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Research Article

# Malignant Minor Salivary Gland Tumors in Quito, Ecuador. Clinical Aspects and Prognostic Factors

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## Introduction

Salivary gland tumors include a group of uncommon heterogeneous neoplasms that represent 3% to 6% of all head and neck malignancies [1,2]. Approximately 70% of these tumors are located in the parotid gland and most of them are benign. However, gland tumors may also originate in the submandibular, sublingual and minor salivary glands [3,4]. There are about 550 to 1000 lobules of minor glands located throughout the submucosa of the mouth and upper aerodigestive tract, including the lips, gingiva, palate, tonsils, tongue, oropharynx, paranasal sinuses and parapharyngeal space. Minor glands are either primarily mucous, primarily serous or both [3-5]. Other extremely rare sites include lymph nodes, thyroid glands, facial bones and the hypophysis. The wide variability of locations challenges diagnosis, hinders staging and delays proper treatment [5]. Salivary gland carcinomas carry an unparalleled histological diversity in comparison with any other organ systems [6]. Despite minor salivary gland tumors account for less than 25% of salivary neoplasms, 50 to 75 percent of them are malignant [2-4,7-9].

The incidence and mortality of malignant minor salivary gland tumors (MMiSGT) in a specific population is difficult to know because these tumors are registered within the lesions of each anatomic site. The aim of this study was to review the clinical presentation, management and results of treatment of a series of patients with MMiSGT tumors treated at a third-level hospital.

## Materials and Methods

From 1980 to 2020, 639 patients were surgically treated for salivary gland tumors at the Social Security Hospital, a third level hospital, in Quito, Ecuador. Among them, 578 were located in major salivary glands, 54 in minor salivary glands, 19 benign and 35 malignant and 7 in ectopic salivary tissue. The clinical records of 35 patients with MMiSGT were reviewed. A university ethics committee permission was obtained. All these patients underwent a surgical resection, by a single surgeon and adjuvant therapy was given at the same institution. All of them signed an informed consent before surgery. The anatomical sites were determined by clinical examination and radiological imaging and were categorized as follows: nasal cavity and paranasal sinuses, oral cavity, oropharynx, larynx and trachea. The World Health Organization classification of head and neck tumors was used for histological classification and for definitions of grades within pathological groups. Staging was recorded according to the eighth edition of the American Joint Committee (AJCC) Staging Manual. MMiSGT were staged, by convention, with the mucosal tumor staging classification according to the anatomical site of the tumor.

## Statistical analysis

The clinical information of the patients was organized in a database. For later tabulation and analysis, non-parametric statistics and maximum likelihood, we used the Kaplan-Meier method to calculate estimates of overall survival and to compare the different variables The expected results at 5 and 10 years were calculated. Elaboration and organization of the database was processed in Excel (version 1682 [24021116].2024 Microsoft) and the statistical analysis was carried out in SPSS (version 25; IBM).

## Results

The mean age of patients was 51 (26-77) years (s.d.51 [±14.5] years); 23 were females and 12 were males. One patient was simultaneously treated for a papillary thyroid carcinoma and another developed breast cancer later. Nineteen tumors were located on the left side, eleven on the right side and 5 in the midline. The mean duration of symptoms was 15 (1-60) months (s.d.15 [±17.34] months). The

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mean size was 4.1cm (1-10) (s. d. 4.1 [±1.99] cm). Among 31 patients with tumor consistency description, 22 had hard and 9 had soft lesions. Thirty-two patients had fixed tumors and 3 mobiles. In 4 patients, lesions were ulcerated. Anatomic tumor location and histologic type appears on table 1. Imaging studies were performed in most of them, according to the hospital availability and included Computed Tomography (CT) in 21, Magnetic Resonance Imaging (MRI) in 6 and Ultrasound (US) in one. An angiography was performed in patient with adenoid cystic carcinoma of the nasal cavity who presented with epistaxis during 5 months. A patient, who was initially treated with limited surgery due to an adenoid cystic carcinoma of the palate in another institution, came to our clinic with a previous Positron Emission Tomography (PET) requested by his clinical oncologist. There were no patients with initial distant metastasis. TNM distribution appears on tables 2&3. All patients underwent a surgical procedure for removal of the tumor. Three patients with clinically positive neck nodes underwent a modified neck dissection in 2 and a suprahyoid neck dissection in one. These 3 patients (8.6%) had pathological positive nodes. Three additional patients, underwent suprahyoid neck dissection, one for PET suspicious nodes and 2 because a combined neck and intraoral approach was performed. Finally, a patient with a cricotracheal adenoid cystic carcinoma whose thyroid was attached to the tumor, underwent a lateral paratracheal node dissection. All of these last 4 patients had pathologically negative nodes. Only two patients had been treated initially elsewhere: one patient with radiotherapy for an adenoid cystic carcinoma of the nasal cavity, who underwent a maxillectomy in our service and was lost to follow up; and another patient, a young woman initially treated with both radio and chemotherapy for a myoepithelial carcinoma of the base of the tongue and persistent tumor, who underwent a wide resection and is currently free of disease 2 years later. Surgical modalities appear on table 4. Postoperative complications occurred in 5 patients and were mostly minor.

| Anatomic site | Adenoid cystic carcinoma | Mucoepidermoid carcinoma | Adenocarcinoma | Acinar cell carcinoma | Malignant mixed tumor | Myoepithelial carcinoma | Total |
|---|---|---|---|---|---|---|---|
| Nasal cavity and maxillary sinus | 7 | | | | | | 7 |
| Oral cavity | | | | | | | 20 |
| Tongue | 2 | | | | | | 2 |
| Gum | 3 | 1 | | | | | 4 |
| Buccal mucosa | | 1 | | | | | 1 |
| Retromolar gingiva | | 2 | | | | | 2 |
| Hard palate | 3 | 3 | 1 | 1 | 1 | | 9 |
| Floor of the mouth | 1 | | | 1 | | | 2 |
| Oropharynx | | | | | | | 7 |
| Tonsil | | | 1 | | | | 1 |
| Base of the tongue | 4 | | | | | 1 | 5 |
| Soft palate | | | 1 | | | | 1 |
| Larynx- trachea | 1 | | | | | | 1 |
| Total | 21 | 7 | 3 | 2 | 1 | 1 | 35 |

**Table 1:** Anatomic location and histology of tumors.

| T | N0 | N1 | N2a | N2b | Total |
|---|---|---|---|---|---|
| 1 | 5 | | | | 5 |
| 2 | 16 | 1 | | 1 | 18 |
| 3 | 7 | | 1 | | 8 |
| 4a | 2 | 2 | | | 4 |

**Table 2:** TNM staging.

| Stage | Number of patients |
|---|---|
| I | 5 |
| II | 16 |
| III | 8 |
| IV | 6 |

**Table 3:** Stage distribution.

| Anatomic location (patients) | Surgical type | Number of patients |
|---|---|---|
| Nasal fossa and maxillary sinus (7) | Partial maxillectomy | 4 |
| | Total maxillectomy | 2 |
| | Craniofacial resection | 1 |
| Oral cavity (20) | Wide excision | 12 |
| | Partial maxillectomy | 5 |
| | Transmaxillary resection | 1 |
| | Oral and cervical approach resection | |
| | | 2 |
| Oropharynx (7) | Wide excision | 5 |
| | Transmaxillary resection | 1 |
| | Subtotal glossectomy and total laryngectomy | 1 |
| Larynx/Trachea (1) | Cricotracheal resection | 1 |

**Table 4:** Surgical modalities according anatomic location of tumors.

The report of surgical margins was available in 24 patients and were positive in 15 cases. All tumors arising in the nasal fossa had positive margins and those arising in the oropharynx, clear or close. Adjuvant treatment was given to 16 patients mainly based on aggressive histology and positive surgical margins. Radiotherapy was used in 12 patients and both radio and chemotherapy in 4 patients. Mean follow up was 6 years 5 months (s.d. 86.9 [± 83.4] months; range

3-326 months). Only 2 patients were lost to follow up. Overall five-year and ten-year survival rates were 75.8 % and 55.8%, respectively (Figure 1). Prognostic factor overall survival by univariate analysis appears on table 5. As there is not an available staging classification for minor salivary gland tumors, they were staged similar to squamous cell carcinoma according to the anatomic site of origin [10]. Local recurrence occurred in 10 patients, regional recurrence in 2 and distant metastasis in 8. Location of these metastases was lung in 8 patients, liver in one and brain in one. Patient conditions at last follow up appear on table 6. Age (<60 versus ≥60 years), tumor histology and surgical margins were found to be significant prognostic factors by univariate analysis (Figures 2-4).

| Characteristics | n (%) | 5-year | P value | 10-year | P value |
|---|---|---|---|---|---|
| | | % | | % | |
| Gender | | | | | |
| Male | 12 (34.3) | 70.1 | 0.4563 | 70.1 | 0.1929 |
| Female | 23 (65.7) | 78.8 | | 45.1 | |
| Age | | | | | |
| ≤60 years | 24 (68.6) | 87.9 | 0.0.2830 | 79.1 | 0.04611 |
| >60 years | 11 (31.4) | 74 | | 44.4 | |
| Tumor histology | | | | | |
| Adenoid cystic | 21 (60.0) | 60.8 | 0.03153 | * | |
| Mucoepidermoid | 7 (20.0) | 100 | | 100 | 0.03153 |
| Other | 7 (20.0) | 100 | | 83.3 | |
| Size (cm) | | | | | |
| ≤4cm | 23 (65.7) | 79.7 | 0.4563 | 58.8 | 0.5374 |
| >4cm | 12 (34.3) | 66.7 | | 50 | |
| Site | | | | | |
| Nasal cavity | 7 (20.0) | 41.7 | 0.06277 | * | |
| Oral cavity | 20 (57.1) | 83.9 | | 70.7 | 0.2009 |
| Oropharynx | 7 (20.0) | 83.3 | | 41.7 | |
| Larynx trachea | 1 (2.9) | | | | |
| Stage | | | | | |
| I | 5 (14.3) | 75 | 0.5498 | 75 | 0.4766 |
| II | 16 (45.7) | 86.2 | | 50.6 | |
| III | 8 (22.9) | 58.3 | | 58.3 | |
| IVA | 6 (17.1) | 80 | | * | |
| Margins** | | | | | |
| Clear | 9 (37.5) | 100 | 0.05158 | 100 | 0.01489 |
| Close or positive | 15 (62.5) | 66.9 | | 56,6 | |
| Adyuvant treatment | | | | | |
| Yes | 17 (48.6) | 78.2 | 0.1053 | 75 | 0.5211 |
| No | 18 (51.4) | 48.8 | | 65 | |

**Table 5:** Univariate analysis for overall survival. * No patients at risk **Described in 24 patients.

| Clinical condition | Number of patients |
|---|---|
| Alive without disease | 19 |
| Alive with disease | 3 |
| Local recurrence | 1 |
| Distant metastasis | 2 |
| Dead without disease | 3 |
| Dead with disease | 10 |
| Local recurrence | 4 |
| Metastasis | 4 |
| Local recurrence and metastasis | 2 |

**Table 6:** Clinical condition at last follow up.

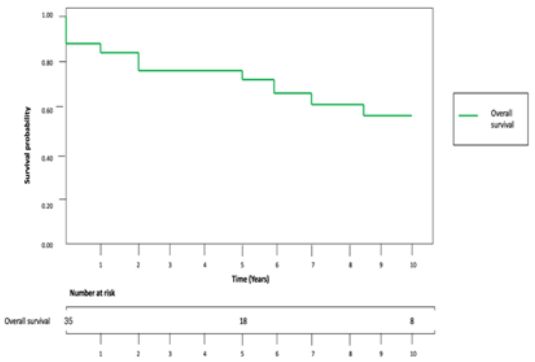


**Figure 1:** Overall Survival.

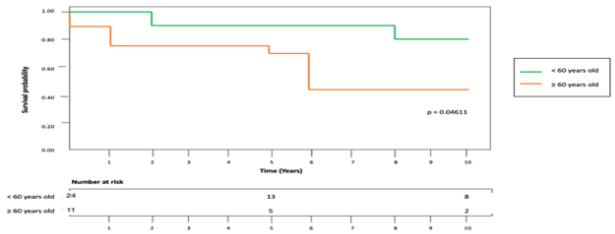


**Figure 2:** Overall survival according to age.

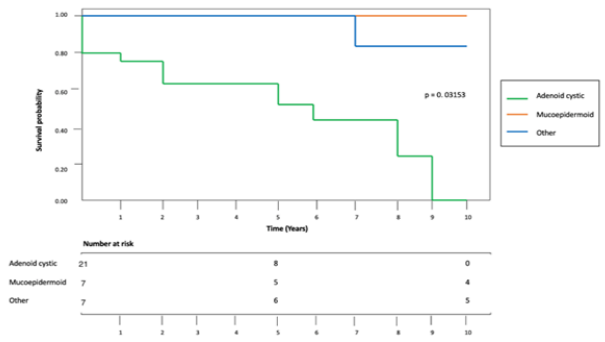


**Figure 3:** Overall survival according to histological type.

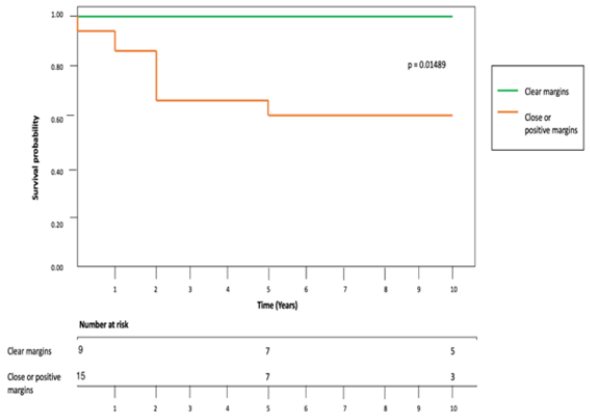


**Figure 4:** Overall survival according to margin.

## Discussion

The most remarkable studies on MMiSGT have been the Baddour's report [11] on 5,334 patients from the Surveillance, Epidemiology and End Results (SEER) database and the Memorial Sloan Kettering Cancer Center's series of 450 patients reported by Hay [6]. In Latin America, only few studies have been published and most of them described demographic, clinical and pathological data [8,12-16]. In only one study current patient status at the last follow up visit was described [17]. No survival results appeared in any of these reports. Age and gender distribution still have discrepancies among literature, possibly due to referral bias and/or ethnic variations [1-2,12,17-18]. Most patients are middle aged and sex distribution seems approximately similar, according to Baddour's and Hay's reports [6,11]. Clinical presentation varies according to the location and the degree of invasion to nearby structures. They usually present as painless submucosal masses or ulcers in the palate, lips, or mucosa. On counterpart, advanced disease is more likely to manifest with nasal obstruction, vision changes, trismus and other symptomatology related to the possibility of skull base invasion, intracranial extension, or cranial nerves impairment [19]. The assessment of location, incidence and natural evolution of MMiSGT is difficult because most studies analyze all minor salivary gland neoplasms together [1-4,7-8,17,20-24]. Site distribution for malignant SG tumors were the oral cavity (59%), followed by the oropharynx (21%), the sinonasal cavity (16%) and the larynx (4%), according to Baddour's study [10], and 68%, 21%, 8% and 4%, for the same sites, according to Hay's series [6]. This distribution was 57%, 20%, 20% and 3% in our series, respectively. The palate is the most common oral cavity site [25,26]. Sinonasal lesions usually have more advanced T-stage at diagnosis, more invaded resection margins and a higher local recurrence rate [27].

The most common MMiSGT are Adenoid Cystic Carcinoma (ACC) (32% to 69%) and Mucoepidermoid Carcinoma (MEC) (15% to 35%) [2,6,8,17,23,28-31]. Other less common tumors are acinic cell carcinoma, polymorphic adenocarcinoma, myoepithelial carcinoma and carcinoma from pleomorphic adenoma [32]. ACC is a slow growing, but aggressive, tumor which tends to present perineural and lymphatic extension and distant metastasis [33]. MEC was the most common histological type in both Baddour and Hay's series. However, adenocarcinoma was the second most common in Baddour's study and ACC in Hay's report [6,11]. ACC was the most common in our study. There may be tumor histology frequency variation when classified by site. Our patients had larger tumors and more advanced stages. In Hay's report, T size was ≤4cm in 81% of patients while it was 67% in our study; and almost half of the patients (49.6%) had stage I disease, but only 14.3% in our series. Any modality of wide excision of the primary tumor is the treatment of choice. In Baddour's study, 67% of patients received a form of surgical therapy [11]. In the other reports [6,34,35], all patients were treated with a curative intent. Neck dissection is indicated in the presence of clinical or cytologically positive nodes. A neck dissection was performed in 29% of patients in Hay's series [6] and in 23% in ours. Lymph node examination was performed in 15% of patients of the SEER program [11]. Forty-nine per cent of patients in our study received postoperative radiation treatment, but ACC patients were more likely to receive it (66%).

Interestingly, Baddour [11] reported an 8.35 of Distant Metastasis (DM) at the time of diagnosis which was higher than in head and neck squamous cell carcinoma and major salivary gland malignancies. Of 152 patients from the SEER database with MMiSGT and DM at presentation, 50 (32.9%) who underwent Primary Tumor Surgery (PTS) had >20% increase in 1- and 2-year Overall Survival (OS) and Cancer-Specific Survival (CSS) compared with their counterparts without PTS [36]. Positive surgical margins have been described in 19.6% to 40% of patients [6,7,37-39]. In the present study, we had 37.5% of patients with positive surgical margins. In our study, the 5- and 10-year OS rates were 75.8 % and 55.8%, respectively, approximately similar to other reports [6,34,35,39]. A higher size of tumors, a higher percentage of stage III and IV cases (40%) and a highest frequency of distant metastases in this study should be considered in the analysis of these figures. In Hay's series, factors predictive of failure for overall survival on univariate analysis were as follows: age greater than or equal to 60 years, male sex, history of tobacco use, history of serious comorbidity, Perineural Invasion (PNI), Lymphovascular Invasion (LVI), close/positive margins, histology risk group, postoperative radiation, pathological T and N stages and AJCC oncological overall stage [6]. In Baddour's study, patients with tumor location in the larynx and nasal cavity and paranasal sinuses, as well as age older than 75 years, had significant worse 5- and 10-year cause specific survival; while race, sex and postoperative radiotherapy were not significant prognostic factors. Additionally, MEC subtype histology and local disease patients had better survival than ACC and adenocarcinoma as well as regional or distant disease [11]. Age [39], sex [34,39], site of occurrence [34,39], grade of tumor [34,39], vascular invasion [34,39], nerve invasion [40], stage [34,39,41], surgical margins [18,38] and postoperative radiotherapy [35] have been found to be significant prognostic factors in other series. Age, tumor histology and surgical margins were found to be significant prognostic factors by univariate analysis in the present series. Nasal cavity tumors had a poorer overall survival when comparing to oral cavity or oropharyngeal tumors, but it did not reach a significant value. This fact could be explained by the fact that all tumors arising in the nasal fossa had more frequent positive margins than those arising in the other locations. Other described predictive factors, such as sex, stage and adjuvant treatment were not significant in our series, probably due to the smaller size of our series. On multivariate analysis, age greater than or equal to 60 years, male sex, larynx/trachea location, high risk histology group, advanced clinical stages and no adjuvant radiotherapy treatment were associated with poorer outcome in Hay's series [6]. In ACC, solid histological subtype and positive surgical margins have been described as important predictors of poor outcome while

postoperative radiation has provided better OS and CSS compared with surgery alone [42]. In patients with ACC of the oral cavity, neck node metastases have been found to have a significant negative impact on OS and CSS [43]. Patients with low- or intermediate-grade MEC exhibit satisfactory survival after surgery, but patients with high-grade tumors, survival rates are poor and do not improve following adjuvant therapy [44]. In a study of sinonasal MMiSGT, isolated from the National Cancer Database (2004-2014), no difference in survival was found among treatment modalities: surgery alone, surgery with radiotherapy and surgery with chemoradiotherapy (CRT), with the exception of RT alone. Positive margins were prognostic in this tumor location. In this subset of patients, CRT did not provide survival benefit over surgery and RT and surgery alone was associated with decrease survival [45]. However, the National Comprehensive Cancer Network (NCCN) guidelines has recommended Chemotherapy (CT) only in the most concerning cases. Pathogenesis of minor salivary gland carcinoma is still not completely elucidated. Factors like smoking, poor hygiene or alcohol seem not to play a significant role as in oral squamous cell carcinoma [41]. However, history of tobacco use has been found to be a predictive factor of failure on univariate analysis in the series of the MSKCC [6]. In Hay's series, there were 21.6% failures: distant, local and regional in frequency order. They occurred in 13 out of 35 cases (37.1%), in the present report; we had distant and local failures but no regional recurrences [6]. Distant metastases occurred in 13.6% of cases in Hay' report and in 22.9% in our series. One strength in this short series could be that surgical treatment was performed by one surgeon and overall management was homogeneous.

## Conclusion

MMiSGT are certainly very uncommon neoplasms so homogeneous institutional studies are occasionally published. We have reviewed the clinical and therapeutic features of our institutional patients over a long-time span and, to our knowledge, this is the only report with analysis of prognostic factors of MMiSGT carried out in Latin America. As younger patients, adenoid cystic carcinoma histology and positive surgical margins were found to be significant prognostic factors, in patients with these features, a more aggressive multimodality treatment should be warranted.

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