types of regional failure were analyzed: regional recurrence and isolated regional recurrence. Regional recurrence was defined as the development of biopsy-proven neck metastases at any time after definitive treatment, in the absence of a second primary head and neck cancer. Isolated regional recurrence was defined as the development of neck metastases in patients without prior neck metastases, in the absence of prior or synchronous failure at the primary site or a distant site.

The cumulative incidences of regional recurrence and isolated regional recurrence were calculated using the Kaplan–Meier method, censoring patients at the time of death or at the development of a second primary cancer. For the incidence of isolated regional recurrence, patients were also censored at the time of local, locoregional, or distant failure. Patients undergoing treatment for regional recurrence were considered to be successfully salvaged if they remained alive without evidence of disease for a minimum period of 24 months.

Disease-specific survival in the presence or absence of regional recurrence was calculated using the Kaplan–Meier method. Patients dying with primary or recurrent disease were counted as disease-specific deaths. Patients lost to follow-up or discharged to their home physician were censored with their last known vital status at the time of their last examination at Memorial Hospital. Any patients lost to follow-up and subsequently registered as deceased were only coded as dying without evidence of disease if they had 60 months of documented disease-free follow-up and an examination within 6 months of their date of death; otherwise, they were censored for disease-specific survival at the time of their last visit.

Regional recurrence-free survival (RRFS) was also calculated using the Kaplan–Meier method. This was defined as the probability of remaining alive and free of neck recurrence. Variables examined for association with RRFS included age, sex, tobacco use, alcohol use, tumor subsite, depth of invasion, histologic grade, margin status, perineural invasion, lymphovascular invasion, pathologic tumor classification, pathologic nodal classification, and use of adjuvant radiotherapy. The log-rank statistic was used for univariate analysis, and Cox proportional hazards regression was used for multivariable analysis. Categorical comparisons were carried out using the chi-square statistic or Fisher exact test. In all cases, the level of alpha was set at 0.05 a priori. All analyses were performed in SPSS version 17.0 (SPSS, Chicago, IL).

RESULTS

Median follow-up time was 57.6 months (range, 1–222). Patient and tumor characteristics are summarized in Table 1. One hundred six patients (76.3%) were over age 60, and 57 patients (41%) were men. Fifty-nine patients (53.2%) were former or active smokers, and 73 (68.9%) were alcohol users. Most tumors (89; 64%) originated from the maxillary alveolus.

At presentation, 36 tumors (29.8%) were clinically classified cT4, and 12 patients (8.6%) were clinically node-positive.

Treatment and pathology details are summarized in Table 2. Eighty-six patients (61.9%) were treated with surgery alone, and 48 (34.5%) with surgery plus adjuvant radiation or chemoradiation therapy. Few patients were triaged to nonsurgical therapy. Five patients (3.6%) not receiving surgery included 2 patients presenting with distant metastases, 2 with locally unresectable disease, and 1 with synchronous lung cancer. On pathological examination, 62 tumors (46.3%) were classified pT4, indicating that half of T4 tumors were clinically understaged at the primary site.

Of the 12 patients who were clinically node-positive at presentation, neck dissections were performed in 11. One patient with an unresectable primary tumor was treated with concurrent chemoradiation. Nine of 11 patients (82%) had confirmed nodal metastases on pathological examination. An additional 8 elective neck dissections were carried out at the attending surgeon's discretion, generally in cases with unusually large primary tumors, or if the neck was entered for microvascular free flap reconstruction. Of 8 elective neck dissections, 2 (25%) harbored occult metastases.

Thirty-two of the patients (29.5%) who were node-negative at presentation recurred in the neck. Two of the patients (18.2%) who were node-positive at presentation also recurred in the neck. The mean time to neck recurrence was 6.2 months (95% confidence interval, 4.6–7.8). Among the 32 initially node-negative patients who developed regional recurrence, there were 7 cases of antecedent local recurrence, 3 cases of locoregional recurrence, and 22 cases of isolated regional recurrence. Therefore, the incidence of isolated regional recurrence in initially node-negative patients was 20.6%, as calculated using the Kaplan–Meier method. Among the 22 patients experiencing isolated regional recurrence, none had received postoperative radiation to the neck, although 2 patients (9.1%) received radiation to the primary site only.

Table 3 details the distribution of cervical metastases on clinical examination and imaging, and on pathologic review among those patients undergoing neck dissection. Comparing rates of neck metastasis at presentation and at recurrence, there was no difference in N classification ($p = .55$) or in neck levels involved ($p = .60$). Clinically apparent involvement of levels IV and V was infrequent. However, patients undergoing neck dissection for recurrence were found to harbor level IV disease in 18.1% of cases. Among patients undergoing neck dissection for regional recurrence, pathologic extracapsular extension was identified in 17 of 19 specimens (89.5%). This was more frequent than the incidence of extracapsular extension at presentation, which was noted in 3 of 9 specimens (33.3%; $p = .004$).

The Kaplan–Meier plot of regional failure rate, stratified by T classification, is shown in Figure 1. The rate of neck failure was highest in patients classified pT4 (38.1%). Altogether, 43 patients (37.7%) developed cervical metastases during their disease course, either at presentation or recurrence. The cumulative incidence of cervical metastasis, both at initial presentation and subsequently, is stratified by T classification in Table 4. There was an escalating risk of cervical metastasis with advancing pathologic T classification ($p = .007$). Of note, tumors classified pT2 to T4 demonstrated rates of regional failure over 20%. More than half of the patients (52.9%) with pT4 tumors developed neck metastases at some point, either at presentation or recurrence. For comparison, neck failure rates limited to isolated regional recurrence are shown in Table 5. In pT4 tumors, 30.4% of patients, in whom the primary site had been controlled, developed recurrence in the neck.

At 5 years, the rate of RRFS among all patients was 59.2%. RRFS stratified by pathologic tumor classification is shown in Figure 2. Five-year RRFS was 81.3% in patients presenting with pT1 tumors, 71.9% in pT2 tumors, 63.5% in pT3 tumors, and 41.0% in pT4 tumors. Log-rank pairwise comparisons confirmed that patients with pT4 primary tumors experienced significantly poorer RRFS, compared to both pT1 ($p < .0001$) and pT2 ($p = .016$) primary tumors. On multivariable Cox regression (Table 6), pathologic tumor classification was an independent predictor of RRFS, with a hazard ratio of 7.65 ($p = .004$) for pT4 tumors.

Mean survival after an episode of isolated regional recurrence was 32.9 months (95% confidence interval, 19.1–46.6). Successful salvage with at least 24 months survival was achieved in 34.4% of patients with regional recurrence. Surgical salvage was attempted in 24 cases (75%), with a 46% rate of successful salvage. None of the 5 recurrences treated with radiation or chemoradiation were successfully salvaged. No therapy was used in 3 patients. Disease-specific survival (from the date of initial treatment) in patients experiencing regional recurrence was significantly poorer than in patients free of regional recurrence (41.2% vs 80.9%; $p < .0001$; Figure 3).

DISCUSSION

The risk of cervical nodal metastasis in SCC arising from the hard palate and maxillary alveolus has traditionally been thought to be low, although there are no contemporary outcome analyses of this issue. The understanding of the risks of cervical metastasis in hard palate and upper alveolus cancers has evolved over time. The earliest large historical series suggested a high rate of regional disease. However, these studies tended to report results from several combined subsites. Janeway,⁵ in 1918, first reported a 33% rate of cervical metastasis among 21 cases of hard palate, soft palate, and upper alveolus cancers, most of which were irradiated. Martin⁶ reviewed 52 patients in 1941, combining upper and lower alveolus cancers. These patients experienced a 33% rate of neck failure. In 1969, Cady and Catlin⁷ reported on 606 upper and lower alveolus SCCs. While 37% of the patients presented with cervical metastasis, only 19% of elective neck dissections harbored occult disease. In this series, neck dissections were more commonly performed for mandibular alveolus cancers than for maxillary alveolus cancers, reflecting an emerging belief that the risk of neck metastasis was lower for the maxillary alveolus.

By the 1980s, diagnostic capabilities had improved, and the risk of occult disease was thought to be low. Evans and Shah,⁸ in 1981, reviewed 252 cases of SCC of the palate, of which 62 were hard palate tumors. Cervical metastases were present in 29% of hard palate tumors at presentation. Elective neck dissections were generally not performed for hard palate tumors, and the rate of regional failure was described as low. In 1988, Soo et al⁹ reviewed 347 cancers of the upper and lower gums. Elective neck dissections were rarely performed for upper gum tumors. Only 5.6% of elective neck dissections contained occult disease, and only 9% of patients experienced neck recurrence. As a result, elective neck dissection has remained uncommon in the management of cancers arising from these subsites.

More recently, however, the role of elective neck dissection in clinically node-negative oral cavity cancer has become better defined. Treatment of the clinically N0 neck is now accepted for certain oral cavity subsites, such as the tongue and floor of mouth,¹⁻⁴ where evidence exists for a survival advantage for elective neck dissection.¹⁵⁻¹⁷

However, there are no contemporary outcomes data to inform consideration of elective neck treatment in hard palate and maxillary alveolus SCC. Recently, 5 small case series have

been published, consisting of single-institutional experiences ranging in size from 13 to 37 patients. These authors have reported a higher-than-expected incidence of regional recurrence in N0 necks, ranging from 14% to 27%.¹⁰⁻¹⁴ Limitations of these prior studies include lack of survival analysis and insufficient sample size to permit multivariable analysis. Cancer failure rates should be determined using survival analysis in order to account for censoring and variable time-to-event data. As patients are lost to follow-up or die of other causes, inclusion of these patients would underestimate the rate of failure, while exclusion of these patients would overestimate the rate of failure. Nevertheless, these case series raised important questions. Therefore, the present study was designed to provide a cohort of sufficient size to permit systematic outcomes analysis. To our knowledge, this is the only such study of SCC of the hard palate and maxillary alveolus.

This study included 139 consecutive patients with median follow-up of nearly 5 years. We report a high incidence of regional failure. While few patients (8%) displayed clinical evidence of nodal metastasis at the time of initial presentation, there was a high incidence of regional recurrence (30%) in patients who were clinically N0. Altogether, 38% of patients developed cervical metastases at some point. Patients with pT2 to T4 primary tumors were at the highest risk of regional recurrence. Of patients with pT4 primary tumors, 38% experienced neck failure, and 53% developed neck metastases at some point, either at presentation or at recurrence. Regional recurrence occurred at a mean time of 6 months, and usually in the absence of local recurrence, suggesting that most cases of cervical recurrence were likely to have been occult metastases at presentation.

Because some cases of regional recurrence may potentially be attributable to seeding from recurrent disease at the primary site, a more conservative estimate (the rate of isolated regional recurrence) was also calculated. In this analysis, patients were limited to those in whom the primary site had been controlled. The overall rate of isolated regional recurrence was 21%. This rate was highest (30%) in patients who had pT4 primary tumors. In all 22 patients who had isolated regional recurrence, the neck was untreated: none had received neck dissection or postoperative irradiation to the neck. This is consistent with occult neck metastases at presentation.

Elective treatment of the neck with staging neck dissection is generally carried out in patients with SCC of the oral cavity when the risk of clinically occult metastases exceeds 15% to 20%.¹⁻³ Because most oral cavity cancers are treated surgically, elective neck dissection is commonly performed at the time of surgery of the primary tumor. However, SCC of the hard palate and maxillary alveolus has traditionally been believed to exhibit a low rate of occult metastasis.⁴ Most clinicians, therefore, do not routinely perform elective neck dissection in the absence of palpable or radiographic metastases, choosing instead to observe the neck. The results of our analysis suggest that elective treatment of the neck should be performed in patients with locally advanced SCCs of the hard palate and maxillary alveolus. While the rates of regional failure appear to be lower than for other oral cavity subsites, the risk does not seem to be low enough to justify observation of the neck in all cases.

It is important to note that of the patients who developed regional recurrence, salvage surgery could only be carried out in 75% of the cases. This may be partly attributable to the less frequent use of surveillance imaging during the early period of the study. It is possible that more cases may be identified at a salvageable stage, with more frequent use of CT, PET, or ultra-sound scan imaging in present day practice. Nevertheless, even among patients able to undergo surgical salvage for regional failure, only 46% survived an additional 2 years. The poor prognosis of regional recurrence was under-scored by differences in disease-specific survival. Patients with regional recurrence experienced 5 year disease-specific

survival of 41%, compared to 81% in patients without regional recurrence. This poor outcome after regional recurrence may be due to a high rate (90%) of pathologic extracapsular extension. Because this study is retrospective, we cannot prove a causal relationship between recurrence and extracapsular extension. There was no difference in the extent of nodal involvement (N classification or number of levels involved) between metastases at presentation and at recurrence. However, these results are consistent with the data reported by Andersen et al,¹⁸ establishing that regionally recurrent oral cavity cancer usually carries adverse pathologic features.

Therefore, because of 3 factors, (1) the high rate of regional recurrence, (2) the limited number of salvageable recurrences, and (3) the poor outcome despite salvage surgery, it would seem justified to recommend elective neck dissection for the majority of tumors of the hard palate and upper alveolus, with the possible exception of localized T1 tumors without bone invasion. In our study, metastatic nodes were most commonly found in levels I and II, and rarely in level V. In the elective setting, we would, therefore, recommend a selective neck dissection of levels I to III.

There are several caveats to our findings. This study carries the limitations of retrospective analyses. Patients in the early period of the study may have been less likely to receive surveillance imaging, potentially leading to a higher rate of recurrence, although we identified no change in recurrence rates over time. Similarly, if patients free of neck recurrence were more likely to not return for clinical follow-up, the rate of neck failure would be overestimated. Eight patients underwent elective neck dissection, potentially removing a small number of high-risk patients from the pool of observed patients, underestimating the rate of recurrence. Finally, without a prospective trial, we cannot make a statement that elective neck dissection improves recurrence or survival outcomes.

In conclusion, the results of this retrospective analysis, spanning 21 years with median follow-up of nearly 5 years, reveal that tumors of the hard palate and upper alveolus are associated with a high rate of regional failure, which results in poor survival, despite attempted salvage. The evidence presented in this study suggests that an elective neck dissection would seem prudent in most locally advanced cases.

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FIGURE 1.

Incidence of regional recurrence, by pathologic tumor (pT) classification. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

FIGURE 2.

Regional recurrence-free survival (RRFS), by pathologic tumor classification. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

FIGURE 3.

Disease-specific survival according to regional recurrence status. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

Table 1

Patient and tumor characteristics at presentation

Characteristic	No.	%
Total patients	139	100%
Age		
<60 y	33	23.7%
≥60 y	106	76.3%
Sex		
Male	57	41.0%
Female	82	59.0%
Tobacco use		
Never	52	46.8%
Former or active	59	53.2%
Alcohol use		
Never	33	31.1%
Social	22	20.8%
Active	51	48.1%
Tumor subsite		
Hard palate	51	36.7%
Maxillary alveolus	89	64.0%
Clinical tumor classification		
T1	33	27.3%
T2	36	29.8%
T3	16	13.2%
T4	36	29.8%
Clinical nodal classification		
N0	127	91.4%
N1	5	3.6%
N2	6	4.3%
N3	1	0.7%
Clinical metastasis classification		
M0	138	99.3%
M1	1	0.7%
Clinical stage		
I	32	23.0%
II	33	23.7%
III	15	10.8%
IV	42	30.2%

Table 2

Details of treatment and pathology

	No.	%
Treatment		
Surgery alone	86	61.9%
Surgery + RT	47	33.8%
Surgery + CRT	1	0.7%
CRT alone	2	1.4%
None	3	2.2%
Neck Dissection		
None	115	82.7%
Therapeutic (TND)	11	7.9%
Elective (END)	8	5.8%
Pathology		
Pathologic tumor classification		
T1	38	28.4%
T2	25	18.7%
T3	9	6.7%
T4	62	46.3%
Pathologic nodal classification (TND performed)		
N0	2	18.2%
N1	2	18.2%
N2	6	54.5%
N3	1	9.1%
Pathologic nodal classification (END performed)		
N0	6	75.0%
N1	0	0
N2	2	25.0%
N3	0	0
Pathologic stage		
I	38	28.4%
II	23	17.2%
III	10	7.5%
IV	63	47.0%

Abbreviations: RT, radiation therapy; CRT, chemoradiation therapy; TND, therapeutic neck dissection; END, elective neck dissection.

Table 3

Distribution of clinical and pathologic neck metastases

Characteristic	No. of patients (%)	
	At presentation	At recurrence
Clinical neck metastases (examination/imaging)		
Clinical N classification		
N1	5 (41.7%)	8 (25.8%)
N2	6 (50.0%)	21 (67.7%)
N3	1 (8.3%)	2 (9.5%)
Levels involved		
I	10 (100%)	18 (51.5%)
II	6 (60%)	17 (48.6%)
III	4 (40%)	2 (5.7%)
IV	1 (10%)	0
V	1 (10%)	1 (2.9%)
Contralateral	0	2 (5.7%)
Pathologic neck metastases (neck dissections)		
Pathologic N classification		
N1	2 (18.2%)	7 (29.2%)
N2	8 (72.7%)	17 (70.8%)
N3	1 (9.1%)	0
Levels involved		
I	10 (100%)	13 (59.1%)
II	6 (60%)	12 (54.5%)
III	4 (40%)	6 (27.3%)
IV	1 (10%)	4 (18.1%)
V	1 (10%)	0
Contralateral	0	1 (4.5%)
ECE		
No	6 (66.7%)	2 (10.6%)
Yes	3 (33.3%)	17 (89.5%)

Abbreviation: ECE, extracapsular extension.

Table 4

Incidence of neck metastases by pathologic tumor classification, by Kaplan-Meier method

T classification	No. of patients (%)		
	At presentation	At recurrence	Total
pT1	0	7 (18.7%)	7 (18.7%)
pT2	2 (10.0%)	4 (23.3%)	5 (25.0%)
pT3	1 (11.1%)	2 (25.9%)	3 (37.0%)
pT4	9 (17.6%)	19 (38.1%)	27 (52.9%)

Table 5

Incidence of overall and isolated regional recurrence by pathologic tumor classification, by Kaplan–Meier method

T classification	No. of patients (%)	
	Overall regional	Isolated regional
pT1	7 (18.7%)	5 (13.9%)
pT2	4 (23.3%)	4 (21.1%)
pT3	2 (25.9%)	0
pT4	19 (38.1%)	13 (30.4%)

Table 6

Variables predictive of regional recurrence-free survival

Variable	No.	5-y RRFs, %	Univariate analysis		Multivariable analysis	
			p value		HR	p value
Sex						
Male	57	60.7	.615		1.01	.968
Female	82	58.1				
Age						
<60 y	33	58.6	.832		1.08	.922
≥60 y	106	59.2				
Tobacco						
Never	52	50.8	.065		2.30	.248
Yes	59	67.6				
Alcohol						
Never	48	49.4	.144		0.88	.862
Yes	55	72.4				
Subsite						
Hard palate	51	48.2	.119		0.70	.429
Max alveolus	89	65.3				
pT status						
T1	33	81.3	Referent		Referent	
T2	36	71.9	.429		1.48	.614
T3	16	63.5	.153		1.77	.676
T4	36	41.0	<.0001		7.65	.004
Depth						
≥5 mm	72	50.2	.403		1.85	.412
<5 mm	20	63.6				
Grade						
Well differentiated	65	63.8	Referent		Referent	
Moderately differentiated	50	51.5	.159		1.13	.812
Poorly differentiated	10	70.0	.827		0.36	.406
Margins						

Variable	No.	5-y RRFs, %	Univariate analysis		Multivariable analysis	
			p value		HR	p value
Positive or close	34	45.3	.115		1.76	.295
Negative	91	65.7				
PNI						
Yes	22	43.2	.115		2.29	.294
No	80	59.2				
PVI						
Yes	11	54.5	.926		0.81	.168
No	90	57.9				
Adjuvant RT						
Yes	48	53.2	.286		0.31	.114
No	86	62.6				

Abbreviations: RRFs, regional recurrence-free survival; HR, hazard ratio; PNI, perineural invasion; PVI, perivascular invasion; RT, radiation therapy. Univariate comparisons were carried out via log-rank test. Multivariable Cox proportional-hazards regression incorporated all variables.