Survival outcome of malignant minor salivary tumors in Pakistani population

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Abstract

Objective: Malignant tumors of minor salivary glands (MSG) are rare. Survival outcome in Pakistani population with malignant MSG tumors remains to be defined. The objective of this study was to report the clinical presentation, treatment modalities, and survival outcome of radically treated malignant tumors of MSG in Pakistani population. **Materials and Methods:** Between April 2003 and March 2011, 45 patients with malignant tumors of MSG were treated at Shaukat Khanum Cancer Hospital and included in the study. Patient characteristics and treatment modalities were assessed and local, regional, and distant failures determined. Relapse-free (RFS) and overall survival (OS) was calculated using Kaplan-Meier curves, and log-rank test was used to determine significance. **Results:** Median age was 40 (17-83) years. Male to female ratio was 1.25:1. Most common site was hard palate in 31 (69%) patients. Adenoid cystic carcinoma (51%) was the most common histological diagnosis. Nine patients (20%) underwent surgery as the only treatment modality, six patients received (13%) radiotherapy alone, and 30 patients (67%) had surgery followed by adjuvant radiotherapy. Eight patients developed recurrence (four local, two regional, one locoregional, and one distant). The 5-year actuarial overall OS and RFS was 77 and 66%, respectively. Age, T-stage, and treatment modality were significant for RFS, whereas T-stage and treatment modality were significant factors for OS. **Conclusion:** Surgery as single modality or combined with radiation therapy resulted in acceptable survival in Pakistani population with malignant minor salivary tumors.

Key words: Adenoid cystic carcinoma, minor salivary glands, survival

Introduction

Malignant tumors of minor salivary glands (MSG) represent a heterogeneous group of tumors. They have complex clinicopathological characteristics, variable growth patterns, and histological subtypes. Malignant tumors of salivary glands account for less than 1% of all neoplasms and almost 3% of all head and neck tumors. Less than a quarter of these tumors originate in MSG.[1,2] Oral cavity resides 450-700 MSG and represents the most frequent site for these tumors. Although rapid growth and short history is associated with squamous cell carcinoma of oral cavity, indolent nature of MSG tumors produces an asymptomatic swelling growing slowly over many months or years prior to diagnosis.[3] Due to relative rarity of these tumors, majority of existing literature consists of retrospective studies with limited sample size. Benign and malignant tumors have generally been lumped together and outcomes thus reported are obscure. Furthermore, literature remains silent as far as survival in Pakistani population with malignant MSG tumors is concerned. The objective of this study was to report 8 year experience with treatment of malignant MSG tumors in Pakistani population from a cancer hospital in Pakistan.

Materials and Methods

Data of patients with diagnosis of MSG malignancy, treated between April 2003 and March 2011 were extracted from head and neck database at Shaukat Khanum Memorial Cancer Hospital and Research Centre. A total of 45 patients were included in the study. All cases were histologically reviewed to confirm the diagnosis according to 2005 World Health Organization (WHO) classification[2] and patients were staged according to American Joint Committee on Cancer sixth edition. All patients underwent a comprehensive clinical examination and nasoendoscopy where indicated. Magnetic resonance imaging (MRI) of face and neck was performed in all patients to radiologically stage the disease. Surgery was the mainstay treatment option. Wide local excision with 1 cm gross negative margins was performed, and specimen was oriented with sutures. Postoperative radiotherapy was reserved for patients with high-grade tumors, T3 or T4, positive surgical margins, and in patients operated elsewhere. Single modality radiotherapy was used in patients with locally advanced disease where curative resection was not possible. Neck dissection was reserved for patients with clinical or radiological evidence of node positive disease. Patient characteristics, clinicopathological variables, and adverse events were assessed. Local, regional, and distant failure was determined. The expected 5-year overall survival (OS) and relapse-free survival (RFS) were calculated using Kaplan-Meier curves, and log-rank test was used to determine significant difference for variables including age, gender, clinical tumor size stage, histology, and treatment modality. OS was calculated by subtracting date of last follow up from date of start of treatment. RFS was determined by subtracting date of recurrence from date of start of treatment. All analysis was performed on Statistical Package for Social Sciences (SPSS) version 20. This was a retrospective, non-interventional study with no potential identifiers and was carried out in accordance with declaration of Helsinki.

Results

Median age was 40 (17-83) years and median follow up was 30 (5-96) months. Male to female ratio was 1.25:1. Nearly 50% patients were less than 40 years of age. Table 1 demonstrates patient characteristics. Clinical stage Tx represented patients operated at an outside facility and referred to Shaukat Khanum Memorial Cancer Hospital for adjuvant treatment. Hard palate was the most frequent site (69%) followed by base of the tongue (16%). Except one patient, all had NO disease clinically and radiologically. Adenoid cystic carcinoma was the most frequent pathological diagnosis with more than 50% patients. A total of 30 patients received adjuvant radiation, whereas radiation was used as sole treatment modality in six patients.

A total of 9 patients (mucoepidermoid carcinoma: Three, adenocarcinoma: Six) were treated with surgery alone, and no locoregional relapse was observed in these patients during follow up. Out of these, six patients had T1/T2 tumors, whereas the rest had T3/T4 tumor stage due to bone involvement despite small tumor size. There were three patients with T3/T4 tumors who underwent surgery alone. All these patients declined radiation. There was no relapse in patients who

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Table 1: Patient demographics and treatment modality

Variables	Number of patients (%)
Age	
<40	22 (49)
>40	23 (51)
Sex	
Male	25 (56)
Female	20 (44)
Site	
Hard palate	31 (69)
Tongue base	07 (16)
Alveolus upper	01 (2)
Floor of mouth	01 (2)
Retromolar trigone	01 (2)
Soft palate	01 (2)
Anterior tongue	01 (2)
Tonsil	01 (2)
Posterior pharyngeal wall	01 (2)
T-stage	
T1	07 (16)
T2	13 (29)
T3	04 (9)
T4	16 (36)
Tx	05 (11)
N-stage	
N0	44 (98)
N2b	01 (2)
Histology	
Adenocarcinoma	09 (20)
Adenoid cystic carcinoma	23 (51)
Mucoepidermoid carcinoma	13 (29)
Grade	
Well	22 (49)
Moderate	17 (38)
Poor	02 (4)
Unknown	04 (9)
Treatment modality	
Surgery	09 (20)
Surgery+radiotherapy	30 (67)
Radiotherapy	06 (13)

underwent surgery. Possible reasons included early T stage of tumors and low grade. Eight patients failed the treatment. Two patients had persistent disease after completion of radical treatment. One of these died of cerebrovascular accident (CVA). Two patients failed regionally and developed relapse in the temporal bone and orbital rim. One patient failed locoregionally after 24 months and was offered palliative radiotherapy. The 5-year actuarial OS and RFS was 77 and 66%, respectively. Age (0.02), T-stage (0.003), and treatment modality (0.001) showed statistically significant difference for RFS, whereas T-stage (0.02) and treatment modality (0.001) showed significant difference for OS. Table 2 demonstrates various factors analyzed for RFS and OS.

Table 2: Log-rank analysis of variables for 5-year RFS and OS

	Expected 5-yearRFS survival (%)	*P* value	Expected 5-year OS (%)	*P* value
Age				
<40	90	0.02	92	0.09
>40	38		58	
Gender				
Male	38	0.7	78	0.5
Female	78		74	
Clinical tumor stage				
T1/T2	100	0.003	100	0.02
T3/T4	28		58	
Histology				
Adenocarcinoma	66	0.2	100	0.3
Adenoid cystic carcinoma	56		60	
Mucoepidermoid carcinoma	90		90	
Treatment modality				
Surgery	100	0.001	100	0.001
Surgery+RT	62		82	
RT	0		0	

RFS=Relapse-free survival, OS=Overall survival, RT=Radiation therapy

Discussion

The current study reports long-term survival of malignant tumors of MSG in Pakistani population. The clinical presentation and histological distribution were comparable with published literature. Younger age at presentation and distinct pattern of relapse was observed. A total of 45 patients represent <2% of patients treated for head and neck cancer in our institute treated over a period of 8 years, thus underscoring the rarity of this tumor quoted in other studies.[4,5] Limitations include retrospective design and small sample size.

Etiology and prognostic factors for malignant MSG tumors are not well known. Old age has been associated with poor outcomes, and these tumors are seen more frequently in older patients.[6,7] In the current study, nearly half of the total sample was <40 years of age. Radiation exposure and silica have been implicated as risk factors in other studies.[8,9] No specific previous history was recorded in the present study indicating exposure to any of these factors. Clinical course of MSG tumors is generally that of prolonged, asymptomatic, and slow-growing lumps in the oral cavity. Not surprisingly, these tumors were called "chronic cancers" in the 20th century.[10,11] Tumor size is an important prognostic factor and has been associated with survival in multiple studies.[6,12,13] In the present study, significant difference in survival was observed between early and advanced tumors for both RFS and OS. It has been shown that malignant MSG tumors are more common in females.[14,15] In the present study, however, they were seen more frequently in males. Adenoid cystic carcinoma and mucoepidermoid carcinoma are the most frequent histological variants and the same was observed in the current study.[16-19] Distant relapse rate for malignant MSG reaching up to 30% has been demonstrated.[20] In the present study, only one patient developed distant metastasis. Adenoid cystic carcinoma has been associated with poor survival and high risk of recurrence when compared with other histopathologies.[6,21] Consistent with other studies, patients with adenoid cystic carcinoma in the present study had relatively poor survival and majority of patients with relapse had adenoid cystic histology but this difference was not significant. Treatment modality was significant for both RFS and OS. Majority of patients with T1/T2 tumors underwent surgery alone, whereas adjuvant radiation was used in patients with aggressive disease. Similarly,

radiation alone was used in patients with locally advanced irresectable tumors. The statistical difference for RFS and OS observed for treatment modalities probably represents the difference in distribution of prognostic factors in treatment groups. Recently, Kruse reported on 27 malignant MSG tumors treated over a period of 10 years. Similar to the current study, adenoid cystic carcinoma was the most common histology, nodal disease was found in only three patients, and hard palate was the most common primary site. Also most common histology for patients who developed relapse was adenoid cystic carcinoma, and no patient with adenocarcinoma developed a local/distant relapse.[22] Indications for treatment were also similar where surgery alone was used for early tumors, and adjuvant radiation was given if negative prognostic factors were present. However, the proportion of patients who received adjuvant radiation was markedly different. High number of T3/T4 tumors, poor differentiation, and inability to assess margins due to surgery performed elsewhere are some of the factors likely to have resulted in this observation. None of the patients who underwent surgery alone developed a recurrence likely due to more favorable prognostic distribution of this group. Male preponderance and young age at presentation were distinct factors in the present study. Literature remains scarce on studies documenting malignant tumors of MSG. In a recent meta-analysis, reporting on nearly 2000 patients with tumors of salivary glands of hard palate, 60% had benign pathology. Out of 30 studies included, only nine had 100 or more patients.[23] A study from Pakistan reported on 21, 168 tumors reviewed over 10 years of which only 70 were MSG origin. Consistent with the present study, hard palate was the most common site of origin, and adenoid cystic carcinoma was the most common histological variant.[24]

The present study reports survival in patients with malignant minor salivary tumors in Pakistani population. To our knowledge, this is the first study of this type reported from Pakistan. Male preponderance and younger age at presentation was observed. In absence of large prospective studies or randomized trials to guide treatment, wide local excision with 1-cm margins and adjuvant radiation in presence of negative prognostic factors resulted in acceptable survival.

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