Abstract: The aims of this study were to determine the incidence of malignant salivary gland tumors (MSGTs) in a specific in Spanish Mediterranean population, evaluate oncological outcomes, and identify prognostic factors for survival. Overall survival and disease-free survival rates were calculated for 23 patients with MSGTs who were treated in our department during 2004-2012. In the recruitment population of the reference hospital, annual incidence per 100,000 inhabitants was estimated, with corresponding 95% confidence intervals (CIs). The mean annual incidence of MSGTs was 0.91 new cases per 100,000 inhabitants (95% CI, 0.14-2.83). The most common histological type was squamous cell carcinoma (34.8%). Overall survival ranged from 2 to 120 months (mean 70.5 months). The 5-year overall survival rate was 52.5%, and the 5-year disease-free survival rate was 50%. The mean disease-free interval was 73.9 months (95% CI 47.1-100.7). Metastatic spread, tumor stage, perineural invasion, a submaxillary location, tumor size, histological grade, positive lymph node status, and presence of positive surgical resection margins were the most important factors in patient survival. Our results are consistent with those of other studies in relation to disease incidence but differ somewhat with respect to histological type. (J Oral Sci 58, 67-73, 2016)

Keywords: epidemiology; oral cancer; salivary glands; head and neck cancer; salivary malignancies; incidence.

Introduction

Salivary gland cancers are rare, less than 5% of all newly diagnosed cancers of the head and neck, and exhibit considerable phenotypic, biological, and clinical heterogeneity (1). Studies of different populations of the world reveal geographical disparities in the incidence and frequency of the various types of these tumors (2,3). The annual incidence of malignant salivary gland tumors (MSGTs) is estimated to be one per 100,000 inhabitants (4).

Salivary gland cancers comprise a heterogeneous group of lesions with complex clinical and pathological characteristics and varied biological behavior (5,6). Their rarity makes it difficult to study the natural history of the disease, patient survival, treatment, and outcome. To obtain a true measure of the incidence of salivary...
tumors it is essential to clearly establish the date of onset, with reliable retrieval of population data, confirmation of the histological diagnosis, and termination of the case as defined by date of recurrence, death, or closure of the study period (7).

A retrospective study of 1,392 patients with MSGTs found that the most frequent tumor type was mucoepidermoid carcinoma (8), as did another study, which enrolled 1,268 patients (9). However, a study of 2,737 patients found that the most common histological type was adenoid cystic carcinoma (10). This illustrates the controversy and variability regarding the different histological types described in the literature.

Few studies of head and neck cancers have focused on the salivary glands (11). In contrast to most head and neck cancers, in which squamous cell carcinomas predominate (12,13), MSGTs encompass at least 20 distinct histological subtypes (14). The present study examined the incidence of MSGTs in a specific Spanish Mediterranean population (the Valencian Community), evaluated oncological outcomes, and identified factors associated with patient survival.

Material and Methods
The cancer information system of the Valencian Community (Spain) was accessed to analyze all MSGTs diagnosed in one area of the integrated healthcare map of this Spanish Mediterranean coastal region. This corresponded to the recruitment population of Arnau de Vilanova Hospital (approximately 300,000 inhabitants). The surgical pathology files of the hospital were reviewed, and all cases of MSGT were selected. We included all tumors identified as incident malignancies during the period between January 2004 and December 2012. Tumor topography was coded accordingly to the ICD-O-3 (International Classification of Diseases for Oncology, World Health Organization) (15). For tumors of the major salivary glands we included the topographic codes C07.9 and C08.0-08.9; tumors of minor salivary glands were coded according to their anatomical location. This study was conducted in accordance with the Helsinki Declaration and was approved by the Ethics Committee of Arnau de Vilanova Hospital, Valencia, Spain (Approval 591/2014).

All tumors were subjected to histological review to confirm the diagnosis, followed by classification according to the International Agency for Research on Cancer (IARC) (14). Mortality data were collected by consulting the mortality registry of the Valencian Community and the Spanish National Mortality Census. These data included date of death, along with verification of the vital status of all patients included in the study (i.e., alive without disease, alive with disease, death due to other causes, or death due to the disease).

Variables related to the patient (age, sex), lesion (localization, size), positive surgical margins, histological type, lymph node status (positive or negative regional lymph node invasion), pathological stage, and type of treatment (surgery, adjuvant radiotherapy, or chemotherapy) were evaluated. Overall survival was defined as time from hospital discharge to the day of death or last follow-up. Local recurrence was defined as tumor recurrence at the primary tumor site, and time to recurrence was calculated as time from diagnosis to the day of local recurrence or last follow-up (16).

The statistical significance level was defined as 5% (α = 0.05). The Kaplan-Meier method was used for analysis of the data, and survival curves were estimated according to the time of each event. The log-rank test was used to determine whether differences in patient or tumor characteristics resulted in significantly different survival curves. The SPSS version 15.0 statistical package (SPSS Inc., Chicago, IL, USA) for MS Windows was used throughout, and MS Excel (Microsoft, Redmond, WA, USA) was used to generate the database.

Results
The mean annual incidence of MSGTs during the study period was 0.91 cases per 100,000 inhabitants (95% confidence interval [95% CI] 0.14-2.83).

The clinicopathological characteristics of the 23 patients are shown in Table 1. There were 10 males and 13 females (age range 11-89 years; mean age 66 years). The major salivary glands were affected in most patients (19 cases, 82.6%); there were 15 parotid gland tumors and four submaxillary gland tumors. No sublingual gland malignancies were documented. The minor salivary glands were affected in four patients (17.4%): three had hard palatal gland tumors and one had a tumor in the cheek mucosa (Table 2).

Tumor size ranged from 1.5 to 5 cm (average size 3.2 cm). Survival curve analysis of tumor size showed a statistically significant effect for malignancies larger than 2 cm (P = 0.041). Tumor histopathology is described in Table 2, and the most frequent salivary gland malignancy was squamous cell carcinoma (34.8%). Regarding histological grade, 16 tumors were classified as low grade (69.6%) and seven as high grade (30.4%). Follow-up ranged from 24 to 120 months. During this period, six local recurrences were recorded after a disease-free interval ranging from 5 to 60 months. Distant metastases were documented in 10 patients (45.5%). Table 1 shows
the distribution of metastases. Mean survival among patients with distant metastases was 4.6 months (95% CI 2.2-6.9). Regarding final clinical staging, 26% of the cases were classified as stage I or II and 74% as stage III or IV.

Patients were treated mainly by surgery alone (12 cases, 52%) and less frequently by surgery with adjuvant radiotherapy (4 cases, 17%), surgery with adjuvant chemoradiotherapy (4 cases, 17%), and surgery with adjuvant chemotherapy (1 case, 4%). Two patients received radiotherapy alone because their tumors were non-resectable. Total or partial parotidectomy was performed in 10 (43%) and three cases (13%), respectively, and sub-mandibulectomy was performed in four cases (17%). Four patients (17%) underwent other types of resection. Positive (infiltrated) resection margins were recorded in 10 cases (47.6%). Two patients (8.6%) received no treatment and were given only supportive care. Thirteen patients (56%) underwent neck dissection.

At the end of the follow-up period, 10 patients were alive (43.5%), while nine deaths from tumor disease were recorded (39.1%), along with four deaths from other causes (17.4%). Among surviving patients, one continued to have neoplastic disease. Overall survival ranged from 2 to 120 months, and the 5-year overall survival rate was 52.5%. Mean survival was 70.5 months (95% CI 46.5-94.5). Six patients developed local recurrence. The mean disease-free interval

| No. | Age | Sex | Location | Size (cm) | Resection margins | RT | CT | Local recurrence | Metastasis | Status | OS (months) | DFS (months) | SSLR (months) | SSDM (months) |
|-----|-----|-----|----------|-----------|------------------|----|----|-----------------|------------|--------|-------------|--------------|---------------|---------------|
| 1   | 82  | F   | Parotid  | 3         | No               |    |    | No              | Death due to other causes | 2      | 2          |             |              |               |               |
| 2   | 89  | F   | Parotid  | 4         | Yes             | Yes | No | No              | Death     | 6      | 6           |              |               |               |
| 3   | 83  | F   | Parotid  | 3         | No              | No  | Yes | Yes             | Death     | 27     | 11 16 9     |              |               |               |
| 4   | 62  | F   | Parotid  | 3         | No              | Yes | No | No              | Alive     | 120    | 60 60       |              |               |               |
| 5   | 76  | M   | Parotid  | 5         | Yes             | Yes | No | No              | Death due to other causes | 50     | 50         |              |              |               |               |
| 6   | 72  | F   | Parotid  | 4         | No              | Yes | No | No              | Alive     | 119    | 119         |              |               |               |
| 7   | 11  | M   | Parotid  | 2         | Yes             | No  | No | No              | Alive     | 116    | 116         |              |               |               |
| 8   | 57  | F   | Submaxillary | 3   | No              | Yes | No | No              | Yes (lungs) | 14     | 0 14        |              |              |               |
| 9   | 81  | M   | Submaxillary | 3    | No              | Yes | No | Yes             | No         | 6      | 6           |              |               |               |
| 10  | 83  | F   | Parotid  | 5         | Yes             | No  | Yes | Yes             | Yes (lungs) | Death | 31 27 4 4     |              |               |               |
| 11  | 41  | M   | Parotid  | 4         | Yes             | No  | No | No              | Alive     | 84     | 84          |              |               |               |
| 12  | 44  | F   | Parotid  | 2         | No              | No  | No | No              | Alive     | 48     | 48          |              |               |               |
| 13  | 62  | M   | Parotid  | 5         | No              | Yes | No | No              | Alive     | 25     | 25          |              |               |               |
| 14  | 56  | F   | Parotid  | 3         | Yes             | Yes | Yes | Yes             | Yes (skin, neck, and axilla) | Alive | 22 13 9     |              |               |               |
| 15  | 62  | M   | Parotid  | 5         | Yes             | Yes | Yes | Yes             | Yes (lungs and liver) | Death | 24 6 3       |              |               |               |
| 16  | 79  | M   | Parotid  | 3         | Yes             | Yes | No | No              | Death due to other causes | 16     | 16         |              |               |               |
| 17  | 65  | F   | Hard palate | 2   | No              | No  | No | No              | Alive     | 84     | 84          |              |               |               |
| 18  | 75  | M   | Hard palate | 3   | No              | Yes | No | Yes             | Death     | 3      | 3           |              |               |               |
| 19  | 75  | M   | Hard palate | 3   | No              | Yes | No | Yes             | Death     | 13     | 7 2         |              |               |               |
| 20  | 60  | F   | Submaxillary | 3   | No              | No  | No | Yes             | Death     | 7      | 2 5         |              |               |               |
| 21  | 33  | M   | Submaxillary | 2   | No              | Yes | No | No              | Alive     | 18     | 18          |              |               |               |
| 22  | 88  | F   | Cheek mucosa | 4    | No              | No  | Yes | Yes             | Death due to other causes | 3      | 0          |              |               |               |
| 23  | 82  | F   | Parotid  | 2         | No              | Yes | No | No              | Alive     | 43     | 29 14       |              |               |               |

OS: Overall survival; DFS: Disease-free survival; SSLR: Survival since local recurrence; SSDM: Survival since distant metastasis

Table 2 Histopathological characteristics and sites of malignant salivary gland tumors

| n  | Site                                      |
|----|-------------------------------------------|
| 23 | 100%                                      |
| 4  | 17.4% 3 in parotid gland, 1 in submaxillary gland |
| 8  | 34.8% 6 in parotid gland, 2 in submaxillary gland |
| 3  | 13.0% 2 in parotid gland, 1 in minor salivary glands of the palate |
| 2  | 8.7% 1 in submaxillary gland, 1 in minor salivary glands of the palate |
| 2  | 8.7% 1 in parotid gland, 1 in minor salivary glands of the cheek mucosa |
| 1  | 4.3% Parotid gland |
| 1  | 4.3% Parotid gland |
| 1  | 4.3% Parotid gland |
| 1  | 4.3% Minor salivary glands of the palate |

ACC: acinar cell carcinoma; SCC: squamous cell carcinoma; MEC: mucoepidermoid carcinoma; CAC: cystic adenoid carcinoma; NOS: not otherwise specified LGPA: low-grade polymorphic adenocarcinoma
was 73.9 months (95% CI 47.1-100.7). Kaplan-Meier curves of overall and disease-free survival are shown in Figs. 1 and 2, respectively. Regarding disease-free interval, 87.1%, 80.4%, and 62.5% of patients developed no disease recurrence during the first, second, and third years, respectively. From the fourth year onward the percentage remained stable (50%) until the eighth year of follow-up. Four factors adversely affected disease-free interval: degree of lymph node involvement, metastatic spread, tumor stage, and perineural invasion.

Table 3 shows the results of the log-rank test in relation to patient survival. The presence of metastases (log-rank test: \( P < 0.001 \)) and tumor stage (log-rank test: \( P < 0.001 \)) were the factors that had the greatest impact on the survival curve. Other adverse prognostic factors with similar effects on survival were perineural invasion (log-rank test: \( P = 0.002 \)) and tumor location. There was no difference in survival between patients with malignancies in the major or minor salivary glands (\( P = 0.261 \)), although a significant difference was observed between those with parotid gland and submaxillary gland tumors (log-rank test: \( P = 0.004 \)). After 2 years of follow-up, the probability of survival was 84% for patients with parotid gland tumors and 25% for patients with submaxillary gland tumors. Patients with no evidence of positive lymph nodes had significantly better survival than did those with positive nodes (log-rank test: \( P = 0.010 \)). Tumor size and histological grade, as well as presence of positive surgical resection margins, had lesser but still significant effects on survival.

### Discussion

This study analyzed the incidence of MSGTs in a specific population, evaluated oncological outcomes, and identified prognostic factors in survival. To our knowledge, this is the first study of MSGT incidence in a specific Spanish Mediterranean population, which corresponded to a reference hospital recruitment population of approximately 300,000. Although a number of retrospective studies have analyzed incidences of salivary gland malignancies, the epidemiological characteristics of these tumors have not been clearly established (17), as the individual studies were often limited to specific populations (18,19), anatomical sites (20), or tumor types (21-23). Comparisons of different populations and clinical series are limited by the use of different inclusion criteria (e.g., benign and malignant tumors, involvement of major or minor salivary glands, histological variants) (24). All this makes it difficult to establish comparisons among studies.
and draw conclusions regarding the incidence of MSGTs in a given population. A US study of the incidence of malignant MSGTs found 6391 cases diagnosed between 1992-2006, which corresponded to an annual incidence of 1.2 cases per 100,000 inhabitants (24). In contrast, we noted an annual incidence of 0.91 cases per 100,000 inhabitants during the period between January 2004 and December 2012. Table 4 (7,10,24-29) shows the reported incidences of MSGTs, according to geographical setting. The figures vary but are low in all cases, ranging from 0.2 to 1.3 cases per 100,000 inhabitants per year.

In recent years, conventional management of patients with MSGTs in a single hospital department has given way to the formation of multidisciplinary head and neck cancer committees in many hospitals, which offer coordinated meetings among specialists treating MSGTs. Specifically, these permanent committees now comprise specialists in maxillofacial surgery, ear, nose, and throat disease, oncology, and pathology, among others, and aim to provide treatment that is as specific and individualized as possible.

| Author                  | Country     | Study period | Total number of cases | Minor salivary glands | Parotid | Submaxillary | Sublingual | Incidence (cases per 100,000 inhabitants) | Most common histological type |
|-------------------------|-------------|--------------|-----------------------|-----------------------|---------|--------------|-----------|------------------------------------------|------------------------------|
| Ostman et al. 1997 (25) | Sweden      | 1960-1998    | 2557                  | Yes                   | Yes     | Yes          | Yes       | 1.3                                       | Cystic adenoid carcinoma    |
| Pinkston and Cole 1999 (26) | USA        | 1968-1989    | 39                    | No                    | Yes     | Yes          | Yes       | 0.9                                       | Mucoepidermoid carcinoma   |
| Koivunen et al. 2002 (27) | Finland    | 1988-1998    | 40                    | Yes                   | Yes     | Yes          | Yes       | 0.43                                      | Mucoepidermoid carcinoma   |
| Przewoźny and Stankiewic 2004 (28) | Poland | 1991-2000    | 63                    | No                    | Yes     | No           | No        | 0.2                                       | Mucoepidermoid carcinoma   |
| Boukeris et al. 2009 (24) | USA        | 1992-2006    | 6391                  | No                    | Yes     | Yes          | Yes       | 1.2                                       | Squamous cell carcinoma     |
| Björndal et al. 2011 (29) | Denmark    | 1990-2005    | 952                   | Yes                   | Yes     | Yes          | Yes       | 1.1                                       | Cystic adenoid carcinoma    |
| Bradley and McGurk 2013 (7) | United Kingdom | 1988-2007   | 147                   | Yes                   | Yes     | Yes          | Yes       | 0.8-1.3                                   | Mucoepidermoid carcinoma   |
| De Ridder et al. 2014 (10) | The Netherlands | 1989-2010  | 2737                  | Yes                   | Yes     | Yes          | Yes       | 0.8                                       | Cystic adenoid carcinoma    |

In contrast, studies in China (35), the Netherlands (10), Sweden (25), and Denmark (29) observed that cystic adenoid carcinoma was the most common salivary gland malignancy. In our series, squamous cell carcinoma was the most frequent malignancy, representing 34.8% of the total sample. This finding is similar to the results of a tumor incidence study covering a period of 14 years and involving 6,391 malignant tumors: squamous cell carcinoma was the most common histological type (24).

A retrospective Spanish study of 24 patients likewise found that squamous cell carcinoma was the most frequent histological type (36). In our series the second most common malignancy was acinar cell carcinoma (17.4%), followed by mucoepidermoid carcinoma (13%), cystic adenoid carcinoma (8.7%), and adenocarcinoma not otherwise specified (NOS) (8.7%). These findings underscore the great variability of histological types reported in the scientific literature, which depend on the geographical setting involved.

Patients with early-stage tumors should be treated with surgery alone, whereas patients with more-advanced-stage cancer, intermediate or high grade tumors, or microscopically positive resection margins require a combination of surgery and radiotherapy (37). Like Stodulska and colleagues (38), we support the use of postoperative radiotherapy (eventually combined with chemotherapy) in cases of poorly differentiated or high malignancy carcinomas, advanced clinical stage cancers, lymph node metastases, incomplete resection or tumor presence close to the resection margin, and perineural or bone invasion, since such treatment is reported to improve locoregional disease control (39,40). Among the
473 trials analyzed by Devaiah and Murchison (41), the most commonly used drugs were cisplatin, cetuximab, and docetaxel, as was the case in the present study, together with paclitaxel.

Regarding the limitations of this study, it is important to highlight the need for longer follow-up periods and larger patient samples. In our series the narrow geographical coverage and low frequencies of the studied tumors might have limited measurement precision—a common limitation of studies of rare tumors. In contrast, a strength of our study is that it provides evidence regarding the distribution of these malignancies in a particular region.

In conclusion, our findings indicate that nine malignant salivary gland tumors present annually per one million inhabitants. Metastatic spread, tumor stage, perineural invasion, a submaxillary location, tumor size, histological grade, positive lymph node status, and the presence of positive surgical resection margins are the most important factors in patient survival. Our results are consistent with those of other studies in terms of disease incidence but differ to some extent with respect to histological type.

Conflict of interest
The authors have no conflicts of interest to declare.

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