# Benign and Malignant Salivary Gland Tumors – Clinical and Demographic Characteristics

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**Abstract.** *Aim: To examine the demographic, ethnic, and clinical characteristics of salivary benign and malignant tumors for better etiological understanding. Patients and Methods: We examined medical records of 287 primary salivary gland tumor patients. Results: Overall, 216 tumors were benign and 71 malignant. The mean age at diagnosis was 56.4 years for those with malignant tumors and 48.5 years for those with benign, a highly significant difference (p=0.001). Females had 45% of malignant tumors and 59% of benign, a significant difference (p=0.037). Ethnic origin, alcohol consumption and cigarette smoking rates were not significantly different (p>0.05) between groups. A total of 87% of benign and 55% of malignant tumors were in the parotid glands, a highly significant predilection (p<0.0001), sublocated mostly in the superfacial lobe; 36.6% of malignant tumors and 4.7% of benign (p<0.0001) were in the minor salivary glands, mostly in the hard palate. Conclusion: Baseline clinical, demographic and locational aspects of benign and malignant tumors are substantiated.*

Cancer of the major salivary glands is a heterogeneous disease with a low overall incidence. There are numerous entities of salivary gland neoplasms and while some are extremely rare, in clinical practice, five carcinoma types are likely to be encountered with some degree of frequency: Mucoepidermoid carcinoma, adenoid cystic carcinoma, carcinoma ex pleomorphic adenoma, acinic cell carcinoma and in the minor glands, and polymorphous low-grade adenocarcinoma (1). Over recent decades, the management of salivary gland cancer has evolved significantly. In 2001, Spiro determined that the clinical stage, particularly tumor size (T), rather than histological grade (2), is the critical factor deciding the outcome of salivary gland cancer. T4 tumors exceed the anatomic borders of the gland and invade adjacent tissues. Spiro emphasized that essentially in those with stage III or IV tumor (more than 4 cm, regardless of nodal involvement and extension) outcome will be adverse regardless of histological grade (2). Similarly, the "4 cm rule" maintains that tumors less than 4 cm (T1 or T2) confer a more optimistic outcome regardless of histological type or grade, while tumors over 4 cm are an absolute indication for postoperative radiotherapy (3-5).

Few prognostic indicators have been reported to have variable importance, including: age, site, involved margins and lymph node metastasis. Age is relatively less important than tumor size and nodal involvement. Signs and symptoms such as the presence of pain, skin invasion and facial nerve paralysis have a high prognostic index (6).

Grading of salivary gland cancer is based on knowledge of individual entities and the cellular and morphological features of individual tumors. Tumors are categorized into low- and high-grade types (Table I) (7). Mucoepidermoid carcinoma, adenoid cystic carcinoma, adenocarcinoma nitric oxide synthase and primary squamous cell carcinoma all have low- and high-grade variants.

The purpose of the current study was to examine various demographic, ethnic, and systemic characteristics of patients diagnosed with benign and malignant salivary gland tumors in order to better understand their possible etiological roles. We, therefore, examined age, gender, ethnic origin, habits of smoking and alcohol consumption. We also examined clinical features of the tumors relating to their size at diagnosis and to the salivary gland involved. Special attention was paid to the specific salivary sublocation of the tumor and to the sporadic extra-salivary gland location of some (maxillary and oral). These were evaluated both within the benign and malignant groups and compared between groups.

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*Key Words:* Salivary glands, benign carcinoma, malignant tumor, clinical characteristics, demographic characteristics.

## Patients and Methods

*Study design and patients*. During the 20-year period from 1996 to 2015, a total of 287 patients received definitive treatment for primary salivary gland tumors at Rambam Medical Center in Haifa, Israel. Of the 287 patients, 216 had benign tumors and 71 had malignant tumors. The treatment administered was based on surgery in 284/287 (99%) of the cases; thus, the definitive diagnosis was based on pathological analysis of the harvested tumor tissue. Diagnosis was based on fine-needle aspiration in the remaining three patients, two with malignant tumors defined as inoperable and one with benign tumor who refused treatment. The medical and demographic analyzed data were harvested from the patients' medical files.

*Statistical evaluation*. For the categorical variables, numbers and percentages were calculated. The distributions for the categorical variables between the two study groups were compared and analyzed by the Chi-square test (a parametric test) or by Fisher-Irwin exact test (a non-parametric test for small numbers). For the continuous variables, range, median, mean and standard deviation were calculated. The Shapiro-Wilk test for normality was used. The results of the continuous variables were compared between the two study groups and analyzed by the two-sample *t*-test for differences in means (a parametric test) or by Wilcoxon rank-sum test (a non-parametric test). All statistical tests were analyzed to a significance level of 0.05.

## Results

*Salivary gland tumors*. Of the 216 benign tumors, 138 (64%) were pleomorphic adenomas (PA), while the prevalence rates of the other diagnosed benign tumors in a descending manner were as follows: Whartin's tumor (23%), recurrent pleomorphic adenoma (5.1%), oncocytoma (2.8%), myoepithelioma (1.9%), cystadenoma (1.4%) and basal cell adenoma (0.9%). As for the malignant tumors, there were 12 different types, with mucoepidermoid carcinoma being most prevalent (22/71 cases, 31%) followed by adenoidcystic carcinoma (16.9%), squamous cell carcinoma (11.3%), polymorphous adenocarcinoma (9.9%) and a cinic cell carcinoma (9.9%).

*Baseline demographic analysis*. The baseline variables age at diagnosis, gender, ethnic origin, alcohol consumption and cigarette smoking of both malignant and benign groups are presented in Table I.

The mean age at diagnosis in the malignant group was 56.4 years (median=57.0 years) and that in the benign group 48.5 years (median=51.0 years). This difference was highly significant ($p$=0.001). By gender, 54% of the patients in the malignant group and 41% in the benign study group were males, while 46% of those in the malignant group and 59% in the benign group were females; this difference was significant ($p$=0.037).

The baseline variables of ethnic origin, alcohol consumption and cigarette smoking rates were not significantly different between the two groups ($p$>0.05).

*Tumor size and location*. There was no difference with respect to tumor size or side of appearance upon diagnosis. In two cases, there was a bilateral appearance at diagnosis and these were Warthin's tumors located in the parotid glands (Table II). The distribution of benign *vs*. malignant tumors among the various salivary glands was significantly different as can be seen in Table II ($p$<0.0001). Most of the tumors were found in the parotid glands: 87% of the benign tumors and 55% of the malignant tumors. Of the parotid glands, 83% of the tumors were benign while only 17% were malignant. This predilection for benign *vs*. malignant tumors in the parotid glands was highly significant ($p$<0.0001). Interestingly, the opposite predilection was found in the minor and sublingual glands, with 36.6% of all malignant tumors being found in the minor salivary glands and only 4.7% of the benign, while the three tumors diagnosed in the sublingual gland were malignant. Regarding sublocation, most of the parotid tumors were located in the superfacial lobe followed by the parotid gland tail, and only a minority in the deep lobe. In the case of minor salivary glands case most of the tumors were located in the hard palate (14 benign tumors and 8 malignant tumors), although minor salivary gland tumors were found in various other oral sites (soft palate, lip and buccal mucosa) and perioral sites (parapharyngeal space, maxillary sinus, dorsum of tongue and mandible) (Table II).

## Discussion

Two of the significant results obtained in the current study were age- and gender-based: lower patient age in those with benign *vs*. malignant tumors, women as the majority of those with benign tumor, while men predominated the malignant group. The fact that the mean age of patients with malignant tumors was higher is not surprising in light of previous articles (1-3, 8) that reported this trend and the common paradigm for incidence of malignancies which rises following prolonged accumulation of genetic aberrations during the life span of an individual (8). The variability of the benign and malignant tumor diagnoses deserves special consideration. Indeed, salivary gland tumors are one of the most complex and relatively rare groups of lesions encountered in oral pathology practice. Their complexity is attributed to heterogeneity of the cells of origin of these lesions. The problem is compounded by the ability of these cells to differentiate and modify into various morphological subtypes, resulting in a myraid of histomorphological patterns. This also leads to a frequent overlap of microscopic features among various neoplasms and sometimes even between benign and malignant lesions, causing a significant diagnostic dilemma which at times may not even be resolved by immunohistochemical studies (9). Our current results support other series previously published. For example, de

Table I. *Summary of demographic characteristics by study groups.*

| Demographic characteristic | Malignant N=71 | Benign N=216 | *p*-Value |
|---|---|---|---|
| Age at diagnosis (years) | | | |
| Median (range) | 57.0 (16-91) | 51.0 (10-84) | 0.001[a] |
| Mean±SD | 56.4±16.5 | 48.5±16.2 | |
| Gender | | | |
| M/F, n (%) | 38/33 (54/46) | 89/127 (41/59) | 0.037[b] |
| Smoker | | | |
| Yes, n (%) | 22 (31) | 70 (32.4) | 0.824[b] |
| Alcohol | | | |
| Yes, n (%) | 2 (2.8) | 4 (1.9) | 0.639[c] |
| Ethnicity | | | |
| Jewish/Arab n (%) | 52/19 (73/27) | 177/39 (82/18) | 0.113[b] |

SD: Standard deviation, M: male, F: female. *p*-Value by [a]Wilcoxon rank-sum test or [b]Chi square test or [c]Fisher exact test; $p \leq 0.05$ accepted as significant.

Table II. *Tumor parameters by study group.*

| Tumor parameter | Malignant N=71 | Benign N=216 | *p*-Value |
|---|---|---|---|
| T Size (cm) | | | |
| Median (range) | 2.5 (0.3-6.5) | 2.3 (0.3-8.8) | 0.6450[a] |
| Mean±SD | 2.6±1.5 | 2.4±1.2 | |
| Side, n (%) | | | |
| Right | 30 (42.3) | 100 (46.3) | 0.8740[b] |
| Left | 40 (56.3) | 111 (51.4) | |
| BLT | 1 (1.4) | 4 (1.9) | |
| ND | 0 | 1 (0.4) | |
| Location, n (%) | | | |
| Parotid | 39 (55.0) | 188 (87.0) | 0.0001[b] |
| SMG | 3 (4.2) | 18 (8.3) | |
| SL | 3 (4.2) | 0 | |
| Minor | 26 (36.6) | 10 (4.7) | |
| Sub-location, n (%) | | | |
| Mandible | 1 (1.4) | 0 | |
| Parotid tail | 12 (16.9) | 66 (30.5) | |
| Parotid superficial lobe | 19 (27.0) | 91 (42.1) | |
| Parotid deep lobe | 7 (9.9) | 19 (8.8) | |
| Accessory parotid | 0 | 1 (0.5) | |
| SMG superficial lobe | 3 (4.2) | 17 (7.9) | |
| MSG of hard palate | 14 (19.7) | 8 (3.7) | |
| MSG of lip | 1 (1.4) | 1 (0.5) | |
| Maxillary sinus | 3 (4.2) | 01 (0.5) | |
| MSG of soft palate | 2 (2.8) | 0 | |
| MSG of buccal mucosa | 2 (2.8) | 0 | |
| MSG of parapharyngeal space | 2 (2.8) | 0 | |
| Tongue dorsum | 1 (1.4) | 0 | |
| Unknown | 4 (5.5) | 12 (5.5) | |

SD: Standard deviation, BLT: bilateral, ND:non-defined, SL: sublingual, SMG: sub-mandibular gland, MSG: minor salivary gland. *p*-Value from [a]Wilcoxon rank-sum test, or [b]Fisher exact test; $p \leq 0.05$ accepted as significant.

Oliveira *et al*. published a study where they reported demographic characteristics of 599 cases from Brazil analyzed over a 10-year period. In that study, benign tumors represented 78.3% of the cases. Women were the most affected (61%) and the male:female ratio was 1:1.6. Parotid gland tumors were the most frequent (68.5% of cases) and the patient age ranged from 1 to 88 years (median=45 years). The most frequent tumors were pleomorphic adenomas (68.4%) and benign tumors were significantly more frequent in the parotid (75.9%), while malignant tumors were more frequent in the minor salivary glands (40%) ($p<0.05$) (10). Those researchers concluded, as we do now, that women were the most affected, the parotid gland was the most frequent locus, and that pleomorphic adenoma was the most frequent lesion, followed by adenoid cystic carcinoma and Warthin's tumor (10). Similarly, in our own report from 1997, where we analyzed 245 Israeli patients who had been treated at our Institute during the previous 25 years, the results were also quite similar with respect to the data we present here regarding 287 additional patients treated in our institute in a later 20-year period (up to 2015). In the earlier study, we found that salivary gland tumors occurred in the parotid (57.9%), submandibular (13.9%), sublingual (0.8%) and minor salivary glands (27.3%). Of these, 73.5% were classified as benign and 26.5% as malignant. The tumors were analyzed according to sex and age of the patients, histopathological type and site. There was a female preponderance (1.16:1.0) for the benign tumors and a male preponderance (1.32:1.0) for the malignant tumors. The mean age for patients with malignant tumors was 12.6 years higher than for those with benign tumors (55.2±2.2 and 42.6±2.6 years, respectively). The principal site for benign tumors was the parotid gland (67.8%), followed by the minor salivary glands (18.9%) and the submandibular gland (13.3%). We did not observe any benign tumors in the sublingual glands. The principal site for malignant tumors was the minor salivary glands (50.8%), followed by the parotid gland (30.8%), the submandibular gland (15.4%) and the sublingual gland (3.0%) (8).

Our current report includes two cases of Warthin's tumors diagnosed in the parotid glands. The synchronous diagnosis of pleomorphic adenoma tumors and especially of Warthin's tumors has been reported before (11, 12). The synchronous diagnosis possibly points to a systemic etiological factor and the fact that it is found with benign, rather than malignant tumors raises very interesting questions relating to the neoplastic pathogenesis of these diseases regarding the salivary parenchyma. This notion is further emphasized by the rare cases in which synchronous benign salivary gland tumors have been reported to arise even in different salivary glands simultaneously. For example, we previously reported

a case of a female patient diagnosed with pleomorphic adenoma in the right parotid and submandibular glands, concomitant with sialolithiasis affecting the submandibular gland. This patient had been exposed to head and neck radiotherapy in childhood, which may have had a role in the development of her tumors (13). Thus radiotherapy could be one such systemic transforming factor as previously suggested (14); however, in the currently reported two cases, no previous exposure to head and neck radiotherapy is known to have occurred. The differences between the salivary parenchyma in the various glands may also contribute to the differences observed in the predilection for benign *vs*. malignant tumors. Thus it seems that the more mucous-like (as opposed to serous-like) the gland is, the more it will favor malignant rather than benign transformation. Sublingual and minor glands are mucous, the submandibular is a mixed gland, while the parotid is a serous gland (15-17).

In summary, the results presented here further substantiate the baseline clinical, demographic and locational aspects of benign and malignant tumors, focusing not only on the glands but also on their subcompartments.

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