

## Clinicopathological and Incidence Analysis of Malignant Salivary Gland Tumours: A 16-year Retrospective Study in the North of Portugal

Pedro Barreiros\*

Rua do Freixo, 979 Habitação A1.3, 4300-218 Porto, Portugal

\*Corresponding author

Pedro Barreiros, Rua do Freixo, 979 Habitação A1.3, 4300-218 Porto, Portugal

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### Abstract

**Objectives:** A) Evaluate the clinical-pathological characteristics of malignant neoplasms of salivary glands: A.1) Quantify the numbers of which tumor subtype. A.2) Gender, age and the type of salivary gland influence tumor behavior? A.3) Describe 16 years of evolution in a target portuguese population. B) What are the treatments chosen in which subtype? C) What is the prognosis? And what can influence the prognosis?

**Study Design:** A 16-year retrospective study of 138 patients with salivary gland tumors from 2000 to 2016 in the Anatomical Pathology Department of Centro Hospitalar do Porto, Hospital Geral de Santo António. The histological diagnoses - according to the 2017 World Health Organization classification.

**Results:** In the present study, we revised all the cases of salivary gland pathology from 396 cases. A total of 138 tumors were identified in 91 male and 47 female patients. The mean age was 58 years. The frequency of major salivary gland tumors was 56.3%, and that of minor salivary gland tumors was 43.7%. Mucoepidermoid carcinoma was the most common malignant tumor.

**Conclusions:** Knowledge of the different clinic characteristics is important and essential to a better prognosis and in many cases a reduction of the mortality.

**Keywords:** Salivary glands neoplasms, Clinical cases analysis, Epidemiology, Malignant tumor, Benign tumor, Treatment, Surgical, Prognosis

### Introduction

Salivary gland tumors are an important issue in oral and maxillo-facial pathology. Although some tumors have a very low incidence when compared with neoplasms of the other organs, they are not rare [1-6]. The worldwide range of the salivary gland tumors incidence is between 0.4% to 13.5% cases per 100.000 individuals [2]. In Portugal, there is not enough data to establish an accurate incidence of salivary gland tumors. Any salivary gland of the oral cavity can be affected. The most common site is the parotid glands representing almost 80% of cases, followed by minor salivary glands, submandibular and sublingual glands [2-4].

Tumoral pathology of the salivary glands represents a heterogeneous group of neoplasms that can be classified in various subtypes according with the clinical and histological characteristics. The World Health Organization (WHO) classifies the malignant

tumors in 24 different entities and recognizes 13 different kinds of benign tumours [2]. The malignant ones are the aim of this paper. Once the etiology remains unknown, it is very difficult to implement a prevention program. Avoiding possible risk factors, as tobacco, alcohol abuse, and unhealthy diets, significantly decreases the probability to develop salivary gland tumors [2-4].

Pathological examination, of the samples obtained by fine needle aspiration biopsy and/or incisional/excisional biopsy, allows an accurate diagnosis. The diagnostic ancillary techniques that can support the diagnosis, as axial computerized tomography (TAC) and the magnetic resonance imaging (MRI), can be useful [3]. The early diagnosis decreases the adverse outcomes of this kind of tumors, insuring an effective treatment on initial stage.

The first-choice treatment of almost all cases of salivary gland

tumors is the surgical excision followed or not by radiotherapy treatment [2,3,6].

Be aware about the different clinical features is important and essential to achieve a better prognosis and in many cases a reduction of the mortality.

**Materials and Methods**

Anatomical Pathology Department data base of Centro Hospitalar do Porto, Hospital Geral de Santo António was analyzed and the patient’s information were organized according to selected parameters. In malignant tumors in particular it was used de North Regional Oncologic Register – RORENO. Owing to the retrospective nature of the study, patient informed consent was waived. The study’s ethical considerations were approved by Centro Hospitalar do Porto, Hospital Geral de Santo António Ethic Commission.

The study includes cases that were diagnosed from January 1st of 2000 to December 31st of 2016 and codified with ICD-O codes for malignant morphology. To this transversal, observational, descriptive and retrospective study, we obtained 736 patients from which 186 patients were excluded because of incomplete clinical information and/or inadequate ICD-O/SNOMED codification. The remaining 550 patients were separated in two groups: neoplastic pathology (n=396) and non-neoplastic pathology (n=157). For the purposes of this study, we only considered the malignant neoplasm of salivary glands cases (n=138).

All malignant cases were diagnosed histologically and all tumors were sited in salivary glands of the oral cavity or oropharynx. The clinical data analyzed was: 1. Gender (Male or Female), 2. Age, 3. Histological subtype (WHO classification), 4. Localization (Major – Parotid, submandibular and sublingual glands; and minor glands), 5. Treatment type, 6. Prognosis (favorable or not favorable), 7. Postoperative adverse outcomes, 8. Risk factors, 9. TNM classification.

The statistical analysis was made with the program IBM SPSS Statistics 21.0 and a value of p>0.05 was considered no statistically significant.

Bibliographic search had Ebscohost, Pubmed and ScienceDirect data basis. We included articles between 2007 and 2017. Keywords, in Portuguese, French and English, included: salivary glands neoplasms; clinical cases analysis; epidemiology; malignant tumor; benign tumor; treatment; surgical; prognosis.

The aim of the present study was:

- A. Study and evaluate the clinical and pathological features of malignant neoplasms of the salivary glands;
  - A.1. Quantify the tumor subtypes;
  - A.2. The role of gender, age and the type of salivary gland in biological behavior of the malignant salivary glands tumors;
  - A.3. Describe 16 years’ follow-up results of all malignant cases of salivary neoplasms in a target Portuguese population;

B) An attempt to ascertain the treatments chosen and what were their postoperative adverse outcomes related to the histological subtype;

C) To find the outcome of the treatments and establish the prognosis related to the tumor subtype and find the parameters that could influence the prognosis.

**Results**

In the present study, were revised all the cases of salivary gland pathology. From 396 cases, 138 are malignant. Male gender is the most affected.

**Age:** The range of ages is between 14 and 93 years old. The mean age is 58 years.

**Gender:** In a total of 138 cases, 65.9% are males and 34.1% are females. Most of malignant tumors in males and females are located in parotid glands (44.9%) (Figure 1). Statistical relevant differences (p>0.05) between affected salivary glands (major/minor) and gender were not observed.

**Topography:** From 138 malignant tumors cases collected, 62 (44.9%) are in parotid glands, 59 (42.8%) in minor salivary glands, 16 (11.6%) in submandibular glands and 1 (0.7%) in sublingual glands (Table 1). Floor of mouth is the anatomical region with the higher frequency of tumors in minor salivary glands, representing 14.5% of all malignant tumors, followed by soft palate (9.4%) and buccal mucosa beside with retromolar area (8.7%) (Figure 2).

**Table 1: Malignant tumor proportion (%) in relation with localization.**

			Malignant_Total
Gland Localization	Parotid	n	62
		%	44.90%
	Submandibular	n	16
		%	11.60%
	Sublingual	n	1
		%	0.70%
	Minor	n	59
		%	42.80%
Total		n	138
		%	100%

**Histological type:** The most frequent tumor is mucoepidermoid carcinoma (23.2%), followed by squamous cell carcinoma (13,8%), adenoid cystic carcinoma (11,6%) and acinar cell carcinoma (10,9%) (Table 2). Minor salivary glands are the preferential site for the mucoepidermoid and squamous cell carcinomas. The remaining histological types are more frequent in parotid salivary gland (Table 2).

**Table 2: Histological types of malignant tumors and their topography frequencies.**

		Parotid	Submandibular	Sublingual	Minor	Total
Malignant Type	Mucoepidermoid Carcinoma	9	3	0	20	32
	Squamous Cell Carcinoma	0	0	0	19	19
	Adenoid Cystic Carcinoma	10	5	1	0	16
	Acinar Cells Carcinoma	13	1	0	1	15

**Treatments and adverse outcomes:** The different treatments and clinic decisions were analyzed and compared with adverse outcomes. The most prevalent casuistic is found at parotid salivary glands, where the majority of malignant neoplasms (n=62) are found, followed by minor salivary glands (n=59). A correlation exists with the number of total cases of neoplasms, and consequently a higher number of adverse outcomes. Dermatitis/mucositis is the most frequent adverse outcome related to surgical and non-surgical treatment followed by Bell's palsy and recurrent infections. Supra-facial sialoadenectomy (tumor excision with security borders) of the affected salivary gland is usually the treatment adopted in most cases. Furthermore, for larger tumors, total excision of the salivary gland (total sialoadenectomy) was the selected treatment strategy followed, if necessary by radiotherapy. All the treatment options depend of the histological type and the TNM staging (Table 3).

**Table 3: TNM stage observed in frequency.**

TNM stage		n	%
TNM stage	T1N0M0	21	15.2
	T1N1M0	3	2.2
	T1N2M1	1	0.7
	T2N0M0	34	24.6
	T2N1M0	13	9.4
	T2N2M1	4	2.9
	T3N0M0	11	8
	T3N1M0	7	5.1
	T3N2M0	1	0.7
	T3N1M1	4	2.9
	T3N3M1	1	0.7
	T3N2M1	6	4.3
	T4N1M0	2	1.4
	T4N2M0	3	2.2
	T4N3M1	7	5
Total	118	85.6	
Missing Information	20	13.7	
Total	138	100	

**Prognosis:** The prognosis will depend, among other aspects, on the patient health conditions, neoplasm progression and staging, and also if key anatomical structures are compromised. It should also be considered the applied treatment and postoperative conditions.

The following parameters were considered in the prognosis:

Normotensive and apyretic patient; hemodynamically stable patient; aware and focused patient; food tolerant patient; eligible for hospital discharge within 10 days (with or without surgical intervention); no voice alterations; no postoperative complications; no anesthesia complications; non associated infection episodes; no spontaneous or provoked local pain; no satellite adenopathy; non vascular invasion; free surgical margins after pathological study of the tissue sample.

At least 5 of the above referred parameters are required for the attribution of a favorable classification.

For a negative or non-favorable classification 3 of the parameters must occur (being these prevalent to the above described): Necessity of ambulatory postoperative treatment; in the case of muscular invasion of adjacent structures; if during surgical procedures the tumor is intersected focally; other systemic pathologies associated (at least 3).

A total of 121 patients had an unfavorable prognosis, in 138 cases studied.

**TNM classification:** this classification is determined by the American Joint Committee on Cancer (AJCC). The data are related to postoperative conditions. The tumors were classified T1 in 25 cases (18.1%), T2 in 51 cases (36.9%), T3 in 24 cases (17.4%) and T4 in 18 cases (12.9%). This variable could not be determined in 20 cases. Cervical lymph node status revealed metastasis in 29 cases (24.6%) with pN1 stage; 9 cases (7.6%) with pN2 stage and 8 cases (6.7%) with pN3 stage. Distant metastasis had been detected in 17 cases (14.4%), all of them to the lungs (Table 3) and the most frequent histological type was mucoepidermoid carcinoma.

**Risk factors:** despite the very limited clinical information, we observed that the alcohol (1.64%) and tobacco (37.70%) were the main documented risk factors and many times associated

(20.49%). In 40.2% of cases, there was not any record related to known risk factors.

Survival rates: evaluating the overall survival, it's observed a follow-up median of 38.2 months (range 1-197) and Overall survival at 5 years of 63.5% (Figure 3).

## Discussion

The present study confirms the main characteristics and behaviors of malignant salivary neoplasms, described in literature. These neoplasms can occur in any life decade. In the present sample medium age is 58 years, a different value when compared with literature [1-8]. Males are the most affected gender [4,6,8,9].

In our case series, 59.84% of all patients referred to have alcoholic or/and smoking habits, suggesting that those etiologic factors don't have the same weight in development of malign salivary tumors but are crucial. We have to consider, for example, the consumption frequency and duration.

Mucoepidermoid carcinoma is the more frequent malignant tumor (23.2%), followed by squamous cell carcinoma (12.8%), adenoid cystic carcinoma (11.6%) and acinar cells carcinoma (10.9%). These results are different to previously advanced by other papers from different country studies [2-4,7,10]. Maybe the explanation of these differences relies in a possible misclassification. We believe that some tumors previously classified like cystoadenocarcinomas are in fact adenoid cystic carcinomas. The preferential localization in salivary minor glands was the mouth pavement (14.5%) [1,3].

The analysis of prognosis value of the various clinical and pathological characteristics concludes that gender and age have not influenced the histological type or the prognosis. However, the presence of smoking and alcoholic habits is consistently associated to a worse prognosis and poor survival rate. In our case series, the survival rate it wasn't calculated due the lack of data (diagnostic data, follow-up data, death data – with or without disease -, recurrence data, and metastasis data).

The main prognostic factors are: clinical stage, tumor size and histological differentiation grade. The results showed that an advanced stage and larger tumors will have worse clinical prognosis [5,11,12]. Prognosis invasion influence, local or not, is well recognized and proven, being included in TMN category [11,12].

Malignant tumors of the salivary glands appear to be a heterogeneous group with different histological types and different behaviors when we speak about evolution and survival [1-12].

The most frequent treatments used were according which histopathology and clinic characteristic. Surgical treatment, suprafacial sialoadenectomy, is the main adopted treatment, if the dimension of the lesion allows it.

The larger neoplasm cases in which diameter and depth of the invasion is bigger, it means, a huge invasion of glandular and peripheral soft tissues, the correct option is the total sialoadenectomy. Treatment analysis revealed high variety of options, immediate-

ly indicating that each patient should be given clinical, adequate and specific treatment. Yet, some procedures can be systematized: surgical (lesion excision or lesion plus affected gland excision), complemented in certain cases with radiotherapy, depending on TNM, positive resection margin, lymph node metastasis, high grade carcinomas, advanced stage or recurrence cases. If there is distant metastasis, the chemotherapy is used [5,6]. The majority of the distant metastasis is in the lungs (100%) [6,12-16]. Dermatitis/mucositis post-radiotherapy, facial paralysis and recurrent infections are, by decreasing order of frequency, the adverse outcomes related to surgical or nonsurgical treatment. The dermatitis/mucositis postradiotherapy and recurrent postsurgical infections help us to conclude that, although the type of treatment, and although the heterogenic type of tumor, technical and surgical errors in the medical practice exist.

Any conclusion can't be made in relation to the evolution. A characteristic pattern can't be established to these malignant tumors in the studied population.

## Conclusion

A.1) Mucoepidermoid carcinoma is the malignant tumor more frequent, representing 23.2%, followed by squamous cell carcinoma (12.8%), cystic adenoid carcinoma (11.6%) and acinar cells carcinoma (10.9%).

A.2) A total of 138 tumors were identified in 91 male and 47 female patients (proportion 2:1). The average age was 58 years. The frequency of major salivary gland tumors was 57.2%, and in minor salivary gland tumors was 42.8%. Mucoepidermoid carcinoma was the most common malignant tumor. In the current study, the floor of mouth was the most frequent location for malignant salivary gland tumors.

A.3) Over the years the efficiency, knowledge and sensitivity to tumor pathology has therefore increased the number of diagnoses gradually too. No evolution pattern can be established.

B) Almost all treatments imply surgery when a favorable prognosis is expected. And other clinical options can be associated.

C) The stage and aggressiveness grade seem to be core prognosis factors to take in account towards most of clinical and pathological variables contributing to the stratification of patients for treatment and prognosis.

## Conflict of Interest

The authors declare that they have no conflict of interest and all authors have read and approved the final draft.

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