

Treatment outcome in patients with salivary gland tumors

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Citation

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Abstract

Introduction - Carcinoma of the salivary glands is an uncommon disease accounting for less than 1% of all head and neck malignant neoplasms; yet it provides a challenge both for the surgeon and the radiation oncologist. These tumors display a diverse biological behaviour and clinical presentation depending on the stage and grade of the tumor. This article reviews the epidemiologic, pathologic, local control and survival characteristics of histopathologically confirmed carcinomas of the major salivary glands over a five year period from our institution.

Materials and Methods - A retrospective analysis of 58 patients with parotid gland malignancies treated in the Department of Radiation Therapy and Oncology, Post Graduate Institute of Medical Education and Research (PGIMER), Chandigarh; between Jan 2000-Dec 2005 was performed. Primary treatment included surgery followed by radiation therapy (RT). Tumor doses ranged from 6Gy as palliative single fraction to 60 Gy (median, 50 Gy). Wedged paired fields on Co-60 fields were used to treat 38 patients, while mixed beam with electron and photon were used in 4 patients.

Results - Mucoepidermoid carcinoma was the commonest histology (39.7%). Follow up ranged from 6 to 66 months (median 33 mo). During this period, there were 12 local recurrences (20.7%) after a disease free interval ranging from 6 to 45 months. Survival was significantly improved in patients who underwent surgery ($p < 0.0001$). In patients who received RT, 6 of 42 patients failed locally as compared to 9 of the 16 patients who did not receive RT. In the operated patients, the presence of postoperative residual disease was associated with a significantly poorer survival. On univariate analysis, presence of residual ($p < 0.0001$) and high grade disease ($p = 0.02$) significantly influenced the DFS. On multivariate analysis, presence of residual disease was the only significant prognostic variable ($p = 0.01$) associated with poor DFS. Grade of tumors was found to have a marginal influence on the DFS ($p = 0.07$).

Conclusions – Local control rates with postoperative RT were good. We have limited experience in the technique using mixed electrons and photons due to rarity of the disease.

INTRODUCTION

Carcinoma of the salivary glands, is an uncommon disease accounting for less than 1% of all head and neck malignant neoplasms; yet it provides a challenge both for the surgeon and the radiation oncologist.¹ Historically, there have been few large scale surveys of these tumors.^{2,3} Salivary gland tumors display a widely diverse biological behaviour and clinical presentation depending mainly on the stage and grade of the tumor.⁴ Low grade tumors have a more or less benign course, while high grade tumors maybe very aggressive locally as well as presenting with distant metastases.⁵ The main therapeutic management of salivary gland tumors is surgical resection. The question whether surgery needs to be complimented with postoperative

radiotherapy and/ or chemotherapy is not completely answered in view of lack of well documented randomized trials. This article reviews the epidemiologic, pathologic, local control and survival characteristics of histopathologically confirmed carcinomas of the major salivary glands in 58 patients over a five year period from our institution.

PATIENTS AND METHODS

Eligible patients included all those registered in the Department of Radiation Therapy and Oncology, Post Graduate Institute of Medical Education and Research (PGIMER), Chandigarh, from Jan, 2000 through Dec, 2005, with histopathologically confirmed malignancies of the parotid glands. Patients with pathologic diagnosis of

sarcoma or metastatic squamous cell carcinoma to the salivary glands were excluded. Patients who did not receive any form of treatment or who were lost to follow up were excluded from our study. Data concerning patient demographics, clinical, histopathological characteristics, treatment modalities and their outcome was obtained from a retrospective review of medical records in our department. All patients fulfilled the World Health Organization criteria for the diagnosis of salivary gland tumors.[6] A total of 68 patients were registered of which 58 patients were found to be evaluable and form part of this analysis. All patients had a complete physical examination including complete hemogram, blood chemistry and a chest X-ray. CT scan or an MRI was performed in 28 patients.

The type of surgery was individualized and was dependent on multiple factors including the extent of disease, histologic diagnosis and referring surgeon. Forty two of the surgeries were performed in our institute. Forty one (77.6%) patients underwent parotidectomy, defined as superficial (21 patients), near total (15), or radical (5). The facial nerve was sacrificed in 16 patients (27.58%). Pathologically, 20(34.5%) patients had positive or close microscopic margins. Six patients (10.34%) had clinical lymphadenopathy at presentation. Fifteen patients (25.8%) had undergone neck dissections, of which 11 patients (19%) had pathologic cervical nodal disease including 2 patients who had intraparotid nodal disease.

Surgical treatment was supplemented with radiation therapy, which was delivered using either a Cobalt-60 or 6MV linac in 42 patients. Each patient's treatment was individualized based on the extent of disease and surgery. The most common radiation technique used was the wedge paired fields which were oriented primarily in an anterior- posterior direction, obliqued slightly such that anteriorly they would avoid divergence into the contralateral orbits and the contralateral parotid. Posteriorly, it was obliqued to encompass the facial canal. Since the installation of the Clinac DHX CD2300 linear accelerator in May, 2005, four patients have been treated with an ipsilateral field covering the entire parotid bed. These patient's fields were treated with a combination of high energy electrons (9-12 MeV) and 6MV photons, with a varying mix of electrons: photons of 3:1 to 4:1.

Tumor doses ranged from 6Gy as palliative single fraction to 60 Gy (median, 50 Gy). The depth of the total prescribed tumor dose ranged from 3-5 cm. Treatment of clinically and pathologically uninvolved neck was individualized, though

mainly done in high grade tumors. Patients with lymph node involvement had the lower borders of the fields extended down to encompass the nodes with a 2cm margin. The disease free survival (DFS) and overall survival (OS) were calculated using the Kaplan-Meier method. DFS was calculated from the date of diagnosis to date of detection of local or distant metastatic disease. OS was calculated from the date of diagnosis to the date of death or last follow up. One of the objectives of the present study was to assess the probability of local disease control. Statistical analysis was performed using the SPSS version 12 statistical software package.

RESULTS

The median age was 42 year (range, 13- 72 years). Males and females were equal, 29 each. There was also an equal distribution of left and right sided tumors. The most common symptom prompting the patient to seek medical advice was sudden increase in size of a painless swelling which was seen in 46(79.3%) of our patients. The time interval between first noticing the mass to seeking medical advice ranged from 3 months to 20 years (median, 3 years). Seventh nerve involvement at presentation was seen in 5(8.6%) of the patients. Mucoepidermoid carcinoma (MEC) and acinic cell tumors were the most prevalent histologies encountered. At presentation 69% of the patient had an advanced disease, (32.8% stage III and 36.2% stage IV). Stage II was 29.3% and only 1.7% patients were stage I. Histopathologically 39.7% tumors were low grade, 17.2% were intermediate grade, 32.8% were high grade, and it was not reported in 10.3% of patients.

Follow up ranged from 6 to 66 months. During this period, there were 12 local recurrences (20.7%) after a disease free interval ranging from 6 to 45 months. One patient had local recurrence 4 times, while 2 patients had local recurrence twice; all 3 of these patients were salvaged with re-surgery. Four patients (6.9%) had local recurrence associated with distant metastases, 1 patient had distant metastasis, while 9 patients (15.5%) had residual disease. The distant metastases were to lung in 2 patients and 1 each to the liver, bone and chest wall. An association between local recurrence and distant metastases might be suggested since 4 of the locally recurred tumors subsequently developed distant metastases.

The median follow up duration was 33 months. Five year DFS survival was 51% (Fig-1) and 5year OS was 59% (Fig-2). At last follow up, 37(63.8%) patients were alive without disease, 14 (22.4%) patients were alive with disease,

while 4 patients (6.9%) had died due to the disease.

We found that survival was significantly improved in patients who underwent surgery ($p < 0.0001$). Stage IV patients were given palliative radiation. Among the patients who had undergone surgery there was no significant difference in the disease free survival between patients who had undergone total parotidectomy or a lesser procedure ($p=0.67$) when adjuvant radiation was given. However the postoperative residual disease in both these groups was associated with a significantly poorer survival. On univariate analysis, presence of residual ($p=0.0001$) and high grade

disease ($p=0.02$) significantly influenced the DFS. We found that intermediate grade disease had a clinical behaviour similar to that of low grade disease. High grade disease had a significantly poorer survival as compared to the intermediate and low grade tumors. On multivariate analysis, presence of residual disease was the only significant prognostic variable ($p=0.01$) associated poor DFS. Grade of tumors was found to have a marginal influence on the DFS ($p=0.07$).

In patients who received postoperative radiation there was no significant improvement in disease free survival ($p=0.16$), however the local control was achieved for 8-9 months.

Figure 1

Table 1: Patient characteristics

Number of patients	58
Age	
<50 yrs	38(65.5%)
>50 yrs	20(34.5%)
Median age	42 yrs
Range	13 yrs- 72 yrs
Sex	
Males	29(50%)
Females	29(50%)
Symptoms	
Painless swelling	(79.3%)
Swelling, VII nerve inv	(8.6%)
Painful swelling	(15.5%)
Histopathology	
Mucoepidermoid ca	23(39.7%)
Pleomorphic adenoma	6(10.3%)
Acinic cell tumor	7(12.1%)
Adenocarcinoma	5(8.6%)
Adenoidcystic ca	4(6.9%)
Basal cell adenoca	7(12.1%)
Myoepithelial tumor	4(6.9%)
Squamous cell ca	2(3.4%)
Postop residual disease	
Present	20(34.5%)
Absent	38(65.5%)
Stage	
I	1(1.7%)
II	17(29.3%)
III	19(32.8%)
IV	21(36.2%)
Grade of tumor	
Low	23(39.7%)
Intermediate	10(17.2%)
High	19(32.8%)
Unknown	6(10.3%)
Nodal status	
Positive	11(19%)
Negative	47(81%)
Treatment	
Surgery alone	15(25.9%)
Surgery + adjuvant RT	42(72.4%)
Palliative RT	1(1.7%)
Dose of RT	
Median	50Gy
Range	6Gy to 60Gy

Response to treatment

Complete response(CR)	37(63.8%)
Partial response(PR)	1(1.7%)
Progressive disease(PD)	13(22.4%)
Stable disease(SD)	1(1.7%)
Dead	4(6.9%)
Recurrence	

Local recurrence	12(20.7%)
Distant metastasis	1(1.7%)
Local + distant metastases	4(6.9%)

Figure 2

Figure 1

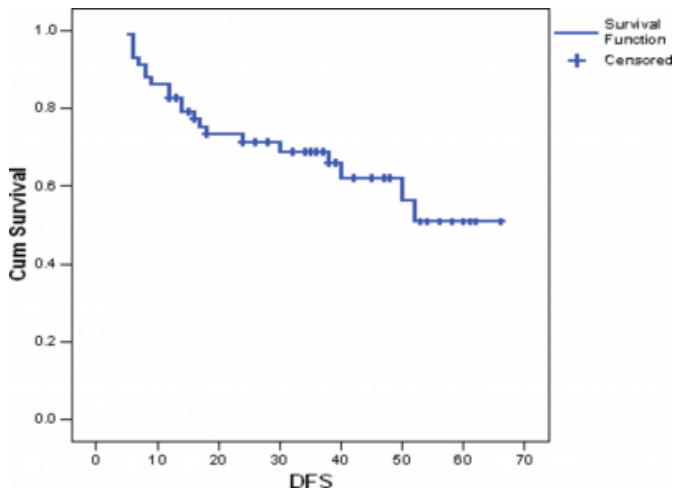


Figure 5

Figure 4

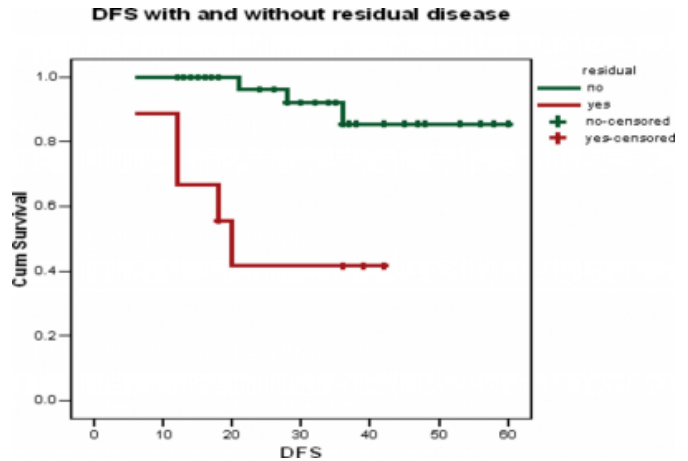
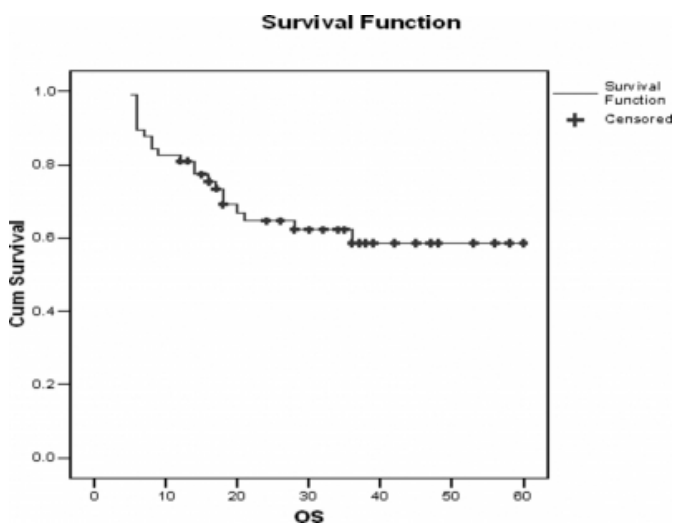


Figure 3

Figure 2

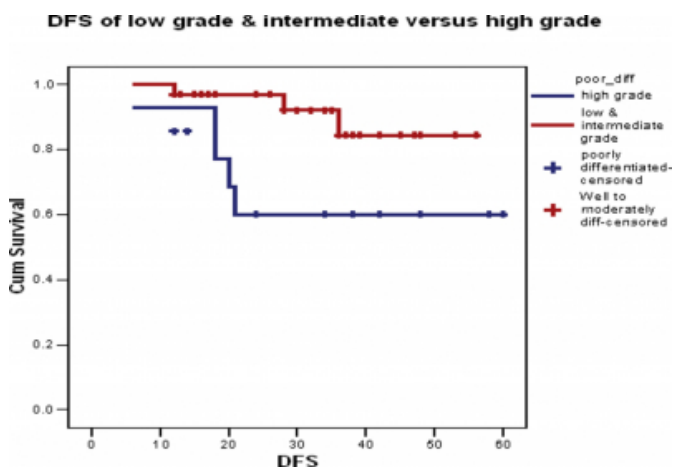


DISCUSSION

Salivary gland tumors are rare malignancies with variable biologic behaviour. In our department, they constitute nearly 0.5% of all malignancies and 3.7% of all head and neck malignancies. In our survey, MEC was the commonest histopathologically proven tumor at 39.7% followed by acinic cell tumor at 12.1% and adenoicycstic carcinoma (ACC) forming 6.9% of the total. This is consistent with the findings of Bhattacharyya and Fried, ⁶ wherein 903 patients studied, the prevalence of MEC was 40.6% and that of ACC was 2% only. Similarly, Bell et al [⁷] reporting on 85 salivary malignant tumors found MEC to be the commonest tumor with 47% of cases followed by ACC in 18%. In our series the male to female ratio was 1:1 however other authors have reported slightly higher incidence in males ⁶.

Figure 4

Figure 3



Histological grade carried a statistical correlation with patient's survival. Our results suggest that intermediate grade tumors have a biological behavior closer to that of the low grade tumors. Our local control rates were 63.8%. Several series in literature have shown local control rates with surgery combined with radiation therapy to be in the range of 51 to 90%.^{9, 10, 11, 12} Our study was spanning over a shorter time period, with limited follow up. At a median follow up of 33 months, the 5 year mean overall survival in our patients was 52%. Bhattacharyya et al, ⁶ in SEER data spanning 10 years, at a median follow up of 51.8 months found the mean survival to be 66.6%. Our results are slightly inferior to the Western literature, as most of the patients present in advanced stage (69%), surgical techniques and partly due to the rarity and lesser experience in the management of these tumors. The 5-year overall disease specific survival rate of our patients was 59% which is very

much comparable to that reported by Guzzo et al.⁴ and Clode et al.¹⁴ however Plambeck et al.¹⁵ have reported a higher disease specific survival rate (92%). The low 5-year survival rate observed in our patients is probably due to the inadequate surgical treatment in the majority of patients due to heterogeneous surgical approaches as postoperative residual disease was seen in 20(34.5%) of our patients. It can be also attributed to the anatomical location, extend of disease and most of the patients presenting in advanced stage (70%). Histological grade and residual disease after surgery were factors carrying a statistical correlation with DFS. Patients with low and intermediate grade tumors had 5 year DFS of 88% (Fig 3) as compared to high grade tumors where it was only 59% ($p=0.021$). Similarly patients with residual disease after surgery had DFS of only 40% as compared to 83% (Fig 4) in patients who had no residual disease when treated with radiotherapy ($p=0.040$).

Patients with residual disease left after surgery 43% had poorly differentiated histology, other factor leading to such a poor local control. All of them received postoperative radiotherapy showed a potential benefit to control locoregional recurrences. Similar studies suggest an improved locoregional disease control in patients who received adjuvant radiotherapy.^{16,17,18} Tran et al.¹⁸ questioned the beneficial effect of postoperative radiotherapy in patients with disease free margins and proposed its use in patients with positive margins or when evidence of recurrence is present.

Our experience with the use of mixed beams with electrons and photons is also at a learning stage, till so far only 4 of our patients have been treated using the combination. Mendenhall et al,^[13] reported on the role of radiation therapy in treatment of salivary gland tumors mentioned that lack of randomized studies does not allow the assessment of efficacy of adjuvant radiotherapy but postoperative radiation therapy has an important role to play in patients with advanced stages, high grade and positive margins. Patients treated with surgery and adjuvant RT had improved local control compared with patients treated with RT alone, though they also stated that in advanced stages of disease, the efficacy of RT as a sole treatment modality has a curability rate of nearly 20%. Thus, it can be concluded that postoperative RT is recommended in bulky tumors with high grade irrespective of the surgical margins. Surgery followed by postoperative RT is the norm for management in our department where majority of patients present at advanced stages.

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