Journal of Cranio-Maxillo-Facial Surgery 47 (2019) 500–504

Contents lists available at ScienceDirect

Journal of Cranio-Maxillo-Facial Surgery

journal homepage: www.jcmfs.com

Salivary malignancies– medical, demographic and diagnostic analysis

Yair Israel [a, c, 1], Adi Rachmiel [a, c, 1], Konstantin Gourevich [b, c], Rafael Nagler [a, c, *]

[a] Department of Oral and Maxillofacial Surgery, Rappaport Family Institute for Research in the Medical Sciences, Technion – Israel Institute of Technology, Haifa 31096, Israel
[b] Department of Nuclear Medicine Rambam Medical Center, Rappaport Family Institute for Research in the Medical Sciences, Technion – Israel Institute of Technology, Haifa 31096, Israel
[c] Faculty of Medicine, Rappaport Family Institute for Research in the Medical Sciences, Technion – Israel Institute of Technology, Haifa 31096, Israel

ARTICLE INFO

Article history:
Paper received 3 October 2018
Accepted 4 January 2019
Available online 11 January 2019

Keywords:
Salivary malignancies
Medical
Demographic
Diagnosis

ABSTRACT

We examined systemic medical and demographic characteristics of patients diagnosed with salivary malignant tumors in order to better understand the pathogenesis of the disease. Of 101 patients who received definitive treatment for malignant salivary gland tumors in our medical center, 22 died with disease (DwD) and were compared with the remaining 79 patients (Other). Mean ages were 66.7 years (median 68.0) in DwD group and 58.7 years (median 59.0) in the Others. The difference is significant ($p = 0.037$). Mucoepidermoid carcinoma was the diagnosis in 27.3% of DwDs and 27.8% of the others, Adenoidcystic carcinoma in 36.4% vs 21.5%, SCC and Acinic cell carcinoma were diagnosed in 18.3% vs 7.6% and 4.6% vs 7.6%, respectively. Alcohol consumption, concomitant malignancies, and chronic illnesses other than hypertension, were similar in the two groups, but hypertension (63.6%) in the DwD group was significantly higher than in the Other group (26.6%), ($p = 0.0010$). Smoking was also significantly different between the two groups: 50% of the DwD vs. 27.9% of the Others group smoked cigarettes. Similar distribution of the various malignant tumors in both groups emphasizes the relative importance of systemic factors such as smoking, aging and hypertension, in the salivary carcinogenesis process.

1. Introduction

Salivary gland malignancies vary in form, dimension and histopathological characteristics while their incidence is rather low. The pathogenesis of these malignancies varies and is mostly considered enigmatic though it is well established that both local and general factors affect the disease (Nagler and Laufer, 1997; Jones et al., 2008; De Oliveira, 2009; Speight and Barrett, 2009; Guzzo et al., 2010; Dwivedi et al., 2013). Sometimes tumors are diagnosed following complaints from patients who have palpable new masses either in the major or minor salivary glands. However, diagnosis is often based episodically on routine imaging performed for various unrelated purposes. A comprehensive diagnosis of salivary gland malignancies must encompass a thorough understanding of the anatomy and natural history of the disease as well as its local and metastatic spreading profiles. CT and MRI imaging are considered the diagnostic tools of choice while other tools are available for the clinician as well. These include tissue analysis, FNA, US, PET-CT etc (Nagler and Laufer, 1997; Jones et al., 2008; De Oliveira, 2009; Speight and Barrett, 2009; Guzzo et al., 2010; Dwivedi et al., 2013). Yet it is unclear which tools are preferable for each type of tumor and whether use of a certain tool creates an advantage for the therapeutic outcome. Moreover, while the significance of smoking and alcohol consumption as well as gender and age with respect to survival have been examined (Nagler and Laufer, 1997; Israel et al., 2016), other interesting systemic and demographic parameters, such as general medical history, oncological background analysis, ethnic origin etc., have not.

We examined patients diagnosed with salivary malignancies, comparing various systemic and demographic parameters with respect to survival.

* Corresponding author. Department of Oral and Maxillofacial Surgery, Rambam Medical Center and Faculty of Medicine, Rappaport Family Institute for Research in the Medical Sciences, Technion – Israel Institute of Technology, Haifa 31096, Israel. Fax: +972 4 6541295.
E-mail address: nagler@tx.technion.ac.il (R. Nagler).
[1] Equal contribution.

https://doi.org/10.1016/j.jcms.2019.01.006
1010-5182/

2. Methods and materials

2.1. Study design and patients

In the current study we analyzed 101 patients diagnosed with primary salivary gland tumors in our tertiary medical center. Of the 101 patients 22 (21.8%) died with disease (DwD group) and 79 did not (Other group). Patients defined as "died with disease" (DWD) were those who definitively died due to the salivary gland malignancy and not due to any other disease or condition including other types of cancer or age-related diseases or other systemic diseases. Of the Other group, 4 (4%) died of causes unrelated to the salivary malignancy and 75 (74/2%) were considered disease-free. There were 13 different types of malignant tumors with mucoepidermoid carcinoma most prevalent (28 cases) followed by adenoidcystic carcinoma (25 cases), squamous cell carcinoma (SCC) (10 cases), polymorphous-adenocarcinoma (9 cases), acinic cell carcinoma (7 cases), adenocarcinoma (6 cases), carcinoma ex pleomorphic adenoma (5 cases) and pleomorphic adenoma with squamous metaplasia (4 cases). Another five different types of malignancies were diagnosed in only 1–2 patients and these included: salivary duct carcinoma, myoepithelial ca carcinoma, ep. myoepithelial carcinoma, basal cell adenocarcinoma and cribriform cyst adenocarcinoma. There was no significant difference between the distribution of various tumors in the two groups: 27.3% of the DwD group and 27.8% of the Other groups were diagnosed with mucoepidermoid carcinoma, prevalence of adenoidcystic carcinoma was 36.4% vs 21.5% in the two groups and that of SCC and acinic cell carcinoma were 18.3% vs 7.6% and 4.6% vs 7.6%, respectively.

The mean ages were 66.7 years (median 68.0) in the DwD group and 58.7 years (median 59.0) in the Other group. The differences are significant ($p = 0.0373$).

The mean age at diagnosis in the DwD group was 60.9 years (median 61.0) and 54.6 years (median 56.0) in the Other group. The difference was not significant ($p > 0.05$). About three quarters (77.3%) of the patients in the DwD group were male and 22.7% female compared to about half (50.6%) males and half (49.4%) females in the Other group. The difference was significant ($p = 0.0260$). Half (50.0%) of the patients in the DwD group were smokers compared to only 27.9% in the Other group. The differences were significant ($p = 0.0500$) (Table 1).

The baseline variables (ethnicity and alcohol use) of all patients in the two study groups were not significantly different ($p > 0.05$). Apart from age and gender data we examined ethnic origin (Jew vs. Arab) and their smoking and alcohol consumption habits. Of these three parameters only smoking was found to be significantly different between the two groups: 50% of the DwD group smoked while only 27.9% of the other group smoked (Table 1). Apart from these demographic characteristics we examined the medical and oncological background of these patients as well as at the diagnostic analyses utilized in order to achieve a definitive diagnosis.

The treatment modalities administered to the patients included various surgical procedures, radiotherapy and chemotherapy. Sometimes a combination of radiotherapy and chemotherapy were concomitantly administered. The surgical procedures included local removal of the tumor which was often accompanied by neck dissection. Local removal of major salivary gland tumors often required the performance of procedures such as superficial, partial or total parotidectomy or submandibular sialadenectomy. When minor salivary glands were involved either a wide local excision or, when required, a maxillectomy (partial, subtotal or even total), were performed and in a few cases also partial glossectomy or partial mandibulectomy.

2.2. 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 ranges, medians, means and standard deviations were calculated. Test for normality was done by Shapiro–Wilk. The results of the continuous variables between the two study groups were compared and analyzed by the 2 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.

3. Results

3.1. Medical history

The past medical history parameters of patients in both study groups (DwD and Other) are presented in Table 2. There were no statistical differences in the distributions of DM (Diabetes mellitus),

Table 1
Summary of Demographic characteristics by mortality group.

Demographic Characteristic		DWD N = 22	Other N = 79	p value
Age at the end of the study (years)	Median	68.0	59.0	^{f}0.0373*
	Mean ± SD[a]	66.7 ± 17.1	58.7 ± 15.4	
	Range	[32–94]	[26–92]	
Age at diagnosis (years)	Median	61.0	56.0	^{f}0.1114
	Mean ± SD	60.9 ± 17.2	54.6 ± 15.8	
	Range	[18–85]	[16–91]	
	ND[b]	1		
Gender	M/F	17/5	40/39	$^{\vdash}$0.0260*
	%/%	77.3/22.7	50.6/49.4	
Smoker	Yes	11	22	$^{\vdash}$0.0500*
	%	50	27.9	
Alcohol	Yes	3	2	$^{\perp}$0.0680
	%	13.6	2.5	
Ethnicity	Jews	19	55	$^{\perp}$0.1730
	%	86.4	69.6	

P value by ^{f}Ttest for differences in means o$^{r\ j}$ Wilcoxon ranksum test or $^{\vdash}$Chi square test or $^{\perp}$Fisher exact test.
**$p \leq 0.01$ (Sig); *$p \leq 0.05$ (Sig) or $p > 0.05$ (NS).
[a] Standard Deviation.
[b] ND=No Data.

CVA/cardiology, hyperlipidemia (HL) or hypothyroidism diseases between the two study groups. However, the percentage of patients with hypertension (63.6%) in the DwD group was significantly higher than in the Other group (26.6%), ($p = 0.0010$) (Table 2).

3.2. Oncological history

The oncology history (previous malignancy) parameters of patients in both study groups (DwD and Other) are presented in Table 3.

The percentage of patients with other malignancy history in the DwD group (22.7%) and in the Other group (24.0%) is similar. The differences were not significance ($p > 0.05$) (Table 3).

3.3. Diagnosis, Stage and TNM

The diagnosis examination parameters of patients in both study groups (DwD and Other) are presented in Table 4. The percentage of patients tested by PET-CT, FNA, US or FNAguUS in the DwD group are significantly higher compared to the Other group ($p < 0.05$).

Comparing the percentage of patients tested by CT, MRI or Biopsy between the two study groups, the differences were not significant ($p > 0.05$) (Table 4). The stage was decided according to TNM analysis. As demonstrated in Table 5 the 'stage' distribution of the involved salivary glands was not statistically different. The table shows the stage distribution in the parotid gland group as well as in the submandibular (SMG), sublingual (SL) and minor salivary glands (Table 5). In the DWD group 36.4% of patients had small tumor ($\leq$2 cm) upon diagnosis vs 43% of the patients in the surviving group. The N analysis revealed 36.4% positive neck lymph nodes in the DWD groups upon diagnosis vs only 20% in the surviving group. Most striking was the difference in distant metastasis (M) between the DWD and the surviving groups: 45.5% of DWD patients vs. only 8.9% in the surviving patients.

4. Discussion

The profile of the patient suffering from salivary malignancy who is prone to die from the disease is that of an older man with a mean age of 68 years, who smokes and suffers from hypertension. Women and younger men with a mean age of 50 years tend to have higher survival rates. While smoking has been shown to significantly worsen the outcome, alcohol consumption has also shown a tendency toward a negative effect (although the latter did not reach statistical significance ($p \leq 0.068$)). It is well established that smoking plays an important role in the pathogenesis of the benign Warthin tumor while no such role has been shown for the much more prevalent benign pleomorphic adenoma (Sadetzki et al., 2008). Horn-Ross et al. (1997) found that cigarette smoking in men as well as alcohol drinking increase the risk for developing cancer in the major salivary glands, but that neither smoking nor drinking had such a significant effect in women. The effect of alcohol and its association with salivary malignancies has been dealt with previously by Riedel et al. (2005) who stated that the systemic impact of alcohol on the development of salivary malignancies is mediated via the interaction between the alcohol and the salivary gland parenchyma and function. The mechanism by which smoking causes cancer often has been attributed to free radicals and other inborn carcinogens such as aldehydes inhaled by smokers which lead to DNA mutations that induce damage to the immune system at a later stage. The association between more advanced age and salivary gland tumors has already been reported previously (Ungureanu et al., 2014); however, the association between hypertension and salivary malignancies and especially the observed lower survival rate is intriguing and reported here for the first time.

Another most interesting result currently reported is the relatively high prevalence of patients suffering from salivary malignancies who concomitantly suffer from other forms of cancer, mostly solid tumors. No less than 24 patients (24%) suffered from other, concomitant forms of cancer. This is a relatively very high rate of cancer incidence in the salivary patients. Butcher (2008) predicted in her study that by 2020 no less than 18.2 million patients in the US (approximately 5% of all Americans, 1:19) will be cancer patients or cancer survivors. Erikson's (Erikson et al., 2007, 2009) estimate was quite similar, approximately 4% (1:26) of all Americans are cancer patients.

This high prevalence of other concomitant forms of malignancies in salivary cancer patients supports the notion that a decrease in the potency of the general immune and cancer machinery which is systemic in nature, is responsible for these higher rates of malignancies. Thus, perhaps not only local factors but also systemic factors play a part in the salivary carcinogenesis process. It is worth noting that aging is thought to be mediated by free radicals which are released from damaged mitochondria at much higher rates at a later age in a process exhibited in all tissues (Blagosklonny, 2007; Van Remmen, and Jones, 2009). The effect of free radicals on the potency of the immune system is also well established (Ivanov et al., 2016; Li et al., 2017). Regarding the role of systemic factors in the pathogenesis of the illness, while 5 of the patients who have survived salivary cancer also suffered from hypothyroidism, none of those who died from the disease suffered from hypothyroidism; this difference almost reached statistical significance ($p < 0.058$). We recently reported a much higher prevalence (10:1) of hypothyroidism rate in patients suffering from benign tumors than in those suffering from malignant tumors (Israel et al., 2016). We thus assume that salivary tumors in patients with hypothyroidism are less aggressive in nature even if they are malignant. Finally, one can appreciate from the findings reported that the diagnostic stage may have an influence on the survival rate as there are several significant differences between the two groups of patients in the diagnostic analysis employed. While there were no differences in survival rates of the two groups between patients who had undergone MRI or CT, those who had FNA and/or US as well as PET CT have fared less well. We think that two opposite explanations may explain these observations. Patients who have PET CT are usually those with a more advanced disease, often suspected to have malignancies and thus are more prone to die. FNA and US, however, are known to be less accurate and have lower values of specificity and sensitivity, and thus lead to higher rates of underestimating the disease and to inadequate, limited therapy with lower rates of success.

Table 2
Summary of medical history by study group.

Medical-history		DWD N = 22	Other N = 79	p value
Diabetes (DM)	Yes	2	15	⊥0.3500
	%	9.1	19.0	
CVA/Cardiology	Yes	5	9	⊥0.1790
	%	22.7	11.4	
Hypertension	Yes	14	21	⊦0.0010**
	%	63.6	26.6	
Hyperlipidemia	Yes	5	11	⊥0.3320
	%	22.7	13.9	
Hypothyroidism	Yes	0	5	⊥0.5830
	%	0	6.3	

P value by ⊦Chi square test or ⊥Fisher exact test or *$p \leq 0.05$ (Sig) or $p > 0.05$ (NS).

Table 3
Summary of cancer medical history by study group.

Oncology & Cancer type		DWD N = 22	Other N = 79	p value
Oncology	No previous (%)	17 (77.3)	60 (76.0)	┞0.8970
	Other malignancy (%)	5 (22.7)	19 (24.0)	
Oncology type	Other malignancy	5	19	
	Breast		4	
	Skin SCC		2	
	Thyroid Papillary	1	2	
	Prostate	1	1	
	Laryngeal SCC		2	
	Colo-rectal		1	
	Colo-rectal & Prostate	1		
	Lymphoma		1	
	Bone sarcoma	1		
	CLL		1	
	Sezary's disease (cutaneous lymphoma)		1	
	Malignant Poroma		1	
	Uterine Sarcoma		1	
	Warthin's tumor		2	
	Teratoid tumor	1		

P value by ┞Chi square test.

Table 4
Summary of diagnosis examination by study group.

Diagnosis examination		DWD N = 22	Other N = 79	p value
CT	Yes	20	64	┸0.3500
	%	90.9	81.0	
PET CT	Yes	17	38	┸0.0170*
	%	77.3	48.1	
MRI	Yes	12	29	┞0.1320
	%	54.6	36.7	
Biopsy	Yes	9	30	┞0.8030
	%	40.9	38.0	
FNA	Yes	18	44	┞0.0280*
	%	81.8	55.7	
FNAguUS	Yes	11	18	┞0.0130*
	%	50.0	22.8	
US	Yes	14	27	┞0.0130*
	%	63.4	34.2	

P value by ┞Chi square test or ┸Fisher exact test or *$p \leq 0.05$ (Sig).

Table 5
Summary of location parameter by staging.

Location/Staging	Parotid N = 59 n (%)	SMG N = 10 n (%)	SL N = 3 n (%)	Minor N = 29 n (%)	Total N = 101 n (%)
I	11 (18.6)	2 (20.0)		6 (20.7)	19 (18.8)
II	11 (18.6)	1 (10.0)		9 (31.0)	21 (20.8)
III	9 (15.3)	3 (30.0)		6 (20.7)	18 (17.8)
IV	28 (47.5)	3 (30.0)	3 (100.0)	8 (27.6)	42 (41.6)
Unknown		1 (10.0)			1 (1.0)

p value by ┸Fisher exact test; ┸$p = 0.2470$ (NS).

5. Conclusion

In summary, the current study emphasizes the importance of systemic factors in the salivary glands carcinogenesis process. Smoking, aging, other concomitant malignancies (mainly solid) and hypertension act in concert with local factors such as the type of tumor. Although it is well established that there are very significant differences among the survival rates of different types of salivary tumors, the fact that the distribution of the various malignant tumors in both groups was similar emphasizes the relative importance of systemic factors in salivary carcinogenesis. Furthermore, it seems that proper estimation of the extent of the disease together with appropriate therapy may increase survival rates.

Patient consent

No patients were actively involved in this retrospective study.

Ethics approval

This retrospective study was not in need of approval from the Institutional Review Board.

Conflicts of interest

None of the authors declare any conflict of interest, financial or otherwise.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jcms.2019.01.006.

References

Blagosklonny MV: Program-like aging and mitochondria: instead of random damage by free radicals. J Cell Biochem 102: 1389–1399, 2007
Butcher L: Solid tumors: prevalence, economics, and implications for payers and purchasers. Biotechnol Healthc 5: 20–21, 2008
De Oliveira FA, Duarte EC, Taveira CT, Máximo AA, De Aquino EC, Alencarrde C, Vencio EF: Salivary gland tumor: a review of 599 cases in a Brazilian population. Head Neck Pathol 3: 271–275, 2009
Dwivedi N, Agarwal A, Raj V, Chandra S: Histogenesis of salivary gland neoplasms. Indian J Cancer 50: 361–366, 2013
Erikson C, Salsberg E, Forte G, Bruinooge S, Goldstein M: Future supply and demand for oncologists: challenges to assuring access to oncology services. J Oncol Pract 3: 79–86, 2007
Erikson C, Schulman S, Kosty M, Hanley A: Oncology workforce: results of the ASCO 2007 program directors survey. J Oncol Pract 5: 62–65, 2009
Guzzo M, Locati LD, Prott FJ, Gatta G, McGurk M, Licitra L: Major and minor salivary gland tumors. Crit Rev Oncol/Hematol 74: 134–148, 2010
Horn-Ross PL, Ljung B–M, Morrow M: Environmental factors and the risk of salivary gland cancer. Epidemiology 8: 414–419, 1997
Israel Y, Rachmiel A, Ziv G, Nagler R: Hypothyroidism, autoimmunity and systemic characteristics of salivary tumors. Oral Oncol 58: e13–e14, 2016
Ivanov AV, Valuev-Elliston VT, Ivanova ON, Kochetkov SN, Starodubova ES, Bartosch B, Isaguliants MG: Oxidative stress during HIV infection: mechanisms and consequences. Oxid Med Cell Longev, 2016 8910396

Jones AV, Craig GT, Speight PM, Franklin CD: The range and demographics of salivary gland tumours diagnosed in a UK population. Oral Oncol 44: 407–417, 2008

Li Z, Xu X, Leng X, He M, Wang J, Cheng S, Wu H: Roles of reactive oxygen species in cell signaling pathways and immune responses to viral infections. Arch Virol 162: 603–610, 2017

Nagler RM, Laufer D: Tumors of the major and minor salivary glands: review of 25 years of experience. Anticancer Res 17: 701–707, 1997

Riedel F, Goessler UR, Hormann K: Alcohol-related diseases of the mouth and throat. Dig Dis 23: 195–203, 2005

Sadetzki S, Oberman B, Mandelzweig L, Chetrit A, Ben-Tal T, Jarus-Hakak A, Duvdevani S, Cardis E, Wolf M: Smoking and risk of parotid gland tumors: a nationwide case-control study. Cancer 112: 1974–1982, 2008

Speight PM, Barrett AW: Prognostic factors in malignant tumours of the salivary glands. Br J Oral Maxillofac Surg 47: 587–593, 2009

Ungureanu LB, Ciobanu D, Danciu M, Costan V, Ungureanu C, Nicolau A, Popescu E: Epidemiology and pathology of parotid tumors five-year retrospective study. Rev Med Chir Soc Med Nat Iasi 118: 1101–1107, 2014

Van Remmen H, Jones DP: Current thoughts on the role of mitochondria and free radicals in the biology of aging. J Geront A Biol Sci Med Sci 64: 171–174, 2009