The Laryngoscope

Long-term Outcomes and Prognosis in Submandibular Gland Malignant Tumors: A Multicenter Study

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Objectives/Hypothesis: Submandibular gland tumors (SMGTs) are rare and characterized by heterogeneity in histologic profiles. The aim of the present study was to retrieve data on submandibular gland (SMG) malignancies and identify factors influencing survival.

Study Design: Retrospective study.

Methods: A multicenter, retrospective study on patients who underwent primary surgery for SMGTs at three referral centers was performed.

Results: Among 204 patients with SMGTs, 50 (24.5%) with SMG malignancies were analyzed in detail. Definitive pT status was: 21 (42%) pT1, 14 (28%) pT2, 10 (20%) pT3, and five (10%) pT4. Nodal metastases and perineural spread were diagnosed in 15 (30%) and 25 (50%) patients, respectively. High-grade lesions were identified in 32 (64%) patients. Follow-up status, available for 49 (98%) patients, was as follows: 23 (47%) patients were alive without disease, 11 (22.5%) died of disease, five (10.2%) alive with disease, and 10 (20.4%) died of other causes. Five- and 10-year overall survival (OS), disease-specific survival (DSS), and recurrence-free survival (RFS) were 66.4% and 57.1%, 76.6% and 72.1%, 69.1% and 62.4%, respectively. At univariate analysis, OS, DSS, and RFS were influenced by pT status, pN status, and perineural spread. OS and RFS were also affected by the presence of facial palsy and pain. RFS was negatively influenced by positive margins. Multivariate analysis confirmed that OS, DSS, and RFS were independently affected by perineural spread, whereas nodal involvement influenced only RFS.

Conclusions: The malignancy rate of SMGTs is comparable to that reported for parotid tumors. Most patients presented with high-grade lesions. pT status, pN status, and perineural spread significantly affected prognosis.

Key Words: Salivary gland, submandibular, parotid.

Level of Evidence: 4.

***Laryngoscope*, 00:000–000, 2018**

INTRODUCTION

Salivary gland neoplasms are rare, accounting for 3% of all head and neck tumors; approximately 80% originate in the parotid gland, and only 5% to 15% arise in the submandibular gland (SMG).[1–7] In the literature, the malignancy rate of SMG is generally higher than in the parotid gland, ranging between 35% and 50%.[3–6,8] Tumors of the SMG are also associated with a less favorable prognosis compared with their parotid counterpart.[4,5,9,10] Due to the relatively low prevalence of submandibular gland tumors (SMGTs), limited information concerning treatment guidelines and prognosis is available; moreover, analysis of data is made difficult by the high histologic variability that is typical of salivary neoplasms.

In the present study, we retrospectively evaluated a series of 204 patients treated for SMGTs at three tertiary referral centers from 1995 to 2015, with the aim to obtain information on the rate of malignancy, long-term outcomes, and identify possible prognostic factors.

MATERIALS AND METHODS

Data Collection and Study Population

A medical record search was carried out to identify all patients treated for SMGTs at the Unit of Otorhinolaryngology–Head and Neck Surgery of the University of Brescia, Brescia, Italy; Department of Otorhinolaryngology–Head and Neck Surgery of the University Hospital of Leuven, Leuven, Belgium; and at the Unit of Otorhinolaryngology–Head and Neck Surgery of the Regina Elena National Cancer Institute in Rome, Italy, from January 1995 to December 2015. All data concerning demographics, clinical and radiologic findings, and histologic

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Editor's Note: This Manuscript was accepted for publication March 22, 2018.

The authors have no funding, financial relationships, or conflicts of interest to disclose.

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DOI: 10.1002/lary.27236

diagnosis were collected. Exclusion criteria were previous surgical treatment at another hospital and/or diagnosis of secondary or metastatic tumor. Data concerning benign tumors were included to assess their prevalence compared to malignant lesions. Data on 204 patients treated for SMGTs were retrieved. At definitive histologic examination, SMG malignancies were identified in 50 (24.5%) patients (male/female ratio: 1.6, mean age: 57 years).

Preoperative Staging

All patients underwent ultrasonographic (US) evaluation and US-guided fine-needle aspiration cytology (FNAC); cross-sectional imaging (contrast-enhanced magnetic resonance imaging [MRI] or computed tomography [CT]) was performed whenever US and/or clinical evaluation was suspicious for extraglandular extension and/or in the presence of complaints consistent with perineural spread (PNS). In the presence of lesions displaying high biological aggressiveness at presentation (cT3–T4 category, nodal involvement, high-grade cytology at FNAC), distant metastases were ruled out by positron emission tomography-computed tomography (PET-CT) or chest–abdomen CT.

Surgical Treatment

All patients underwent surgery with radical intent, and submandibular gland excision (SGE) was at least accomplished in all cases. Radicality of resection, especially when extraglandular extension or PNS were identified, was checked by frozen sections. Modified radical neck dissection (I–V) ipsilateral to the gland was performed in all patients with preoperative evidence of nodal involvement, whereas selective neck dissection (I–III) with elective intent was performed whenever clinical and/or cytological signs suggesting an aggressive primary neoplasm were encountered.[4] In c-N0 patients without clinical cytologic features consistent with a high-grade lesion and with intraoperative evidence of enlarged lymph nodes, a conservative policy, including superselective neck dissection of sublevel IB with frozen sections, was adopted. In case of positivity, the procedure was converted into a formal modified radical neck dissection. Finally, contralateral neck dissection was performed exclusively with therapeutic intent.

Histologic Examination

Lesions were histologically classified into low-, intermediate-, and high-grade. Oncocytic carcinoma, low-grade mucoepidermoid carcinoma (MEC), myoepithelial carcinoma (MC), and low-grade adenoid cystic carcinoma (AdCC) (tubular pattern) were included in the low-grade group. The high-grade tumors encompassed adenocarcinoma not otherwise specified (AcNOS), salivary duct carcinoma (SDC), high-grade MEC, carcinoma expleomorphic adenoma (CEPA), neuroendocrine carcinomas (NE), squamous cell carcinoma (SCC), and high-grade AdCC (mixed pattern with solid component >30%). Intermediate-grade was included only for MEC and AdCC (mixed growth pattern with solid component <30%).

Adjuvant Therapy and Post-treatment Surveillance

Adjuvant treatment (radiotherapy [RT] ± chemotherapy [ChT]) was planned according to definitive histology findings and the patient's biologic profile. Indications for adjuvant RT included high pT category (pT3–T4), PNS, nodal involvement, and high grade of the lesions; concomitant RT–ChT was performed in very selected patients with unusual histologic findings.

The follow-up protocol for malignant tumors included periodic clinical evaluations and MRI or neck US every 4 months for the first 2 years after treatment, and then every 6 months until the fifth year; for high-grade lesions, patients also underwent PET-CT scan or chest–abdomen CT.

Statistical Analysis

Univariate survival curves were estimated using the Kaplan-Meier method and compared by the log-rank test for relevant variables: patient factors (age ≤ 60 or > 60 years, pain at presentation, preoperative palsy of the facial nerve marginal branch), tumor factors (T classification, N classification, histological grade, PNS), and treatment-related variables (status of surgical margins). Due to the low number of cases of SMG malignancies, PNS was arbitrarily analyzed as a dichotomic variable (present or absent) and not further differentiated into microscopic and macroscopic (along named nerves). A multivariate analysis was performed using a Cox proportional hazard model with backward logistic regression and expressed as hazard ratio (HR) with 95% confidence intervals (CI).

Three survival outcomes were analyzed: overall survival (OS), disease-specific survival (DSS), and recurrence-free survival (RFS). For the first two, the endpoint was death or last follow-up (censored observations). For DSS calculation, patients dying of unrelated causes were excluded from the analysis. For RFS, the endpoint was set at the date of recurrence or at the last available visit (censored observations).

Association among risk factors were assessed using χ^2 or Fisher exact tests as appropriate. Analysis was performed using Stata version 13.0 software (Stata Corp., College Station, TX). A P value $< .05$ was considered statistically significant. OS, DSS, and RFS were calculated and compared graphically using Kaplan-Meier survival curves. The study was approved by the local ethics committees and performed within the framework of the Multidisciplinary Salivary Gland Society (formerly the European Salivary Gland Society).

RESULTS

Presenting Complaints

In the malignant group, the most common presenting symptom was neck swelling; seven (14%) patients reported pain, and seven (14%) regional numbness, whereas in three (6%) cases, preoperative impairment of the facial nerve marginal branch was present. No patient presented metastatic lymph nodes, which were detected with imaging techniques in 11 (22%) cases.

Surgical Results

Eleven (22%) patients underwent SGE, five (10%) SGE and superselective neck dissection (sublevel Ib), 18 (36%) selective neck dissection (level I–III), 14 (28%) modified radical neck dissection (level I–V); bilateral neck dissection was accomplished only in two (4%) patients. Two (4%) patients each required revision surgery for postoperative hematoma, or developed chyle leak that was conservatively managed. Another two patients suffered postoperative systemic sequelae (one pneumonia and one sepsis).

TABLE I.
Kaplan-Meier Univariate Analysis of Prognostic Factors

Prognostic Factors (*P*)	OS, *P* Value	DSS, *P* Value	RFS, *P* Value
High grade vs. low grade	.368	.630	.353
T category (pT1–2 vs. pT3–4)	.003*	.002*	.001*
N + vs. N0	.014*	.006*	.006*
Preoperative facial palsy	.008*	.150	.002*
Pain at presentation	.033*	.111	<.001*
Perineural spread	<.001*	<.001*	<.001*
Positive margin of resection	.478	.251	.015*
Age > 60 vs. < 60 years	.277	.787	.700

*Significant *P* value (<.05).
DSS = disease-specific survival; OS = overall survival; RFS = recurrence-free survival.

Histologic Results

The most frequent histology among benign tumors (N = 154) was pleomorphic adenoma (89.2%), whereas other histologies were only occasionally diagnosed. The most frequent histology among SMG malignancies was AdCC (n = 20, 40%), followed by AcNOS (n = 11, 22%), MEC (n = 6, 12%), and CEPA (n = 5, 10%). Other histologies were more rarely diagnosed: SDC in three (6%) cases, NE and MC in two (4%) cases each, and SCC in one (2%) patient. Notably, only 18 (36%) lesions were defined as low (n = 7, 14%), or intermediate grade (n = 11, 22%), whereas the remaining 32 (64%) were considered high grade. Interestingly, all 11 patients with intermediate-grade lesions were AdCC without a solid component.

Definitive pT classification was pT1 in 21 (42%) cases, pT2 in 14 (28%), pT3 in 10 (20%), and pT4a in five (10%); notably, 70% of patients had a lesion with a low pT category (pT1–2). Among 39 (78%) patients treated with any type of neck dissection, 15 (30%) were N + at pathological examination; occult nodal disease was identified in four (8%) cases. The number of positive nodes ranged between 1 and 40 (mean: 6.5); moreover, 12 (24%) patients had two or more positive nodes in the specimen. Analyzing the two (4%) cases who also underwent contralateral neck dissection, multiple nodal metastases were bilaterally found in the patient with SDC, whereas in the patient with CEPA, definitive histology did not confirm the presence of metastatic nodes in the contralateral neck, as suggested by preoperative US-guided FNAC and MRI.

Surgical margins were clear, close (<5 mm), and involved in 24 (48%), five (10%), and 21 (42%) patients, respectively. Among 21 patients with involved margins, 14 (67%) were affected by AdCC. Extracapsular spread (ECS) was present in eight (16%) cases; PNS and lymphovascular invasion was found in 25 (50%) and 17 (34%) cases, respectively.

Adjuvant Therapy and Post-treatment Surveillance

Thirty-five (70%) patients underwent adjuvant RT alone, and four (8%) patients received concomitant RT–ChT (one SDC, one high-grade AdCC, one ACNos, one NE). Follow-up status was available for 49 patients; mean and median follow-up were 78.6 and 60 months, respectively (range, 3–237 months). Twenty-three (47%) patients were alive without disease, 11 (22.5%) died of disease (two from locoregional and nine for distant recurrence), five (10.2%) were alive with disease (four locoregional and one distant failure), and 10 (20.4%) died of other causes. The mean age of death among patients who died for other causes was 68 years (median: 71 years), equally distributed among the three centers. Five-year OS, DSS, and RFS were 66.4%, 76.6%, and 69.1%, respectively; 10-year OS, DSS, and RFS were 57.1%, 72.1%, and 62.4%, respectively.

Statistical Analysis

At univariate analysis, pT status (pT1-T2 vs. pT3-T4), pN status, and presence of PNS affected OS, DSS, and RFS, and the presence of preoperative facial palsy and local pain negatively influenced OS and RFS; the latter was also influenced by positive margins (Table I, Figs. 1–5). Multivariate analysis confirmed the role of PNS in OS (HR: 7.89; 95% CI: 2.20-28.27; *P* = .002), DSS (HR: 13.14; 95% CI: 1.41-122.31; *P* = .024), and RFS (HR: 6.45; 95% CI: 1.20-30.45; *P* = .029). Conversely, nodal status was significant only when considering RFS (HR: 4.84; 95% CI: 1.24-18.93; *P* = .024), with borderline significance in DSS (HR: 4.41; 95% CI: 0.85-22.87; *P* = .077) (Tables II and III). The study of correlations among risk factors found that PNS was significantly associated with positive resection margins (*P* = .006) and pain at presentation (*P* = .043).

DISCUSSION

The present study, with some obvious limitations related to the restricted number of patients and

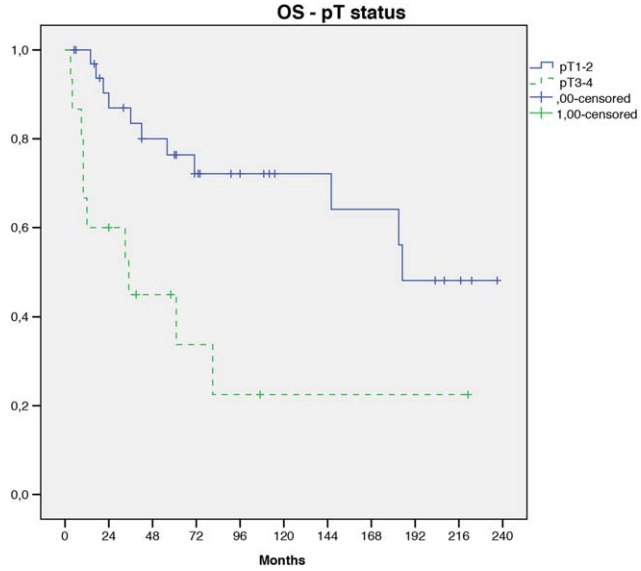

Fig. 1. Kaplan-Meier overall survival (OS) curves according to T category (pT1–2 vs. pT3–4). [Color figure can be viewed in the online issue, which is available at www.laryngoscope.com.]

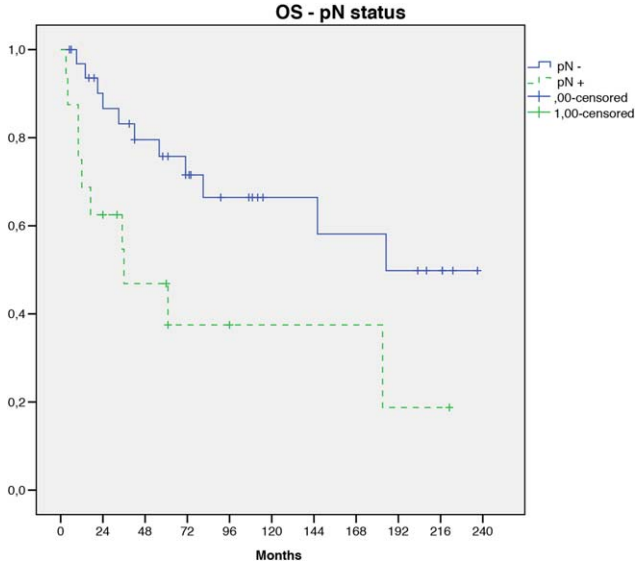

Fig. 2. Kaplan-Meier overall survival (OS) curves according to pathologic lymph node involvement (pN + vs. pN−). [Color figure can be viewed in the online issue, which is available at www.laryngoscope.com.]

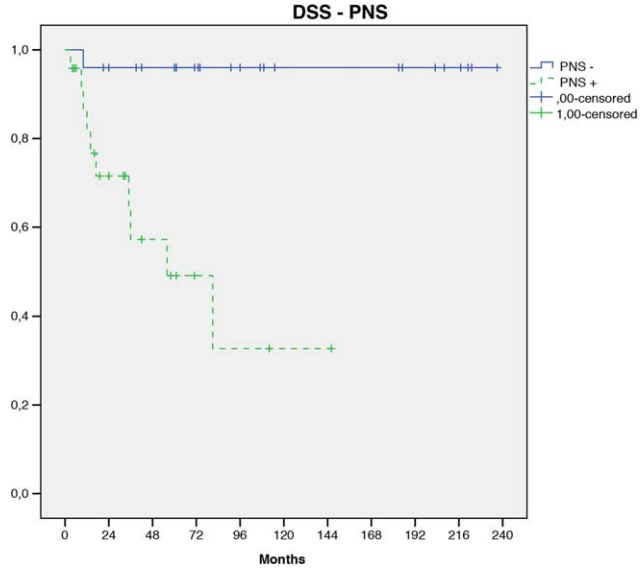

Fig. 4. Kaplan-Meier disease-specific survival (DSS) curves according to the presence of perineural spread (PNS). [Color figure can be viewed in the online issue, which is available at www.laryngoscope.com.]

retrospective design, reached some significant conclusions. First of all, the rate of malignancy in the SMG was lower than expected and similar to that of the parotid gland. Second, the well-known high aggressiveness of primary cancers of the SMG was confirmed by an unexpectedly high rate of high-grade lesions (64%). In spite of the high rate of high-grade tumors, oncologic outcomes were in agreement with published data. Last, the well-known prognostic factors (pT and pN status, PNS) for salivary tumors confirmed their value in malignancies of the SMG.

The malignancy rate in our cohort (24.5%) was lower than expected (34%–50%),[5,7,11] even though some recent reports seem to confirm our observation.[12–14] Mizrachi et al. reported a malignancy rate of 24% in 85 patients with SMGTs.[14] Atula et al., in a series of 83 patients with SMGTs, retrieved data on patients treated at other hospitals in the same area during the same period, and concluded that their rate of malignancy (30%) accurately represented the distribution of tumor types.[13] In fact, only a population-based registry could provide the true ratio between benign and malignant

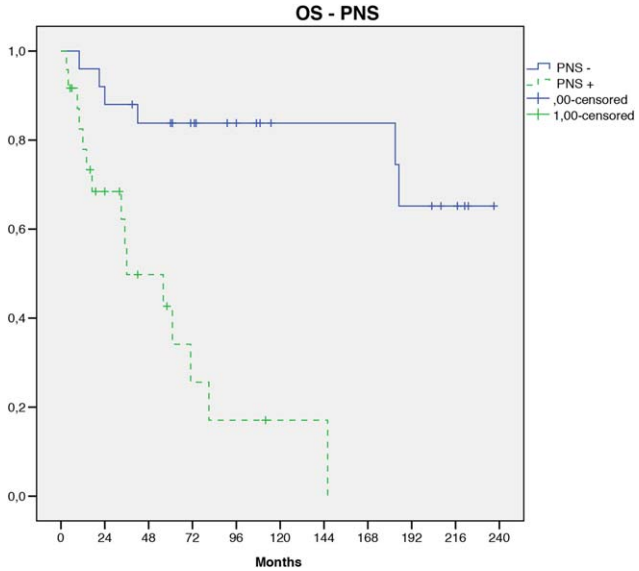

Fig. 3. Kaplan-Meier overall survival (OS) curves according to the presence of perineural spread (PNS). [Color figure can be viewed in the online issue, which is available at www.laryngoscope.com.]

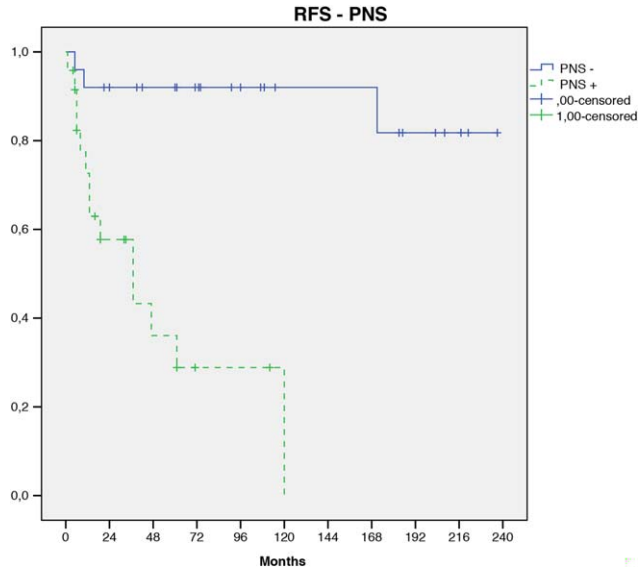

Fig. 5. Kaplan-Meier recurrence-free survival (RFS) curves according to the presence of perineural spread (PNS). [Color figure can be viewed in the online issue, which is available at www.laryngoscope.com.]

TABLE II.
Multivariate Analysis of Prognostic Factors on Overall Survival

Variable	Hazard Ratio	*P* Value	95% CI
T category (pT1–2 vs. pT3–4)	1.55	.405	0.55-4.34
N+	1.81	.311	0.57-5.70
Facial palsy	3.18	.216	0.51-19.91
Pain at presentation	1.77	.323	0.57-5.53
Perineural spread	7.89	.002*	2.20-28.27
Positive margins of resection	0.60	.381	0.19-1.87

*$P < .05$.
CI = confidence interval.

SMGTs, but National Cancer Registries do not include benign tumors, so this information is difficult to acquire.

Regarding the prevalence of histologies, our data confirm that pleomorphic adenoma (PA) is by far the most common lesion in the benign subgroup (almost 90% of cases), whereas other types are less frequently encountered.[12–16] The distribution of histologies in the malignant subgroup was consistent with published data, with AdCC, AcNOS, MEC, and SDC being the most frequent tumors.[8,11,13,17–20] The most striking difference between our study and data from the literature is the rate of high-grade lesions. Our series of patients included seven (14%) low-grade, 11 (22%) intermediate grade, and 32 (64%) high-grade lesions. An accurate grade definition, especially if three categories are identified, is not always available in previously published articles, especially for MEC, and the number of patients with an unknown tumor grade may be as high as 46.4%.[8] This may reflect the hesitancy to excessively stratify rare tumors such as MEC, provided that in SMG the risk of failure is also relevant for low-grade lesions.[4,11,21] Although a universally accepted system of classification for AdCC is lacking, with some authors favoring the division in two (low and high grade) categories and others in three (low, intermediate, and high grade), there is general agreement that the presence of a solid component has a negative prognostic impact.[8,22,23] To confirm the lack of uniformity, some authors prefer to consider all AdCCs high-grade lesions in view of the biological aggressiveness shown even by nonsolid AdCC.[4] Rayess et al. reported on 534 patients with SMG cancer from the Surveillance, Epidemiology, and End Results database; the overall rate of patients with poorly or undifferentiated SMGTs was 60.1% (n = 321), in agreement with our results. From their data, it was concluded that in patients with stage II, III, and IV tumors, differentiation was an independent predictor of survival.[24] Han et al. identified high-grade tumors in 32 of 64 (50%) SMG malignancies, whereas the remaining patients were almost equally divided into low (n = 15, 23.4%) and intermediate grade (n = 17, 26.6%); however, histologic grade failed to demonstrate an independent prognostic impact on survival.[19] Even in our cohort of patients, tumor grade was not found to have prognostic relevance. This may be the combined result of the disproportion between high-grade and non–high-grade lesions and small numerical entity of the cohort, with both factors probably leading to the lack of statistical significance. Analyzing our data, we observed that a non-negligible number of intermediate-grade AdCCs (5/11, 45.6%) displayed a more aggressive clinical behavior than expected, only on the basis of histologic differentiation (three died of disease, two alive with disease). In this regard, Rayess et al. advanced the hypothesis that the high rate of AdCC, with its very well-known propensity for local and distant failure, may justify the poor prognosis of SMGTs.[24]

Our OS data (66.4% and 57.1% after 5 and 10 years, respectively) compare favorably with those in the literature, with 5- and 10-year OS ranging between 50% and 69% and between 36% and 40%, respectively.[4,8,14,18,19,22] It is noteworthy, however, that in most publications, 5-year OS is in the 50% to 56% range[4,8,14,18,19]; moreover, our data also confirm that the OS decrease between 5 and 10 years is generally about 12% to 14%.[4,8] Not unexpectedly, OS was affected, on univariate analysis, by pT status, pN status, PNS, facial nerve palsy, and pain at presentation, thus confirming the results of previous studies in which high pT category (pT3–4), nodal involvement, and PNS were the factors associated with dismal prognosis.[4,9,14,18,19,22,25] The same factors also clearly impacted DSS (5-year DSS, 76.6%; 10-year DSS, 72.1%) and RFS (5-year RFS: 69.1%; 10-year RFS: 62.4%), both in line with previously reported values (5-year DSS: 61%–76%, 5-year RFS: 57%).[4,8,20] This is further reinforced by our multivariate analysis, underlining the independent impact of PNS and nodal involvement on most survival and recurrence outcomes (Figs. 3–5). The local aggressiveness of SMG cancer was confirmed by the high rate of patients with positive margins (42%), a value in line with recent experiences (38.7%).[18] The high probability of involved surgical margins may also be due to the high proportion of ADCC, which escape the gland of origin by PNS; another reason may be the possibility that SMG malignancies mimic inflammatory lesions, with the consequence that diagnosis is only reached at definitive histology.[20] In our series, there was a statistically significant association between PNS and the risk of involved margins, a finding that, though not univocally, is reported to carry a higher risk of recurrence but not to affect OS or DSS.[4,18] Not

TABLE III.
Multivariate Analysis of Prognostic Factors on Recurrence-Free Survival

Variable	Hazard Ratio	*P* Value	95% CI
T category (pT1–2 vs. pT3–4)	1.57	0.418	0.53-4.68
N+	4.84	0.024*	1.24-18.93
Facial palsy	1.43	0.719	0.20-10.05
Pain at presentation	2.51	0.129	0.76-8.27
Perineural spread	6.45	0.029*	1.21-34.45
Positive margins of resection	2.80	0.135	0.73-10.80

*$P < .05$.
CI = confidence interval.

unexpectedly, 67% of patients with involved margins had a diagnosis of AdCC.

Our favorable survival outcomes suggest that SMG malignancies are more similar in behavior to parotid cancer than expected. Some recent experiences in the treatment of parotid gland cancer, in fact, report a 5-year OS ranging between 60% and 82%.[26–30] Some speculations may be advanced to explain our encouraging results: first of all, meticulous diagnostic workup is essential to properly define local extension of the tumor and to obtain clues about its biologic aggressiveness. Second, the surgical technique by itself, with proper use of frozen sections and meticulous management of the neck, reduced the number of patients with positive margins and/or occult nodal disease left in place. Thorough histologic evaluation performed by experienced pathologists minimized the risk of misdiagnosis and thus improper treatment. Moreover, the vast majority of patients (78%) underwent what is considered the ideal treatment protocol for salivary cancer (i.e., surgery plus adjuvant RT-ChT), with exclusive surgery adopted only for low-risk patients.[4,31–33] Finally, the availability of advanced RT techniques (three dimensional and intensity-modulated radiotherapy) was of utmost importance to improve locoregional control. Our data confirm that distant rather that locoregional failure is the most critical pattern of recurrence in patients with SMG malignancies.[4,9,18] This is true for both high-grade lesions and for AdCC, regardless of tumor differentiation. This finding inherently addresses the concept that further improvement in terms of survival requires the identification of new targets for systemic treatment of these aggressive and elusive tumors.

CONCLUSION

Our study confirms that the malignancy rate in SMGTs does not significantly differ from that reported in parotid gland neoplasms, but the rate of poorly differentiated lesions is higher than expected. PA and AdCC are the most frequently encountered benign and malignant histologies, respectively. Prognosis of SMG malignancies seems comparable to that of parotid gland carcinomas; pT category, nodal involvement, and PNS were the most relevant factors.

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