Outcomes in Minor Salivary Gland Tumors—A 20+ Year Tertiary-Care Center Experience

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Abstract

Objective. Minor salivary gland carcinomas are challenging to study due to their rarity and heterogeneity. We aim to further characterize clinical characteristics, treatment, and outcomes over 20 years within a single institution.

Study Design. Retrospective chart review was conducted on 210 patients who received primary treatment for minor salivary gland malignancy from 2000 to 2022.

Setting. Single tertiary-care center.

Methods. Multivariable Cox proportional hazards method was used to examine the relationship between pre-determined clinically important variables and outcomes.

Results. Five-year overall survival was 77.8% (72.0-84.1). Advanced clinical T stage portended over a 2 times higher risk of death and recurrence. High pathologic grade was associated with a near 3 times higher risk of death and recurrence. There was a predominance of occult nodal metastases in level II for oral cavity and oropharynx site tumors.

Conclusion. Clinical T stage and grade were important for overall survival, local, regional, and distant recurrence-free survival. Occult nodal metastases occurred most often in level II.

M inor salivary gland carcinomas are rare, with a reported annual incidence of 0.16 to 0.4 cases per 100,000,[1] comprising 10% to 15% of all salivary carcinomas.[2] While there are only 3 pairs of major salivary glands, there are over 500 minor salivary glands distributed along the upper respiratory tract, with up to 90% in the oral cavity or oropharynx.[3] This results in tumors that can present at many different anatomic sites. In contrast to parotid tumors, up to 80% of minor salivary gland tumors are malignant.[4] Over 20 different histologic types can present in minor salivary glands,[5] with the most common being adenoid cystic carcinoma, mucoepidermoid carcinoma, and adenocarcinoma.[6]

As a result of the low incidence, variety of anatomic sites, and heterogeneity of pathologies, minor salivary gland carcinomas are challenging to study. Many studies subcategorize by analyzing only a single pathology or anatomic site, which may limit the study population and provided a restricted view of the behavior of these tumors. Of the few studies that include all minor salivary gland carcinomas, the majority use databases,[7–9] which confines the types of variables that can be included. Even fewer studies include information about nodal metastases. Thus, we aimed to further characterize clinical characteristics, treatment, and outcomes, including nodal disease, of minor salivary gland malignancies over 20 years within a single institution.

Methods

Retrospective chart review was conducted on patients identified from a tumor registry with Institutional Research Board approval. Patients who received primary treatment for minor salivary gland malignancy at Cleveland Clinic facilities from 2000 to 2022 were included. Patients without

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documented in-house pathology review were excluded. Variables included patient demographics, tumor and treatment characteristics, and overall survival as well as local, regional, and distant recurrence-free survival. Staging was based on the American Joint Committee on Cancer Staging Manual 8th Edition.[8]

Anatomic sites included oral cavity, nasal cavity, paranasal sinuses, oropharynx, larynx, and trachea. Histopathology and grading were based on the WHO classification of head and neck tumors.[10] The accepted histological convention was used for grading of adenoid cystic carcinoma and mucoepidermoid carcinoma. Overall survival in months was calculated from date of biopsy to date of death or last known alive. Recurrence was calculated in months from the date of biopsy until the first local, regional, or distant recurrence reported in chart.

Multivariable Cox proportional hazards method was used to examine the relationship between pre-determined clinically important variables including sex, tumor site, lymph node dissection, clinical T-stage, tumor grade, and radiation therapy, and overall survival, local recurrence free survival, regional recurrence free survival, and distant recurrence free survival. The Kaplan-Meier method was used to visualize time-to-event curves. Significance was defined as $\alpha = 0.05$. No adjustment for multiple comparisons was performed.

Results

A total of 210 patients were included, with demographic and preoperative information shown in **Table 1**. Median age was 58.5 years, and 54% were female. Fifty-six percent of patients had a history of smoking. CT scan was performed in 82% of patients, while 39% underwent MRI, and 31% underwent PET scan. More than half (54%) of tumors were in the oral cavity. More than half also presented with cT1-2 disease (54%). Eighty-seven percent of patients presented with cN0 neck disease. Forty-three percent presented with low-grade malignancy on pathology, 17% with intermediate-grade, and 20% with high-grade.

Table 2 shows treatment and final pathology characteristics. Surgical resection was the primary treatment in 86% of patients, and 28% underwent neck dissection. Fifty-five percent underwent radiation and 15% underwent chemotherapy. In those who underwent surgery, final margin status was negative in 48% of patients, positive in 28%, and close in 19%, while 6% were unknown. Twenty-four percent of patients had bone invasion, 40% had perineural invasion, and 24% had lymphovascular invasion. Pathologic T stage was 1 to 2 in 55% of patients, and of those that underwent neck dissection, 37% had pathologic nodal disease. Of these, 42% had extranodal extension. The most common histologies (**Table 3**) were adenoid cystic carcinoma (34%), mucoepidermoid carcinoma (23%), adenocarcinoma (14%), and polymorphous adenocarcinoma (12%).

Table 1. Demographics and Preoperative Characteristics of Patients Treated Definitively for Minor Salivary Gland Carcinoma

Variable	n = 210
Age (y, median) (IQR)	58.5 (47.8-68.6)
Sex	
M	96 (46)
F	114 (54)
Smoking history	
Never smoker	89 (42)
Former smoker[a]	70 (33)
Current smoker	49 (23)
Unknown	2 (1)
Diagnostic testing	
CT	173 (82)
MRI	82 (39)
PET	66 (31)
Tumor site	
Oral cavity	113 (54)
Nasal cavity	26 (12)
Paranasal sinus	26 (12)
Oropharynx	19 (9)
Larynx	14 (7)
Nasopharynx	12 (6)
cT stage	
T1	80 (38)
T2	33 (16)
T3	17 (8)
T4	64 (30)
Unknown/not reported	16 (8)
cN stage	
N0	182 (87)
N1	8 (4)
N2	15 (7)
N3	2 (1)
N4	0 (0)
Unknown/not reported	3 (1)
Tumor grade	
Low	91 (43)
Intermediate	35 (17)
High	42 (20)
Unknown/not reported	42 (20)

Abbreviation: IQR, interquartile range.
[a]Former smoker denotes quitting >3 months ago.

Table 4 shows nodal levels dissected as well as levels that were positive. Twelve percent of patients had clinically positive nodal disease. Of the 51 patients who underwent neck dissection, Level II underwent dissection in the majority (80%) of cases. Most positive nodes (89%) and occult positive nodes (83%) were also in level II. Neck dissection was elective in 34 patients, of which 6 (18%) had occult nodal metastases (ONMs). Characteristics and final pathology results of the 6 patients with ONMs are shown in **Table 5**. All ONMs had primary sites in the oral cavity or oropharynx.

Table 2. Treatment and Final Pathology Characteristics of Patients Definitively Treated for Minor Salivary Gland Carcinoma

Variable	
Treated with surgery	n = 210
No	29 (14)
Yes	181 (86)
Neck dissection	
No	159 (76)
Selective	34 (16)
Modified Radical	8 (4)
Nodal sampling (<5 nodes)	9 (4)
Treated with radiation	
None	93 (44)
Definitive	27 (13)
Adjuvant	85 (40)
Palliative	5 (2)
Treated with chemotherapy	
No	179 (85)
Yes	31 (15)
Final margin status[a]	
Negative	86 (48)
Positive	51 (28)
Close (<5 mm)	34 (19)
Unknown/not reported	10 (6)
Bone invasion[a]	
No	87 (48)
Yes	43 (24)
Unknown/not reported	51 (28)
Perineural invasion[a]	
No	94 (52)
Yes	72 (40)
Unknown/not reported	15 (8)
Lymphovascular space invasion[a]	
No	116 (64)
Yes	44 (24)
Unknown/not reported	21 (12)
pT stage[a]	
T1	73 (40)
T2	27 (15)
T3	15 (8)
T4	57 (31)
Unknown/not reported	9 (5)
pN stage[b]	
N0	32 (63)
N1	3 (6)
N2	11 (22)
N3	5 (10)
N4	0 (0)
Extranodal extension[c]	
No	11 (58)
Yes	8 (42)

[a]Of those treated with surgery.
[b]Of those with neck dissection.
[c]Of those with +pN disease.

Table 3. Distribution of Tumor Histologies

Tumor histology	Total (%)
Adenoid cystic carcinoma	72 (34)
Mucoepidermoid carcinoma	48 (23)
Adenocarcinoma	29 (14)
Polymorphous adenocarcinoma	25 (12)
Undifferentiated carcinoma	8 (4)
Clear cell carcinoma	8 (4)
Epithelial-myoepithelial carcinoma	7 (3)
Lymphoepithelial carcinoma	3 (1)
Acinic cell carcinoma	2 (1)
Salivary duct carcinoma	2 (1)
Secretory carcinoma	2 (1)
Myoepithelial carcinoma	1 (0.5)
Basal cell adenocarcinoma	1 (0.5)
Cystadenocarcinoma	1 (0.5)
Carcinosarcoma	1 (0.5)

**Table 4.** Distribution of Nodal Levels Dissected and the Levels With Positive Nodal Metastases

Nodal level	Dissected n = 51	Positive n = 19
Level I	32 (63)	4 (21)
Level II	41 (80)	17 (89)
Level III	33 (65)	3 (16)
Level IV	25 (49)	3 (16)
Level V	8 (16)	0 (0)

Three of the 4 oropharyngeal tumors were in the base of tongue, with the last in the soft palate. The two tumors in the oral cavity were in the oral tongue and alveolar ridge. Of note, both oral cavity tumors were cT4a, with the alveolar ridge tumor extending to mandible. The oral tongue tumor also did extend to the base of tongue. Histologies included mucoepidermoid carcinoma (n = 3), adenoid cystic carcinoma (n = 2), and adenocarcinoma (n = 1). Four of the tumors were high grade, with 1 low grade and 1 indeterminate. Four of the tumors also had both lymphovascular invasion (LVSI) and perineural invasion (PNI). There was extranodal extension in 2 of the dissections. The overall number of positive nodes was low, and all presented in levels I or II. The ONM rate was 25% for mucoepidermoid carcinoma but 13% and 14% for adenoid cystic carcinoma and polymorphous adenocarcinoma, respectively. ONM rates were 18% for low grade tumors and 13% for high grade.

Figure 1 shows Kaplan-Meier curves for (a) overall survival, (b) local recurrence-free survival (LRFS), (c) regional recurrence-free survival (RRFS), and (d) distant recurrence-free survival (DRFS). Five-year overall

Table 5. Characteristics and Final Pathology Results of the Six Patients With Occult Nodal Metastases

Tumor site	Tumor subsite	cT stage	Tumor histology	Grade	LVSI	PNI	Extranodal extension	Number of positive nodes	Nodal levels positive
Oropharynx	Soft palate	2	Adenocarcinoma	High	Positive	Negative	NA	6/(NA)	NA
Oropharynx	Base of tongue	3	Mucoepidermoid carcinoma	High	Negative	Positive	No	1/67	II
Oral cavity	Oral tongue	4a	Adenoid cystic carcinoma	NA	Positive	Positive	Yes	2/9	II
Oral cavity	Alveolar ridge	4a	Mucoepidermoid carcinoma	High	Positive	Positive	No	2/40	I
Oropharynx	Base of tongue	2	Adenoid cystic carcinoma	Low	Positive	Positive	Yes	2/34	II
Oropharynx	Base of tongue	2	Mucoepidermoid carcinoma	High	Positive	Positive	No	2/16	II
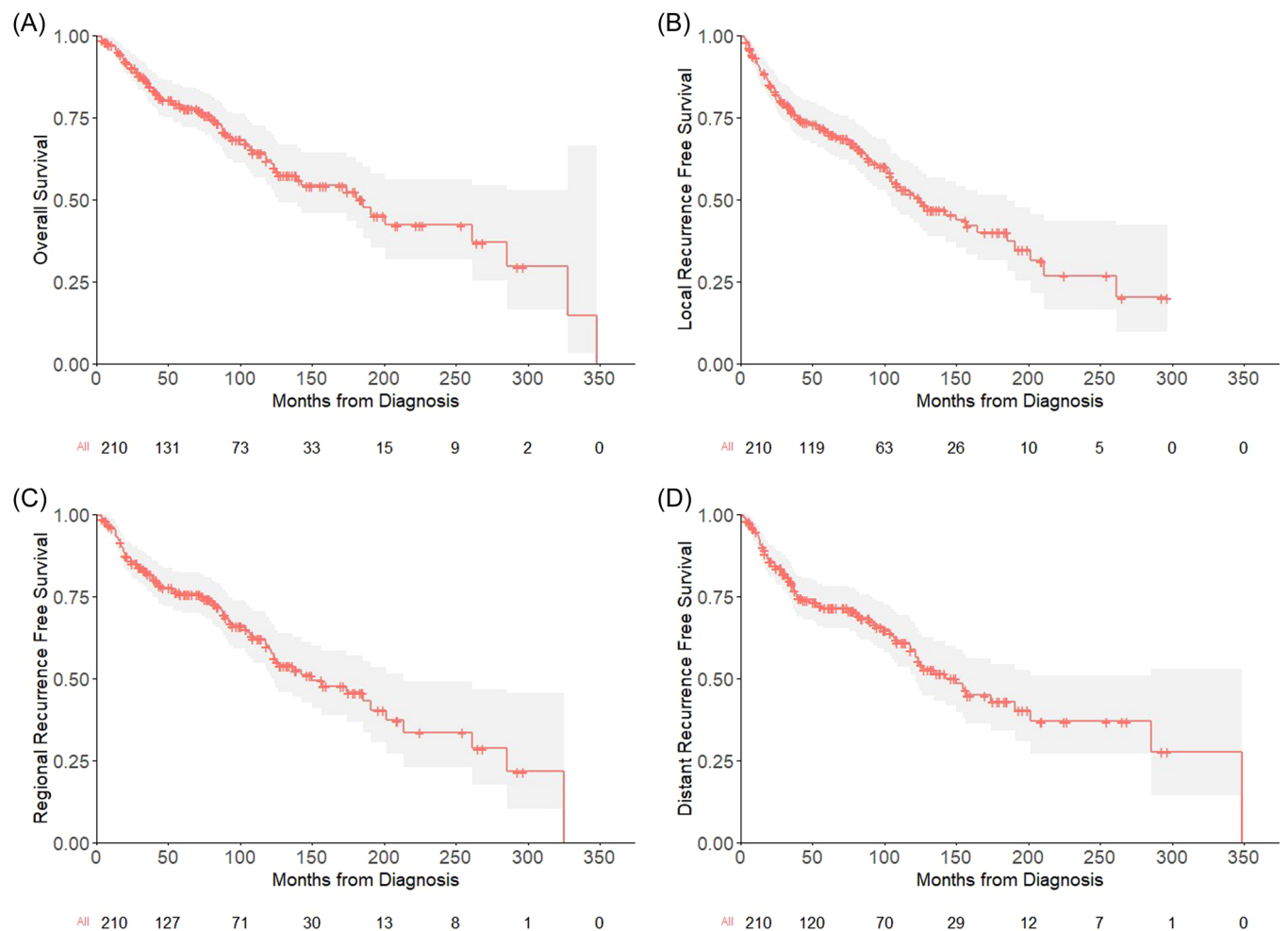
Figure 1. Kaplan-Meier curves for (A) overall survival, (B) local recurrence-free survival, (C) regional recurrence-free survival, and (D) distant recurrence-free survival.

survival was 77.8% (72.0-84.1) and 10-year overall survival was 62% (54.3-70.8). Five-year LRFS was 71.2% (65.0-78.0), RRFS was 75.8% (69.8-82.2), and DRFS was 71.5% (65.2-78.3). Ten-year LRFS was 53.9 (46.1-62.9), RRFS was 60.9% (53.3-69.6), and DRFS was

59.8% (52.3-68.4). Results of multivariable Cox proportional hazards analysis evaluating predictors of overall survival, local, regional, and distant recurrence-free survival are shown in **Table 5**. Advanced clinical T stage portended over a 2 times higher risk of death (hazard
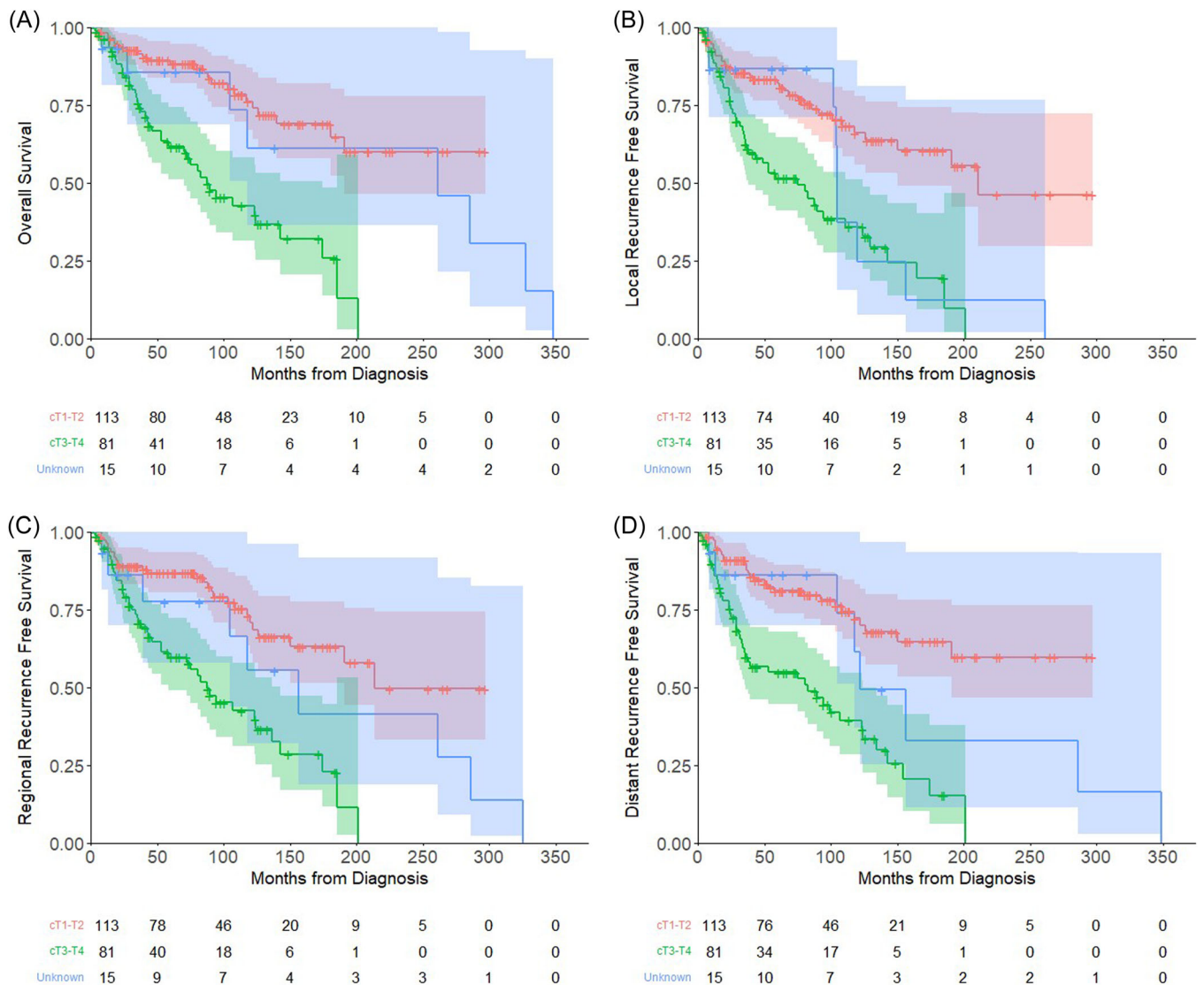
Figure 2. Kaplan-Meier curves stratified by cT1-2 and cT3-4 for (A) overall survival, (B) local recurrence-free survival, (C) regional recurrence-free survival, and (D) distant recurrence-free survival.

ratio [HR] 2.33, 95% confidence interval [CI] 1.31-4.15, $P < .01$) and local (HR 2.05, 95% CI 1.20-3.50, $P < .01$), regional (HR 2.18 95% CI 1.25-3.78, $P < .01$), and distant recurrence (2.41 95% CI 1.40-4.18, $P < .01$). Kaplan-Meier curves stratified by clinical T stage are shown in **Figure 2**. Overall survival for those with cT1-2 disease was 76.2% (95% CI 66.9-86.9) versus 42.6% (95% CI 31.3-58.1) for cT3-4 disease at 10 years. High pathologic grade was associated with a near 3 times higher risk of death (HR 3.20, 95% CI 1.56-6.58, $P < .01$) and local (HR 2.66, 95% CI 1.39-5.08, $P < .01$), regional (HR 2.82, 95% CI 1.44-5.52, $P < .01$), and distant recurrence (HR 2.34, 95% CI 1.22-4.53, $P < .01$). Kaplan-Meier curves stratified by grade are shown in **Figure 3**. Overall survival for those with low-grade disease was 76.7% (66.5-88.4) versus 33.4% (17.2-64.6) for high-grade disease at 10 years. Sex, primary site, neck dissection, and radiation were not statistically significant as predictors of overall survival,

local, regional, and distant recurrence-free survival (**Table 6**).

Discussion

This is a series of 210 patients treated for minor salivary gland tumors at a large tertiary-care institution between 2000 and 2022. The slight female predominance and older age is similarly seen in previous studies.[5,11] Although oral cavity was the most common site at 54%, our cohort had a significant portion of nasal cavity and nasopharynx tumors (24%), which is higher than previously seen.[6] This may be due to more rare tumors being referred to a large tertiary-care center.

Most patients presented with early-stage tumors and did not have clinical nodal disease at presentation, similar to studies from other institutions.[11] The most common histologies were adenoid cystic carcinoma, mucoepidermoid
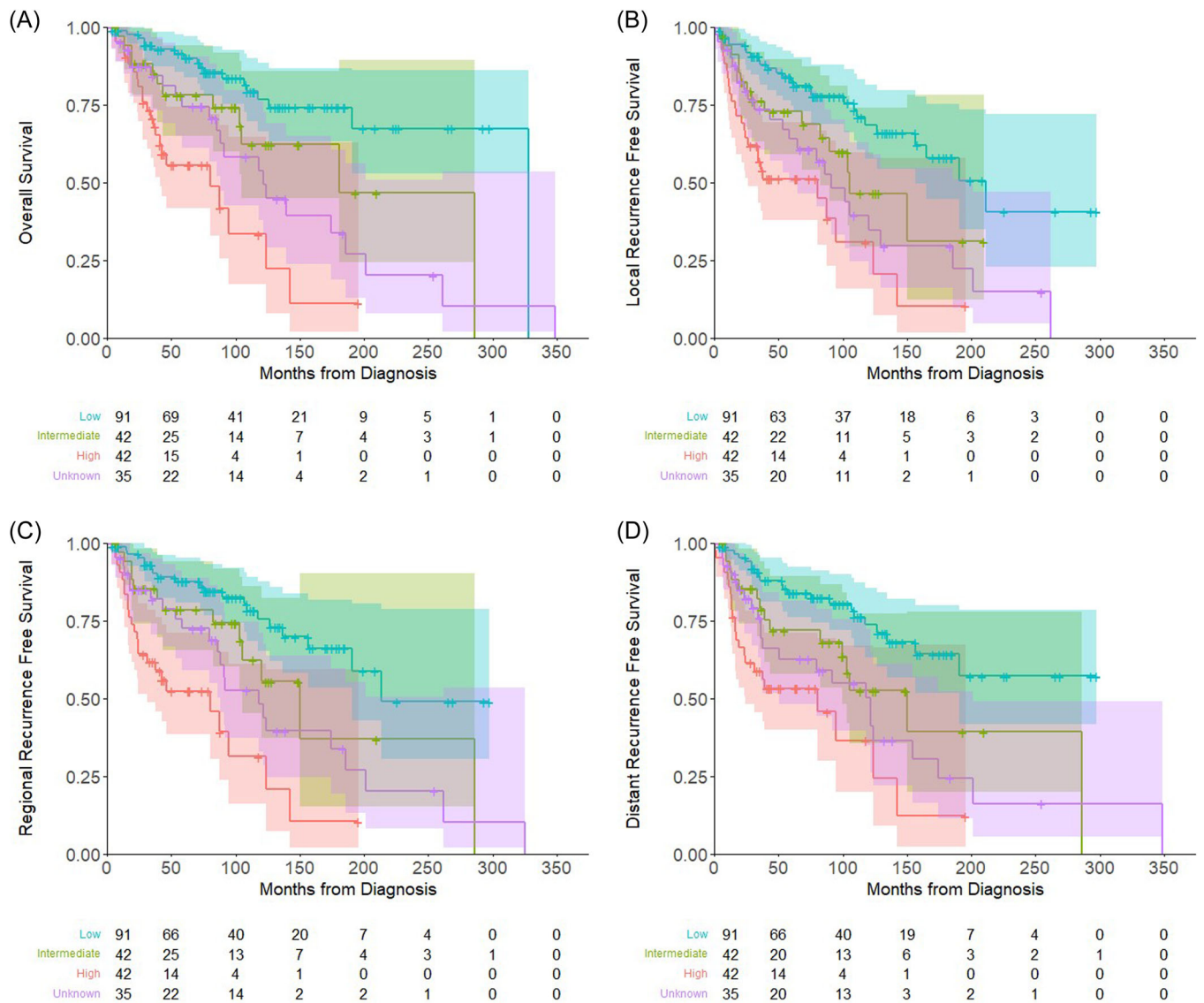
Figure 3. Kaplan-Meier curves stratified by low, intermediate, and high grade for (A) overall survival, (B) local recurrence-free survival, (C) regional recurrence-free survival, and (D) distant recurrence-free survival.

carcinoma, adenocarcinoma, and polymorphous adenocarcinoma, which is similar to studies from databases such as SEER and NCDB as well as international studies.[6–9,11,12] The rate of high-grade tumors (20%) is on par with what has been previously seen.[7,11] There was a bimodal distribution of clinical T stage, with a peak at T1 and another at T4. Of the 19 patients who had pathologic nodal disease, 42% had extranodal extension, suggesting that while most patients do not present with nodal disease, those that do tend to be more severe.

Five-year overall survival rate at 78% mirrors that seen in other studies.[6,11,13] Previous studies have identified sex as prognostic factor in overall survival, with females having longer median survival,[6,11] however, we did not find that to be the case in our data. Additionally, previous studies have shown sinonasal tumors having worse outcome,[14,15] but we did not find tumor site to be a significant factor in overall survival or recurrence on

multivariable regression. Of the variables tested, advanced clinical T stage (3-4) had statistically significant lower rates of overall survival and all recurrence-free survival measures. High grade on pathology also had lower rates of overall survival and recurrence-free survival when compared to low grade, but intermediate grade did not show a statistically significant difference. In one previous study, no statistically significant difference was found in overall survival between low and intermediate-risk pathologies, but there was a difference in recurrence-free survival.[11] Most of the intermediate-grade tumors in our cohort were adenoid cystic or mucoepidermoid carcinoma, and the lack of difference in outcomes between low and intermediate grade could be a reflection of the less aggressive behavior of these tumors. Alternatively, the number of intermediate-grade tumors was smaller and the lack of difference could be a reflection of type II error. These two variables have been

Table 6. Multivariable Cox Proportional Hazards of Predetermined Variables for Overall Survival, Local, Regional, and Distant Recurrence-Free Survival

Variable	OS		LRFS		RRFS		DRFS	
	HR	*P*	HR	*P*	HR	*P*	HR	*P*
Sex								
Female	-	-	-	-	-	-	-	-
Male	1.16 (0.71-1.88)	.55	0.91 (0.58-1.41)	.66	1.05 (0.67-1.67)	.82	1.12 (0.71-1.77)	.62
Site								
Oral cavity	-	-	-	-	-	-	-	-
Sinonasal	1.16 (0.71-1.88)	.63	1.31 (0.76-2.27)	.33	0.85 (0.48-1.51)	.59	0.93 (0.52-1.66)	.81
Oropharynx	1.55 (0.62-3.87)	.35	1.34 (0.55-3.28)	.52	1.29 (0.52-3.17)	.58	1.71 (0.73-4.02)	.22
Larynx	1.34 (0.60-2.97)	.48	1.63 (0.77-3.45)	.20	1.39 (0.66-2.95)	.39	1.94 (0.92-4.07)	.08
LND								
No	-	-	-	-	-	-	-	-
Yes	1.23 (0.67-2.26)	.50	1.03 (0.60-1.79)	.91	1.17 (0.67-2.06)	.58	0.96 (0.54-1.72)	.90
Unknown	0.32 (0.07-1.57)	.16	0.94 (0.22-3.90)	.93	0.36 (0.09-1.44)	.15	0.65 (0.15-2.78)	.56
cT								
1-2	-	-	-	-	-	-	-	-
3-4	2.33 (1.31-4.15)	**<.01**	2.05 (1.20-3.50)	**<.01**	2.18 (1.25-3.78)	**<.01**	2.41 (1.40-4.18)	**<.01**
Unknown	1.60 (0.52-4.99)	.41	0.94 (0.30-2.94)	.91	1.49 (0.49-4.51)	.48	1.04 (0.32-3.36)	.95
Grade								
Low	-	-	-	-	-	-	-	-
Intermediate	1.57 (0.70-3.52)	.27	1.66 (0.82-3.36)	.16	1.36 (0.63-2.91)	.44	1.42 (0.69-2.93)	.35
High	3.20 (1.56-6.58)	**<.01**	2.66 (1.39-5.08)	**<.01**	2.82 (1.44-5.52)	**<.01**	2.34 (1.22-4.52)	**.01**
Unknown	2.30 (1.13-4.69)	**.02**	1.71 (0.89-3.31)	.11	1.65 (0.83-3.26)	.15	1.54 (0.79-3.01)	.20
RT								
No	-	-	-	-	-	-	-	-
Yes	1.33 (0.74-2.40)	.34	0.96 (0.57-1.63)	.88	1.60 (0.90-2.83)	.11	1.62 (0.91-2.87)	.10

Bold values indicate *P* < .05.

consistently shown in the literature to be prognostic for overall survival.[6–9,11,14,16] Lymph node dissection and radiation treatment did not show significant survival outcomes. Although some studies have shown adjuvant radiation to improve locoregional control,[17] there was no statistically significant difference on multivariable analysis in other studies.[7,11,16]

One large meta-analysis showed an ONM rate of 17% in adenoid cystic carcinoma,[18] similar to our ONM rate of 13% for adenoid cystic carcinoma. Another review showed an average ONM rate of 14%,[19] which was similar to our overall minor salivary gland ONM rate of 18%. All ONMs in our dataset were in the oral cavity or oropharynx, supported by previous data showing higher ONM rates in these sites.[20] In particular, those involving the base of tongue tended to have ONMs. In addition to presenting at a higher grade, most also tended to have LVSI and PNI. Previous studies have shown ONMs only in levels I to III,[21,22] and our data show most ONMs occurring in level II, with 1 occurring in level I and none in level III to V. Overall, the number of positive nodes was small.

Our study is limited by its retrospective nature and the heterogeneity of pathologies. The data presented here likely reflect the behavior of the most common pathologies of mucoepidermoid carcinoma, adenoid cystic carcinoma, and adenocarcinoma. There were too few ONMs to make any conclusions regarding predictive variables.

However, this remains a large single-institution cohort of minor salivary gland tumors. Many previous studies analyzing minor salivary gland carcinomas were performed on national database data, which prevent full knowledge of some clinical and treatment characteristics, such as extent of neck dissection, which is not a limitation in our cohort. We demonstrate the importance of cT stage and grade on overall survival, local, regional, and distant recurrence-free survival. There was a predominance of ONMs in level II for oral cavity and oropharynx site tumors, particularly for mucoepidermoid and adenoid cystic carcinoma in the base of tongue, which suggests the inclusion of level II in elective neck dissection for these tumors with less emphasis on levels III to V.

Author Contributions

All authors participated meaningfully in multiple core aspects of the original study (hypothesis generation, data collection, data analysis, manuscript composition).

Disclosures

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