Asian Pacific Journal of Cancer Care
Vol 7 No 2 (2022), 261-266
Original Research

Clinical and Pathological Features and Outcome of Patients with Salivary Gland Cancer a Single Centre Report

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Introduction: Salivary gland tumors are rare tumors that account for 3 to 4% of head and neck neoplasms. These tumors may arise from 6 major and numerous minor salivary glands. This study was designed to investigate the factors affecting the prognosis of salivary gland tumors.
Methods: This study is a retrospective descriptive study in which the records of patients with salivary gland tumors referred to the Radiotherapy and Oncology Center of Namazi Hospital from 2005 to 2015 were reviewed.
Results: 158 patients were included in this study with a mean age of 55.37 years. 49% of the patients were men. Adenoid Cystic Carcinoma was the most common histological type (30.57%) and Adenocarcinoma with a prevalence of 1.91% had the lowest prevalence rate in this study. 65.19% of salivary gland neoplasms in this study had parotid gland involvement and sublingual gland involvement had the lowest prevalence (3.8%). The results of survival analysis clearly illustrated that surgery, pathology type and stage was statistically significant in survival.
Discussion: Clinical, pathological and therapeutic factors in people with malignant salivary gland neoplasms have a significant relationship with their survival. controversies on treatment and outcome continues.

Introduction

Salivary gland tumors are diverse and rare tumors and consists both benign and malignant lesions [1, 2]. They account for 3 to 4% of head and neck neoplasms. These tumors are more common in adulthood and older ages and about 5% of cases occur under 16 years of age (8-10). The prevalence

of salivary gland carcinoma has increased [3]. The risk factors are not well known. Suggested Risk factors may be radiation, immunosuppression and some foods, viruses (EBV), history of cancer [3]. In the histological classification of salivary gland cancers by WHO in 2005, there were 10 subtypes in the benign group and 24 subtypes in the malignant group, and benign subtypes are 5 to 7 times more common than malignant types and most of them (more than 80%) are PA (pleomorphic adenoma) [4].

Regarding diversity of these tumors and variation in pathology, tumor site and probably behavior, this study has been conducted.

Materials and Methods

This study is a retrospective descriptive study in namazi hospital, Shiraz University of Medical Sciences, Shiraz, Iran. That is the referral cancer center in south of Iran. the records of all patients with salivary gland tumors referred to the Radiotherapy and Oncology Center of Namazi Hospital from 2005 to 2015 were reviewed. All information about patients, including demographic and clinical criteria (age, sex, primary site, surgery, pathology, radiotherapy, chemotherapy, local control, presence of distant metastasis) were collected and analyzed. Surgery included biopsy alone that was done in those patients who were not able to tolerate radical surgery or tumor was not operable. For others complete tumor resection was done. Radiotherapy was done with Elekta and Oncor, linacs and treatment planning system was Prowess. Target volumes in different sites were defined according to reference radio-oncology guidelines and books and the dose of radiation was according to extent of surgery and site of primary lesions. Chemotherapy was administered in metastatic and some non-metastatic patients that were cisplatin-5FU. Disease free Survival (DFS) was defined as the time between surgery and time of recurrence or metastasis and overall survival (OS) was defined the time between surgery and death.

Results

158 patients were included in this study with a mean age of 55.37±15.58 years and 80 (51%) were women and 77 (49%) were women. Mean age in men was 58.06±16.64 and 52.75±14.09 years in women.

Adenoid Cystic Carcinoma was the most common (48 patients or 30.57%) type of pathology in our patients and the least common was adenocarcinoma (2 patients or 1.3%). Other types in order of prevalence were MUC, SCC, carcinoma ex-pleomorphic, acinic cell carcinoma, salivary duct carcinoma, polymorphous low grade adenocarcinoma and adenocarcinoma (Table1).

Variable	Frequency (%)
Gender	
Female	80 (51)
Male	77 (49)
Age (year)	
<30	11 (7)
30-60	85 (54.1)
>60	61 (38.9)
Histologic Type	
Mucoepidermoid Carcinoma	43 (27.4)
Adenoid Cyst Carcinoma	48 (30.6)
Carcinoma ex-pleomorphicadenoma	20 (12.7)
Squamous Cell Carcinoma	23 (14.6)
Acinic Cell carcinoma	8 (5.1)

Polymorphous low grad adenocarcinoma	5 (3.2)
Adenocarcinoma	2 (1.3)
Salivary duct carcinoma	7 (4.5)
Tumor origin	
Parotid	102 (65)
Submandibular	41 (26.1)
Sublingual	6 (3.8)
Minor salivary gland	8 (5.8)
T Stage	
T1	11 (7)
T2	45 (28.7)
T3	52 (33.1)
T4	49 (31.2)
N Stage	
0	86 (54.7)
1	57 (36.3)
2	14 (9)
M Stage	
0	141 (89.8)
1	16 (10.2)
Tumor Stage	
1	10 (6.4)
2	36 (22.9)
3	54 (34.4)
4	57 (36.3)
Radiotherapy	
0	24 (15.3)
1	133 (84.7)
Surgery Type	
Only Bx	13 (8.3)
Partial Resection	52 (33.1)
Complete Resection	92 (58.6)

Table 1. Demographic and Pathologic Characteristics of the 157 Patients with Salivary Gland Tumor.

Parotid gland was the origin of tumor in most (103 or 65.19%) patients and about (6 or 3.8%) of salivary gland cancers were originated from sublingual gland. Most patients (52 or 33.1 %) had T3, then T4 (49 or 31%), T2 (45 or 28.7 %) and T1 (11 or 7%) tumors. Most patients (86 or 54.7 %) had N0 and 57 (36.3%) patients N1 and 14 (9%) patients had N2 lesion. Sixteen (10.1%) patients had metastasis at presentation, and all had lung metastasis. Complete radical surgery was done for 92 (58.6%) patients, and 52 (33.1%) and 13 (8.3%) of patients had undergone complete tumor resection and biopsy alone. Radiotherapy was done for 134 (84.8%) of patient (Table1).

Patients were followed for a mean time of 31.5 months. 69 (43.9%) patients had passed away and 88 (56.1%) patients are alive with no evidence of malignancy and 23 (26.1%) patients were alive with malignancy. Mean OS was 68.06 months and 2-5 and 10 year OS were 76%, 57%, 47%, and 24%. As shown in Table 2 age, radiotherapy, chemotherapy were not statistically significant.

Variable	Univariate Analysis		Multivariate Analysis	
	HR (95%CI)	P value	HR (95%CI)	P value
Gender		0.057		0.78
Female	1		1	
Male	1.59 (0.98-2.96)		1.07 (0.62-1.85)	

Age(year)				
<30	1	0.24	1	
30-60	2.02 (0.61-6.61)	0.048	0.54 (0.14-2.00)	0.84
>60	3.29 (1.01-10.77)		0.88 (0.24-3.21)	0.08
Histologic Type				
Mucoepidermoid Carcinoma	1		1	
Adenoid Cyst Carcinoma	1.10 (0.57-2.13)	0.76	1.15 (0.59-2.25)	0.67
Pleomorphic Adenoma	1.35 (0.58-3.10)	0.47	1.27 (0.54-2.97)	0.57
Squamous Cell Carcinoma	2.97 (1.40-6.31)	0.004	1.42 (0.63-3.18)	0.38
Others	1.47 (0.64-3.38)	0.35	3.39 (1.31-8.38)	0.01
T Stage				
T1	-	0.96	-	0.97
T2	0.12 (0.05-0.29)	<0.0001	0.18 (0.07-0.45)	<0.0001
T3	0.86 (0.52-1.42)	0.86	1.02 (0.61-1.71)	0.71
T4	1		1	
N Stage				
0	1	<0.0001	1	
1	5.13 (3.03-8.67)		2.56 (1.45-4.51)	0.001
M Stage				
0	1	<0.0001	1	<0.0001
1	18.51 (8.68-39.44)		31.48 (10.56-93.76)	
Chemotherapy				
0	1	0.005	1	0.82
1	1.98 (1.22-3.22)		0.93 (0.53-1.63)	
Radiotherapy				
0	1	0.09	1	0.56
1	0.54 (0.28-1.05)		0.76 (0.31-1.9)	
Surgery Type				
Only Bx	1		1	
Partial Resection	0.04 (0.01-0.11)	<0.0001	0.27 (0.03-2.16)	0.21
Complete Resection	0.01 (0.003-0.03)	<0.0001	0.19 (0.02-1.6)	0.12

Table 2. Univariate and Multivariate Analysis of Association of Prognostic Factors and Overall Survival in 157 Patients with Salivary Gland Tumor.

But surgery, pathology type and stage were significant factors in OS and DFS. Sex was significant in DFS rather than OS (Tables 2 and 3).

Variable	Univariate Analysis		Multivariate Analysis	
	HR (95%CI)	P value	HR (95%CI)	P value
Gender		0.09		0.012
Female	1		1	
Male	2.43 (0.86-6.89)		1.83 (1.14-2.95)	
Age(year)				
<30	1	0.048	1	
30-60	0.30 (0.09-0.99)	0.048	0.74 (0.20-2.72)	0.65
>60	0.61 (0.37-0.99)		0.86 (0.24-3.06)	0.82
Histologic Type				
Mucoepidermoid Carcinoma	1		1	
Adenoid Cyst	0.68 (0.16-2.74)	0.59	0.62 (0.32-1.18)	0.14

Carcinoma				
Pleomorphic Adenoma	1.14 (0.21-6.28)	0.87	0.47 (0.21-1.03)	0.06
Squamous Cell Carcinoma	4.31 (1.05-17.61)	0.04	1.82 (0.87-3.80)	0.11
Others	0.70 (0.07-6.32)	0.75	2.15 (0.90-5.14)	0.08
T Stage				
T1	-	0.98	-	
T2	0.26 (0.06-1.13)	0.07	0.57 (0.21-1.50)	0.25
T3	1.03 (0.32-3.29)	0.95	0.65 (0.35-1.21)	0.17
T4	1		1	
N Stage				
0	1	0.2	1	
1	1.96 (0.68-5.66)		0.85 (0.43-1.66)	0.63
Chemotherapy				
0	1	0.007	1	0.63
1	4.93 (1.53-15.83)		1.6 (0.71-1.88)	
Radiotherapy				
0	1	0.11	1	0.58
1	23.28 (0.007-4.56)		0.77 (0.30-1.96)	
Surgery Type				
Only Bx	1		1	
Partial Resection	0.30 (0.09-0.99)	0.04	0.04 (0.005-0.36)	0.004
Complete Resection	0.61 (0.37-0.99)	0.04	0.02 (0.002-0.18)	0.001

Table 3. Univariate and Multivariate Analysis of Association of Prognostic Factors and Disease-free Survival in 157 Patients with Salivary Gland Tumor.

Then analysis was done for different pathology types. (Median of survival in) DFS for ACC, MUC, SCC, pleomorphic adenoma and other types were 32, 13.5, 7.6, 30 and 16 months. And OS for ACC, MUC, SCC, pleomorphic adenoma and other types were 88.73, 78.9, 20.6, 63.9 and 1.8 months respectively. For ACC, radiotherapy and surgery were statistically significant in OS and surgery for DFS. For MUC none of factors were significant and in pleomorphic adenoma only surgery was significant. Interestingly chemotherapy and radiotherapy and stage were significant for SCC (Table 4).

Characteristic	Overall Survival	P Value	Disease Free Survival	P Value
	HR (95%CI)		HR (95%CI)	
Mucoepidermoid Carcinoma				
Age	1.76 (0.63-4.90)	0.27	0.57 (0.26-1.25)	0.16
Sex	0.68 (021-2.25)	0.53	1.17 (0.36-3.79)	0.17
Chemotherapy	1.31 (0.40-4.30)	0.64	1.22 (0.46-3.27)	0.78
Radiotherapy	--	-	- -	--
Surgery Type	0.57 (0.22-1.47)	0.24	1.22 (0.46-3.27)	0.66
Tumor Stage	1.49 (0.75-4.98)	0.25	0.80 (0.35-1.84)	0.6
Adenoid Cyst Carcinoma				
Age	1.90 (0.76-4.71)	0.16	1.17 (0.50-2.72)	0.7
Sex	0.99 (0.34-2.87)	0.98	0.44 (0.18-1.08)	0.07
Chemotherapy	0.97 (0.33-2.87)	0.95	1.83 (0.76-4.42)	0.17
Radiotherapy	0.077 (0.007-0.87)	0.03	- -	- -
Surgery Type	0.082 (0.033-0.200)	<0.001	0.11 (0.035-0.36)	<0.001
Tumor Stage	0.96 (0.43-2.13)	0.93	1.05 (0.36-3.06)	0.92
Pleomorphic Adenoma				

Age	1.42 (0.22-9.03)	0.7	-	-
Sex	70 (0.14-3.56)	0.65	0.12 (0.009-1.75)	0.12
Chemotherapy	1.76 (0.38-8.23)	0.46	4.88 (0.42-56.38)	0.2
Radiotherapy	1.53 (0.15-15.17)	0.71	- -	-
Surgery Type	0.093 (0.019-0.43)	0.003	- -	-
Tumor Stage	1.14 (0.23-5.60)	0.86	0.37 (0.046-3.42)	0.35
Squamous Cell Carcinoma				
Age	0.470 (0.08-2.50)	0.37	1.13 (0.20-6.27)	0.88
Sex	2.62 (0.44-15.57)	0.28	1.61 (0.25-10.24)	0.61
Chemotherapy	0.13 (0.024-0.71)	0.019	0.37 (0.10-1.33)	0.13
Radiotherapy	0.090 (0.015-0.54)	0.009	0.53 (0.14-1.94)	0.33
Surgery Type	0.54 (0.092-3.15)	0.53	0.36 (0.075-1.71)	0.19
Tumor Stage	18.31 (1.96-171.05)	0.011	0.22 (0.017-2.86)	0.24
Others				
Age	4.67 (0.95-22.79)	0.056	11.36 (0.86-148.90)	0.064
Sex	0.93 (0.19-4.52)	0.93	0.047 (0.004-0.60)	0.019
Chemotherapy	7.74 (1.06-56.43)	0.043	2.97 (0.12-70.17)	0.5
Radiotherapy	0.74 (0.12-4.56)	0.75	7.0 (0.25-193.84)	0.25
Surgery Type	0.79 (0.072-8.81)	0.85	0.008 (00-0.57)	0.027
Tumor Stage	3.55 (1.23-10.27)	0.019	1.41 (0.29-6.78)	0.66

Table 4. Univariate and Multivariate Analyses of Various Histologic Type for OS and DFS in 157 Patients with Salivary Gland Tumor.

Discussion

Salivary glands are divided into major and minor ones. Major salivary glands include parotid, submandibular, and sublingual glands and minor ones include hundreds of small glands scattered throughout the oropharynx, nose, sinuses, larynx, and trachea [5]. Both benign and malignant lesions may be seen in salivary glands. Chance of being benign or malignant varies in different sites [6].

Bjørndal, et al in a retrospective study in 1990-2005 found that the incidence of salivary gland carcinoma in Denmark was 1.1/100000 annually. About half of tumors were located in parotid gland. Among remainder of cancers, 26% of were originated from oral cavity minor salivary glands. Among minor salivary glands, most were in palate (41%) [2]. We had fewer minor salivary gland tumors. In our report, 103 (65.5%) of patients had parotid gland and 41 (25.9%), 6 (3.8%) and 8 (5.1%) patients had submandibular, sublingual and minor salivary gland tumor.

These cancers are more prevalent in men and those patients who are the 6th and 7th decades of their lives, and it must also be mentioned that the average age varies according to the type of tumor [1]. But in the study in Denmark, mean age was 62 years old and male/female ratio was 0.97 [2]. In our study mean age was 55.37 years and male patients were 51% of all.

Boukheris et al. studied major salivary gland carcinomas in the United States in 2006, in 6391 patients and they found that the incidence of M-SGC was about 11.5 cases per million and men had a higher incidence rate than women. The most common cancer in men was Squamous cell carcinoma and mucoepidermoid carcinoma. In women, the most common pathology types were mucoepidermoid carcinoma, acinic cell carcinoma and adenoid cystic carcinoma. They concluded that major salivary gland tumors have different epidemiological patterns based on the patients' sex, age and race [7]. In a study in India during a 14-year period on both benign and malignant salivary gland tumor, 262 patients with malignant salivary gland tumors were reported. Mean age of malignant lesions were 56 years and male/ female ratio were 1.08 [5]. Most common primary site

was parotid (61%), minor salivary glands (23%) and submandibular gland (15%) [5]. In minor salivary glands, palate was the most common site (68%). In this study most common pathological type was ACC (25%) and then MUC (19%) [5]. Another report from UK during the period 1973–1988, 7.7% of 3378 salivary gland lesions were malignant and most (32%) were ACC and MUC (23%) [8]. In our study most common type of pathology was ACC and then MUC. SCC was only seen in 14.6% of patients. In addition in our study fewer patients had minor salivary gland cancer. Only 8 (5.1%) had minor salivary gland cancer.

In a study by Terhaard et al. in a large study on 565 patients with both minor and major salivary gland carcinoma 5 and 10 years DFS were 63% and 55%. In their study most patients had parotid gland tumor (332) and then minor salivary gland tumor (157). Oral cavity minor glands (66% 10 year survival) had the best outcome. Among in their study, age, stage, site, male gender, Were statistically significant in OS. While most of their patients had ACC, treatment and pathology were not related to survival [9]. In our study, Pathology type had correlation with survival.

In a study on 78 patients with major salivary gland carcinoma 5 years DFS was 65%. In this study submandibular gland tumors (14 patients) comparing to parotid (64 patients) had lower stages but poorer outcome. Most pathology in submandibular gland was adenoid cystic carcinoma. Tumor location, grade, LVI, LN involvement was important factors in prognosis. In this study, lymph node metastasis and perieural invasion were statistically significant in surgery. In their study, there were 14 patients with submandibular gland cancer. Although half of them had stage 1, 43% developed metastasis [10]. Role of RT in salivary gland cancer is a debate.

In a study on 126 patients with parotid gland cancer in Brazil, most common pathology in parotid was MUC (40%) and adenocarcinoma was only 12%. In their study 5- and 10-year OS was 72% and 69%, respectively. In multivariate analysis, stage and grade were significant in outcome. RT was effective in high grade lesions. Patients operative RT in high grade group improved local recurrence (17.4% versus 47.2%). Even in different stages, RT did not improve survival [11]. The results of this study was not in consistent with Frankenthaler’s report in which among 155 patients who had parotid cancer. The most common pathology was MUC and RT has improved local recurrence. They reported that stage and grade, size and LVI were prognostic factors. 25% of patients developed metastasis, mostly lung. Local recurrence occurred in 16% of patients and positive lymph node, deep or superficial tumor and size were statistically significant. But tumor grade and size were statistically significant in metastasis. In their study median time to recurrence was 14.5 months and 5 years OS was 75% [12].

Although Submandibular masses are 5-15% of salivary gland tumors, they have higher chance (43%) for being malignant. In a study on 2626 patients with submandibular salivary gland carcinoma found Median age was 61.3 (7-101) years and 52.9% of patients were male. In this study most common pathology was ACC (36%), SCC (18.1%) and then MUC (16.9%). 5 yeas OS was 54% and tumor grade, stage and patients’ age and sex, doing surgery were statistically significant in OS. In this study 87% of patients had surgery and 58% received RT after surgery. Mean tumor size was 3 cm [6]. In our study submandibular gland cancers consist of 25.9 % or 49 patients. In another study that was carried out only in patients with submandibular gland cancer, after a mead follow up of 29 months, 5 yeas local control and DFS was 80.5% and 71.8%. In this study 57.4% of patients were male and median age was 50 years. In multivariate analysis, none of factors, even stage or pathology type, were statistically significant in survival and recurrence [13].

In conclusion, salivary gland carcinomas are a diverse group of disease and each patient must be treated individually. Studies must focus on special type or gland in order to draw a firm and precise conclusion.

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