Salivary Gland Tumours Through 5-Year Follow-Up: A Retrospective Single-Centre Study

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Abstract

The aim of our study was to analyse the prevalence of salivary gland tumours through 5-years of follow-up.

Study was designed as a retrospective analysis of patients, who underwent surgery of tumour removal in our centre between 2005 till 2017 and were followed up for 5 years. The demographic characteristics (age and gender) were obtained from 247 patient records. Pearson's χ-square test and logistic regression were used to analyse the data, where $p<0.05$ was considered as statistically significant.

Overall 247 cases were analysed and followed up for 5 years after surgical removal of tumours. Mean age of patients was 51.0±19.5 years. The male-to-female ratio was 1.1:1. Female patients were statistically younger compared to male patients ($p=0.017$). The most common tumour was found at parotid gland in 154 (62.3%) cases. Adenoma pleomorphe was diagnosed in 125 (50.6%) cases. Superficial parotidectomy was performed in 44 (17.8%), and surgical extirpation in 143 (57.9%) cases. Recurrences of tumour occurred in 16 (6.5%) patients and metastases occurred in 6 (2.4%) patients.

This was the first study of such kind from the region. Female show a bimodal age distribution and were more affected with adenoma pleomorphe than men. Relatively low recurrence rate was observed after at 5 years of follow-up. Risk factors for recurrence were positive on histological type of tumour and patients's age.

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Introduction

Salivary gland tumors are common tumors in maxillofacial region. They occur in 1 in 100,000 people, and they present 3% of all head and neck neoplasm. Salivary gland cancers (SGCs) are uncommon and one of the most diverse cancers consisting of up to 24 different pathologic subtypes.[1-3] Malignancy is found in roughly 14% of lesions.[4,5] Cancers differ substantially in clinical behaviour and according to this are often categorized as low, intermediate, or high-risk for recurrence and metastasis. Recurrent SGCs should be considered as a high-risk by definition, especially if they were previously appropriately treated, and required aggressive multimodality therapy in order to achieve adequate local control and disease-free survival.[1]

The most common histological type of SGT is pleomorphic adenoma (SGPA), which accounts for more than 70% of benign epithelial tumours, followed by mucoepidermoid carcinoma (MEC), adenoid cystic carcinoma (ACC), adenocarcinoma and salivary duct carcinoma. In general, all can arise from the major salivary glands or from the minor salivary glands. Parotid gland is the most common of major SGCs.[3,6,7] Oral cavity is the most common site of minor SGCs, and hard palate is the most frequent subsite.[6,8-11] In contrast to major salivary gland, tumours are almost always benign, however up to 80% of tumours arising from the minor salivary glands are malignant.[12,13] Tumour's recurrence varies, but was reported in 0–3% of patients.[14,15] In the past, enucleation was performed as treatment of choice, but it was associated with

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high recurrence rates of up to 45%.[16,17] Nevertheless, some complications could also occur during surgical procedure. The main is temporary/permanent facial nerve paralysis.[18] The replacement of enucleation of tumour with surgical procedures such as superficial parotidectomy (SP), total parotidectomy (TP), and extracapsular dissection (ECD) reduced the incidence of recurrences and facial damage.[19-21]

In the future to avoid invasive techniques in treating tumours more sophisticated techniques will come through. Statistically, oral cancer is increasing each year worldwide. Thus, approaches of new surgical techniques, adjuvant therapy and molecular targeted therapy are urgently needed. For instance, enzyme ribonuclease reductase (RNR) plays an important role in DNA synthesis and repair and has been found to be an attractive target for anticancer agents. Increased activity of RNR is associated with malignant transformation and tumour cell growth which suggest that the inhibition of RNR might have a treating potential for cancers.[22] The future is also prevention or rapid detection or SGTs. Saliva as a complex biological mixture of fluids from 3 major glands (parotid, submandibular and sublingual gland) contains large number of biomarkers which can help in the diagnosis of many diseases, including cancer. Due to the ease of collection, it has shown a great potential in the detection of tumour markers similar as in blood of such patients. This could be used in prevention, diagnosis and monitoring without using high invasive methods used in todays practice.[23]

The aim of our study was to analyse the prevalence of salivary gland tumours, observe occurrence of tumour recurrence and metastasis rates in cases according to the patient's gender, age and histological type of tumour through 5 years of follow-up.

Materials and methods

Study was designed as a retrospective analysis of cohort of patients from our tertiary Department of Maxillofacial Surgery in Clinical University Centre of Kosovo from year 2005 till 2017, 12 years of data timeline. The research has been conducted according to the Declaration of Helsinki. Institutional ethical review board of Medical Faculty in Prishtina approved the study. Patients did not need to give the consent of participation, since data were obtained from our archive database.

Subjects

The study included all patients (children and adults), who underwent surgery of tumour removal with different surgical procedures, such as partial/total superficial parotidectomy or tumour extirpation/excision, and were followed up for 5 years. Total of 247 patients with proven tumours of salivary glands were selected for the final analysis. Cases were observed for different groups of histopathological diagnosis of cancer type according to the gender.

Outcome parameters

The primary outcome variables were the tumour recurrence and occurrence of metastasis. Demographic characteristics (age and gender) and preoperative histopathologic findings were obtained from retrospective analysis of the medical records. The postoperative complications were not included into the analysis.

Statistical analyses

Statistical Package of Social Sciences SPSS 21 (IBM, New York, USA) was used to calculate statistical analyses. Pearson's chi square test and univariate logistic regression were performed according to the type of variable. Statistical significance for all tests was set at $p<0.05$.

Results

Overall, 247 cases of salivary gland tumours were analysed through 5 years of follow-up after surgical removal of those tumours. The mean age of the patients in the present study was 51.0±19.5 years. The majority of the cases (N=56; 22.7%) were encountered in the 6th (50-59 years of age) decade of life (Fig. 1). However, we have observed bimodal prevalence data among all patients, where another peak was shown in 5th decade of life (N=52; 21.1%) and among female patients (Fig. 2). Altogether 77 cases (31.2%) were found as the elderly (aged 60 and above) (Fig. 1). Furthermore, 5 cases (2.0%) were discovered in children aged 9 years and below.

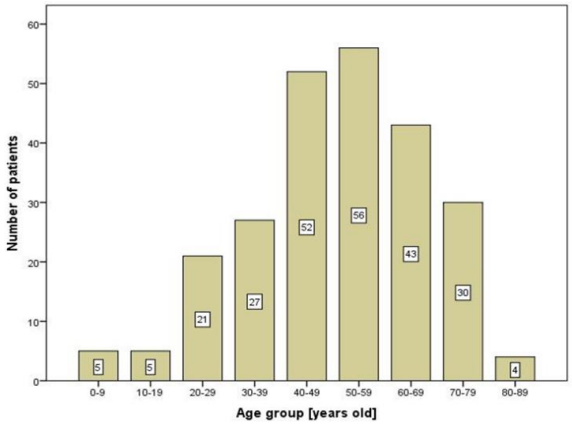

Figure 1. Age distribution of patients with salivary gland tumours.

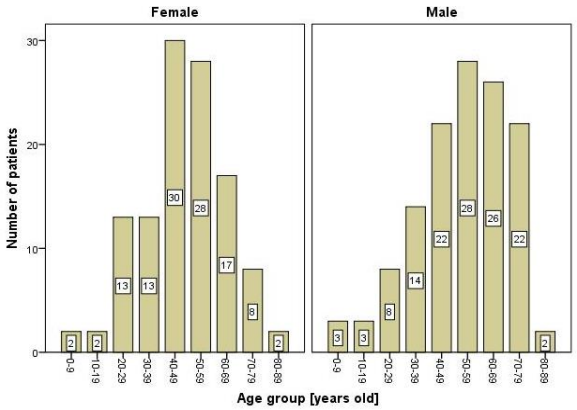

Figure 2. Age distribution of patients with salivary gland tumours between the gender.

The male-to-female ratio was 1.1:1. Distribution of cancers by anatomical regions was different and presented in Table 1 and Table 2. The most common tumour was found at parotid gland in 154 (62.3%) cases, followed by palate region in 51 (20.6%) cases. According to histology adenoma pleomorphe was majorly diagnosed in total of 125 (50.6%) cases. As for surgical procedures, superficial parotidectomy was performed in 44 (17.8%), and surgical extirpation in 143 (57.9%) cases. Recurrence of tumour and metastasis were rare, and occurred in 16 (6.5%) and 6 (2.4%) of patients, respectively.

According to the patients' gender, a statistical difference was observed in age. Female patients were statistically significantly younger than the male patients (Table 2). Moreover, we have found differences in tumour locations and type of the tumours between genders (Table 2).

Most common risk factors for tumour recurrence were age (p=0.020), total parotidectomy as surgical procedure and squamous cell carcinoma as primary diagnosis (Table 3). Other factors showed no statistical significance.

	N=247
Gender	
M/F	129/118
Age [years]	51.0±19.5
Salivary gland	
Buccal	5 (2.0%)
Labial	1 (0.4%)
Parotid	154 (62.3%)
Submandibular	27 (10.9%)
(sub)lingual	7 (2.8%)
Palate	51 (20.6%)
Operation	
Biopsy	4 (1.6%)
Surgical excision	31 (12.6%)
Surgical extirpation	143 (57.9%)
Superficial parotidectomy	44 (17.8%)
Total parotidectomy	23 (9.3%)
Histological diagnosis	
Acinic cell carcinoma	6 (2.4%)
Adenocarcinoma	16 (6.5%)
Adenoid cystic carcinoma	13 (5.3%)
Adenoma pleomorphe	125 (50.6%)
B-non Hodking Lymphoma	1 (0.4%)
Squamos cell carcinoma	11 (4.5%)
Wartin tumour	18 (7.3%)
Fibromyoma	1 (0.4%)
Carcinoma	21 (8.5%)
Others*	31)12,6)
Tumour recurrence	16 (6.5%)
Metastasis	6 (2.4%)

*Cystadenolymfoma papillare, lesio lymphoepitelialis benigna, lymphoepitelial sialoadenitis, marginal Zone-B cell lymphoma, fibropapilloma, lymphadenitis granulomatosa, granuloma gigantocellulare, lipoma.

Table 1. Basic characteristics of patients with salivary gland tumours

	Male (N=128)	Female (N=114)	p-value
Age [years]	53.8±21.6	47.8±16.2	0.017
Salivary gland			0.012
Buccal	2 (1.6%)	3 (2.6%)	
Labial	0	1 (0.9%)	
Parotid	93 (72.3%)	61 (53.5%)	
Submandibular	14 (10.9%)	13 (11.4%)	
(Sub)lingual	3 (2.3%)	4 (3.5%)	
Palate	16 (12.5%)	35 (30.7%)	
Operation			0.012
Biopsy	1 (0.8%)	3 (2.6%)	
Superficial parotidectomy	22 (17.2%)	22 (19.3%)	
Surgical excision	10 (7.8%)	21 (18.4%)	
Surgical extirpation	78 (60.9%)	65 (57.0%)	
Total parotidectomy	18 (14.1%)	5 (4.4%)	
Histological diagnosis			0.054
Acinic cell carcinoma	3 (2.3%)	3 (2.6%)	
Adenocarcinoma	9 (7.0%)	7 (6.1%)	
Adenoid cistic carcinoma	6 (4.7%)	7 (6.1%)	
Adenoma pleomorphe	55 (43.0%)	70 (61.4%)	
B-non Hodgking lymphoma	1 (0.8%)	0	
Squamos cell carcinoma	8 (6.3%)	3 (2.6%)	
Wartin Tumour	16 (12.5%)	2 (1.8%)	
Fibromyxoma	1 (0.8%)	0	
Carcinoma	13 (10.2%)	8 (7.0.%)	
Others*	15 (12.8%)	16 (14.0%)	
Tumour recurrence	7 (5.5%)	9 (7.9%)	0.483
Metastasis	5 (3.9%)	1 (0.9%)	0.123

* Cystadenolymfoma papillare, lesio lymphoepitelialis benigna, lymphoepitelial sialoadenitis, marginal Zone-B cell lymphoma, fibropapilloma, lymphadenitis granulomatosa, granuloma gigantocellulare, lipoma.

Table 2. Characteristics of patients according to gender.

	Recurrence of tumour		Recurrence rate	p-value
	No (N=231)	Yes (N=16)		
Age	50.3±19.5	62.3±15.1	/	0.020
Gender				
M/F	122/109	7/9	5.4%/7.6%	0.483
Salivary gland				0.900
Buccal	5 (2.2%)	0	/	
Labial	1 (0.4%)	0	/	
Parotid	144 (62.3%)	10 (62.4%)	6.5%	
Submandibular	26 (11.3%)	1 (6.3%)	3.7%	
(sub)lingual	6 (2.6%)	1 (6.3%)	14.3%	
Palate	47 (20.3%)	4 (25.0%)	7.8%	
Operation				0.045
Biopsy	4 (1.7%)	0	/	
Surgical excision	27 (11.7%)	4 (25.0%)	12.9%	
Surgical extirpation	138 (59.4%)	5 (31.3%)	3.5%	
Superficial parotidectomy	42 (18.2%)	2 (12.5%)	4.5%	
Total parotidectomy	19 (8.2%)	4 (25.0%)	17.4%	
Histological diagnosis				0.039
Acinic cell carcinoma	6 (2.6%)	0	/	
Adenocarcinoma	15 (6.5%)	1 (6.3%)	6.3%	
Adenoid cystic carcinoma	10 (4.3%)	3 (13.0%)	23.1%	
Adenoma pleomorphe	121 (52.4%)	4 (25.0%)	3.2%	
B-non Hodking Lymphoma	1 (0.4%)	0	/	
Squamos cell carcinoma	8 (3.5%)	3 (13.0%)	27.3%	
Wartin tumour	16 (6.9%)	2 (12.5%)	11.1%	
Fibromyoma	1 (0.4%)	0	/	
Carcinoma	20 (8.6%)	1 (6.3%)	4.8%	
Others*	30 (13%)	1 (6.3%)	6.3%	

* Cystadenolymfoma papillare, lesio lymphoepitelialis benigna, lymphoepitelial sialoadenitis, marginal Zone-B cell lymphoma, fibropapilloma, lymphadenitis granulomatosa, granuloma gigantocellulare, lipoma.

Table 3. Risk factors for the recurrence of tumours

Discussion

The purpose of the current study was to retrospectively analyse the prevalence of salivary gland tumours and estimate the prevalence data of tumour recurrence rates in cases according to the patient's gender through 5 years of follow-up. We report results of relatively large cohort of 247 patients from single centre in Kosovo with 5-year period of follow-up. At the same time we investigated SGTs prevalence and recurrence rates. Interesting findings were lower age of female patients compared to males, a bimodal age distribution among all patients and females respectively, an overall 5-year recurrence risk of just 6.5%, and association of patient's age or squamous cell carcinoma with recurrence of tumour.

Patients' & tumours' characteristics

SGCs are uncommon neoplasms that account for approximately 5% of all head and neck malignancies.[24,25] Incidence for these neoplasms varies between 1.5 and 7.2 per 100,000 person-years.[24-29] In the last 12 years in our centre we have collected 247 cases of SGTs. We did not find significant differences between males and females, in aspect of frequencies, but we have observed that the mean age of the females in the present study was statistically lower compared to males. The majority of the cases were encountered in the 6th (50-59 years of age) decade of life. However, most interesting was to found a bimodal distribution of prevalence data among all patients, where another peak was shown in 5th decade of life. The same was observed for female patients, that is also why bimodality was associated to female gender. One possible reason for that is that women are more aware of their appearance than men and are more frequently willing to seek medical attention for any lumps on the face.[30-32] On the other hand, there are also some reports, that an influence of gonadal hormones, as in breast cancer, could have influence on tumour development. For instance salivary gland pleomorphic adenoma

(SGPA) is known to express estrogene and progesterone receptors.[33,34] In the past salivary gland neoplasms have been associated with breast cancer.[35] However, despite these reports, the bimodal age distribution in females remains unexplained. Further research is needed to explore these issues.

Distribution of tumours by anatomical regions was different. The most common tumours were found at parotid gland in 62.3% of cases, followed by palate region in 20.6% of cases. According to the literature, SGTs affect the parotid, submandibular and minor glands in a ratio of 10:1:1.[24] According to histology, adenoma pleomorphe was majorly diagnosed in total of 50.6% of cases. In our cohort, types of salivary gland tumours were equally common in men and in women, but we have observed that adenoma pleomorphe was more common in females and Wartin tumours in males. Once again possibility to this could be associated to hormonal levels.

Since we found no previous mention of any sex differences in SGTs location, we cannot explain the differences of more frequent palate tumour in females and more frequent parotid tumours in men. Further studies are needed to confirm and explain these findings.

Recurrence rates and metastasis rates

After adjustment for gender, age, location and type of tumours the 6.5% first-recurrence rate was found in patients with 5 years of follow-up. This coincides with the previous findings.[36] Our recurrence of tumour was rare, and is lower than stated in most papers. However, some caution is needed here, as populations and follow-up periods vary between studies. For the current research, we excluded analyses of malignant transformations. However, we have observed 2.4% of metastasis rates.

Risk factors for recurrence

First common risk factors for tumour recurrence was patient's age (p=0.020). Mean age at primary diagnosis of recurred tumour was 62.3 and was 12 years higher than in patients who did not develop a recurrence later on. This does not coincide with the findings of Valstar et al.[37], who found that mean age was approximately 40 years of age and 48 years of age in patients who did not developed recurrence. Wittekindt et al.[38] observed a further age difference. In their study population, mean age at primary diagnosis turned out to be lower in single recurrence patients than in multiple-recurrence patients (30.2 versus 40.3). According to the Valstar et al.[37] tumour biology might be different in younger patients, due of hormonal aspects, genetic background, or some other factor as yet unknown.

One of risk factor for recurrence in our cohort was total parotidectomy as surgical procedure, and the type of tumour. We have found that patients with squamous cell carcinoma more frequently developed recurrences. Other parameters were not statistically significant, Furthermore tumour location, which to our knowledge is a novel finding, was observed by Valstar et al.[37], but in our cohort we have not found such association. Some other publications found female gender to be associated as a risk factor for recurrence[38-40], but according to our results and findings by Valstar et al.[37] this was not in line.

Limitations

Our study's main limitation was the period of patients follow-up. We should perform long-term extended follow-up, since we followed up patients for only 5 years, what in case of malignancies is relatively short period of time. So for the future analysis we suggest to follow-up patients for at least 10 years. Therefore, continued follow-up will be needed to further delineate the natural history of this disease. The findings of the current study clearly demonstrate the importance of lengthy follow-up for those patients treated for SGT and have implications for clinical care. Secondly, there was a slight information bias. Given the suboptimal diagnostic accuracy, we included histology-confirmed SGTs, so together with short follow-up only the 6.5% recurrence rate was found and may be something of an underestimate.

Conclusion

This was the first study of such kind from our region. Therefore, our database of SGTs show some remarkable results; female show a bimodal age distribution, and women were more affected with adenoma pleomorphe than men. These findings may suggest some underlying hormonal mechanism. Secondly, relatively low

recurrence rate was observed after at 5 years of follow-up. Risk factors for recurrence were positive on histological type of tumour showed important aspect, since squamous cell carcinoma compared to other histological types more frequently led to tumour recurrence. Observations in the current study stand in contrast to patients treated for localized squamous cell carcinomas of the head and neck, in whom late disease recurrences appear to be significantly less common. This study also shows that age is associated with higher risk of tumour recurrence. The literature shows reports of late recurrences after treatment for SGC appeared, with authors suggesting that this disease has the ability to recur after a prolonged period. It is important to recognize that recurrences were observed among several histologic subtypes of SGC in the current study.

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Declaration of Interest

All authors declare that they have no conflict of interest.

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