

RESEARCH ARTICLE

Outcome of Surgery and Post-Operative Radiotherapy for Major Salivary Gland Carcinoma: Ten Year Experience from a Single Institute

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Abstract

Aims: To determine the clinical characteristics, pathological features, local and distant failure patterns in patients with carcinoma of major salivary glands treated with surgery and postoperative radiotherapy (PORT). **Materials and Methods:** We retrospectively reviewed 106 cases of major salivary gland tumor seen at our centre (1998-2008). Sixty five cases of major salivary gland carcinoma were selected for analysis (exclusions: benign, palliative, non-carcinomas). The patient population treated by surgery and PORT was divided into two groups: 1) Patients who underwent surgery and immediate PORT (Primary PORT); 2) Patients with recurrent carcinoma who underwent at least two surgeries and received PORT in the immediate post-operative period of the last performed surgery (Recurrent PORT). Recurrence free survival (RFS) was assessed using the Kaplan-Meier method. **Results:** Median age was 35 years with a male: female ratio of 1.3:1. The majority of cancers were located in the parotid gland (86.2%) and the most common histology was mucoepidermoid carcinoma (43%). Thirty nine cases (60%) were primary while 26 (40%) were recurrent. Optimal surgery was performed in 59/65 patients (90.8%). 43 patients (66.2%) underwent neck dissection, of which 14 (32.5%) had nodal metastasis. Overall, 61 (93.8%) patients complied with the prescribed radiotherapy. Median dose of PORT was 60 Gy. Median follow-up was 13.1 months (range 2-70). Relapse free survival was 50.4% at 60 months. Some 12 cases (18.5%) recurred with a median time to recurrence of 16.9 months. **Conclusions:** Surgery and PORT is an effective treatment for major salivary gland carcinoma with over 90% compliance and <20% recurrence. Early treatment with postoperative radiotherapy may increase the survival rate in major salivary gland carcinoma patients.

Keywords: Major salivary gland - carcinoma - radiotherapy - surgery - outcome

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Introduction

Salivary gland cancers are uncommon malignancies of the head and neck region. Their site of origin can be major (parotid, submandibular and sublingual) or minor salivary gland (palate, nasal cavity, paranasal sinuses, trachea and lacrimal gland). Of all the salivary gland neoplasms, 85% are benign and 15% are malignant. Salivary gland malignancies comprise 3-6% of all head and neck cancers (Pinkston and Cole, 1999; Jones et al., 2008). It constitutes 0.77% of male and 0.57% of female cancers in India (Raina et al., 2003). Most cancers arise from parotid gland. As a general rule in clinical practice, the smaller the salivary gland, more are the chances of malignancy. In the parotid glands, 20-25% of the tumors are malignant. This rises to 40% for the submandibular glands, and more than 90% of sublingual gland tumors are malignant (To et al., 2012). These cancers have varying histology and diverse biologic behaviours. The most

common histology for malignant salivary gland tumour is mucoepidermoid carcinoma in parotid and adenoid cystic carcinoma in other salivary glands.

Combined modality treatment with surgery followed by postoperative radiotherapy is the mainstay of management. The kind of surgery performed depends on the location of the tumour and its grade. Indications of postoperative radiotherapy include positive or close (<0.5 cm) margin, high grade tumors, skin or bone infiltration, perineural invasion and lymph node metastases. Chemotherapy is largely used in the palliative setting. Due to the rarity of the disease there are no randomised studies to support the above treatment. Hence the treatment guidelines are based on series that are retrospective in nature. Also the long natural history of some histology requires extensive follow up period.

We present ten year experience at a cancer centre of tertiary care hospital with patients of major salivary gland carcinoma treated with surgery and PORT. The purpose

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of this report is to present the outcome of such patients in terms of relapse free survival with respect to timing of radiotherapy.

Materials and Methods

Patient selection

All patients of major salivary gland tumours registered from September 1998 to October 2008 at Dr BRA Institute Rotary Cancer Hospital, All India Institute of Medical Sciences, New Delhi, India were identified. Data regarding patient and treatment characteristics was retrospectively collected and reviewed from the files retrieved from the medical records section. The patient characteristics of the entire cohort are enlisted in Table 1. Of all the registered patients, those with major salivary gland carcinoma treated with surgery and postoperative radiotherapy (PORT) were selected and analysed for clinic-pathologic features, treatment details and relapse free survival. Exclusion criteria included patients with lymphoma, pleomorphic adenoma, patients treated with palliative intent or preoperative radiotherapy.

The patient population treated by surgery and postoperative radiotherapy was divided into two groups. The first being patients who underwent surgery and immediate post operative radiotherapy (Primary PORT). The second group comprised of patients with recurrent carcinoma who underwent at least two surgeries and received post operative radiotherapy in the immediate post operative period of the last performed surgery (Recurrent PORT). Outcome measure was defined in terms of relapse free survival. Patients were followed up clinically and radiologically at regular intervals.

Statistical analysis

Descriptive statistics was analysed using SPSS 15.0. Relapse free survival (RFS) was obtained using STATA. Survival time was calculated from the date of registration. Kaplan Meier method was used for survival analysis. The RFS rates were plotted against time to produce Kaplan-Meier curves. The status at last follow up was used to calculate survival duration.

Results

Patient and tumour characteristics

A total of 106 patients of major salivary gland tumors were registered from September 1998 to October 2008. The median age of presentation of salivary gland tumors was 43 years (Range 7 to 75). The male to female ratio was 1.5:1. Of these 106 patients, 41 patients were excluded from the analysis (31 palliative, 5 pleomorphic adenoma, 3 lymphoma, 2 had missing data). Sixty five patients of major salivary gland carcinoma treated with surgery followed by postop radiotherapy were selected for analysis of clinic-pathological profile, treatment characteristics and relapse free survival.

Median age at presentation of major salivary gland carcinoma was 35 years. Majority of cancers were located in the parotid gland (86.2%). The most common histology was mucoepidermoid carcinoma (43%),

followed by adenocarcinoma (15.4%) and adenoid cystic carcinoma (10.8%). The rarer histology was squamous cell carcinoma, salivary duct carcinoma, poorly differentiated carcinoma, myoepithelial carcinoma and acinic cell carcinoma. Thirty nine cases (60%) were identified to be in primary PORT group while twenty six (40%) were in recurrent PORT group.

Pathology

High risk features such as peri-neural invasion and lympho-vascular space invasion was seen in 9 patients each (13.8%). Ten patients showed facial nerve involvement (15.4%) Bone and skin involvement was seen in 1(1.5%) and 8(12.4%) patients respectively. Soft tissue infiltration was seen in 20 patients. Pathological margins were negative in 41(63.1%), positive in 11(6.9%) and close (<5mm) in 4(6.2%) patients. The various pathologic features are enlisted in Table 1.

Treatment details

Optimal surgery was performed in 59/65 patients

Table 1. Characteristics of Patients of Major Salivary Gland Carcinoma Treated with Surgery and Postop Radiotherapy

Total patients(n)		65
Median age in years (range)		35 (7-75)
Male		37 (56.9%)
Female		28 (43.1%)
Disease presentation	Primary	39 (60%)
	Recurrent	26 (40%)
Gland of origin	Parotid	56 (86.2%)
	Submandibular	9 (15.4%)
Pathological tumor size	T1	7 (10.8%)
	T2	17 (26.1%)
	T3	14 (21.5%)
	T4	20 (30.8%)
	Tx	7 (10.8%)
Pathological nodal stage (n=43)	N0	29 (67.4%)
	N+	14 (32.6%)
	Margins	
	Negative	41 (63.1%)
	Positive	11 (16.9%)
	Close	4 (6.2%)
	Unknown	9 (13.8%)
Grade (n=20)	G1	7 (10.8%)
	G2	6 (9.2%)
	G3	7 (10.8%)

Table 2. Treatment Received and Treatment Details (n=65)

Variable	Primary PORT No. 39 (60%)	Recurrent PORT No. 26 (40%)
Surgery		
Optimal	33 (84.6%)	26 (100%)
Decompression	6 (15.4%)	0
RT Dose planned in Gy	60 (54-64)	60 (50-64)
RT received in Gy	60 (24-64)	60 (10-64)
Compliance		
Yes	37 (94.9%)	24 (92.3%)
No	2 (5.1%)	2 (7.7%)
Duration of RT in days	45 (18-72)	45 (4-65)
RT technique		
e-p combo	21 (53.8%)	18 (69.2%)
Wedge pair p	12 (30.0%)	6 (23.1%)
Parallel opposed p	2 (5.1%)	1 (3.8%)
Direct p	1 (2.6%)	1 (3.8%)
Unknown	3 (7.7%)	0

(90.8%). Forty three patients (66.2%) underwent neck dissection, of which fourteen (32.5%) had nodal metastasis. Median number of lymph nodes dissected was 2.5.

Overall, sixty one (93.8%) patients complied with the prescribed radiation therapy course. Median dose of PORT was 60 Gy at 2 Gy per fraction, five times a week. Common radiotherapy techniques used were electron-photon combination (62.3%) and photon wedge pair (29.5%). Radiotherapy plan was 2-dimensional in thirty six (59%) patients and 3D Conformal radiotherapy in twenty five (41%). Median interval between surgery and PORT was 45 days (range: 20-210 days). Median duration of PORT was 45 days and overall treatment time was 93 days. Treatment details of the two groups were enumerated in Table 2.

Follow up

The median follow-up was 13.1 months (range 2-70) (Table 3). Twelve patients (18.5%) recurred with a median time to recurrence of 16.9 months. Sites of recurrence were local in two patients, nodal in four patients and distal in five patients. One patient had both local and distal recurrence. The site of metastasis was lung, liver, brain and bone. Salvage therapy was given to five patients (Surgery-1; RT-2; Chemo-radiotherapy-1; Surgery+RT-1). At last follow-up, forty four patients (70.5%) were disease free, ten patients (16.4%) were alive with disease and no data was available for the rest.

Survival

The relapse free survival was 50.41% at 60 months (Figure 1). The median relapse free survival in primary

Table 3. Treatment Results of Carcinoma of Salivary Gland (n=65)

	Overall	Primary PORT	Recurrent PORT
Disease status			
Disease free	44	28	16
Recurrent	12	6	6
Local	3	1	2
Nodal	4	0	3
Distal	6	5	1
Unknown	10	5	5
Follow up (months)	13.1	10.7	13.7
(months)	(2.8-69.6)	(2.8-69.6)	(4.2-64.4)
Time to recurrence x	16.9	24.1	13.4
(months)	(4.9-33)	(4.9-33)	(9.1-17.1)
Survival(number of patients alive)			
1 year	16	8	8
2 year	5	4	1
3 year	2	1	1

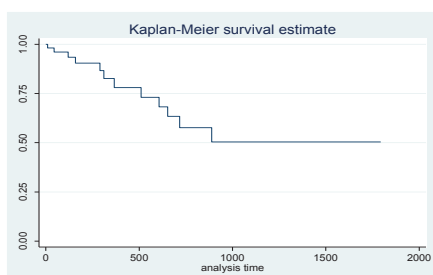


Figure 1. Overall Relapse Free Survival

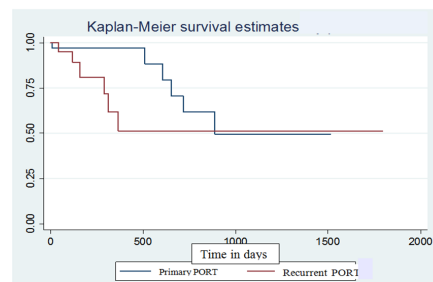


Figure 2. Kaplan-Meier Analysis of Relapse Free Survival in Primary and Recurrent PORT Group

PORT group was 29.6 months, while the recurrent PORT group did not reach median relapse free survival (Figure 2).

Discussion

Salivary gland malignancies constitute a heterogeneous group of diseases. This retrospective study focuses on the clinical characteristics, pathological features, local, and distant failure pattern in patients with carcinoma of major salivary glands treated with surgery and postoperative radiotherapy. It is difficult to conduct a prospective study for this malignancy in view of lower incidence of this disease. However, the median follow up is too less in this patient series to draw any definite conclusion.

This report showed parotid gland (88%) to be the most common location of major salivary gland tumors followed by submandibular gland (10%). A study of 360 cases in Mexican population showed origin of 78% of major salivary gland tumors in parotid gland and 20.7% in submandibular gland (Mejia-Velazquez et al., 2012). A clinic-pathologic study from Iran showed pleomorphic adenoma and adenoid cystic carcinoma to be the most common benign and malignant neoplasms of salivary gland. (Jaafari-Ashkavandi et al., 2013). Mucoepidermoid carcinoma was the most common histology in this study (43%) followed by adenocarcinoma (15.4%) and adenoid cystic carcinoma (10.8%) which is quite similar to the published literature (Bell et al., 2005; Mejia-Velazquez et al., 2012).

Carcinoma of the major salivary gland is usually treated with surgery and adjuvant radiotherapy for high risk features. Moderately high recurrence rates are seen after surgery alone, and postoperative radiotherapy has been used for patients with higher risks for local failure. Although there is no prospective data to support the utilisation of radiotherapy in salivary gland malignancies, most centres across the world practice it. The surgical approach and the extent of resection depend on the location and extent of the tumour. In this series, optimal surgery defined as complete excision of the tumour, was performed in fifty nine patients (90.8%). Forty three patients (66.2%) underwent neck dissection, of which fourteen (32.5%) had pathological evidence of nodal metastasis. Median number of lymph nodes dissected was 2.5.

Various studies have demonstrated the benefit of postoperative radiotherapy in improving local control and overall survival (Garden et al., 1997; Theresa et al., 2005). Treatment with surgery and adjuvant radiotherapy

in locally advanced disease, high grade histology, lymph node or facial nerve involvement and close or positive margins has been shown to provide excellent rates of local control and survival with modest toxicity (Toonkel et al., 1994; Chen et al., 2007; Moriniere et al., 2007). All the patients in the present study underwent conventional radiotherapy. Median radiotherapy dose was 60 Gy (Range 50-64Gy) Postoperative dose of 60 Gy in 30 fractions is recommended to the tumour bed and if there is nerve invasion, the path of the nerve is treated electively to its ganglion. Patients with positive margin and nerve involvement might benefit from dose >60 Gy. Common radiotherapy techniques used were electron-photon combination in 38 patients (62.3%) and photon wedge pair in 18 patients (29.5%). A study comparing the two techniques of radiotherapy delivery showed that high energy electrons mixed with photons is as effective as wedge pair technique with minimal severe late toxicity (Garden et al., 1997).

Radiotherapy has become a significant component of management of malignant salivary gland tumors. A retrospective review of malignant parotid tumors in USA by Pohar et al showed that addition of RT to surgery does not improve overall survival but reduces loco-regional recurrence and improves local failure-free survival. Loco-regional recurrence rate was 37% surgery alone, 11% in surgery plus RT and 15% in RT alone patients (p=0.001) (Pohar et al., 2005). The present analysis shows that radiotherapy is an integral part of management of major salivary gland carcinoma either in primary or recurrent setting. Forty percent of patients treated with surgery plus RT received RT in the recurrent setting.

Patients in the primary PORT group had better relapse free survival than those in the recurrent PORT group. Post-operative radiotherapy (PORT) has been shown to be an independent prognostic factor for major salivary gland cancer (Shang et al., 2005). PORT should be considered for all patients with lymph node metastasis, high grade tumour, positive margins, and T3-4 stage that predict higher rates of LRR after surgery for carcinomas of the major salivary glands (Chen et al., 2007). Histology is an important prognostic factor. For parotid tumours, adenocarcinoma and undifferentiated carcinoma have worse prognosis (10 year survival 55% and 44% respectively) (Wahlberg et al., 2002). Newer treatment modality like Intensity modulated radiotherapy (IMRT) might benefit patients by sparing more normal tissue than conventional methods. One study showed the effectiveness of fast neutrons in local control of parotid carcinomas (Stelzer et al., 1994). Radiotherapy and chemotherapy can also be used in unresectable, recurrent and metastatic disease. Neutron beam therapy may be particularly beneficial in patients with unresectable and recurrent disease however; access to it is still limited for regular treatment. Patients presenting postoperatively with gross residual tumor or recurrence after surgery should be considered for trials of more aggressive treatment with combined chemotherapy or altered fractionation schemes of irradiation.

The relapse free survival was 51% at 60 months. The median relapse free survival in primary PORT group was

29.6 months, while the recurrent PORT group did not reach median relapse free survival. Early diagnosis and early treatment with postoperative radiotherapy may increase the survival rate in major salivary gland carcinoma patients (Moriniere et al., 2007). A study from an Asian country showed 5-year overall survival and relapse-free survival rates to be 78.4% and 63.1%, respectively in patients with salivary gland carcinoma. The authors concluded that optimal loco-regional treatment can reduce distant metastasis, and the optimal use of postoperative radiotherapy may contribute to improved loco-regional control. (Teo et al., 2000). A recent study by Iqbal et al showed that grade was the only independent predictor of disease free survival and nodal involvement was the only independent predictor of overall survival (Iqbal et al., 2014). Patients with adenoid cystic carcinoma of the major salivary glands treated with surgery and radiation have excellent overall control rates with 5 and 10 year local control rates of 94% and 73% (Theresa et al., 2005). A study by Wahlberg et al showed that acinic cell carcinoma had the best prognosis with the 10 year survival rate of 88% (Wahlberg, 2002). The 5-year and 10-year estimates of local-regional control in carcinoma of major salivary glands were 86% and 74%, respectively (Toonkel et al., 1994). Finally, there is a need for the development of effective systemic therapies to prevent distant metastasis.

To conclude, the clinical and histopathological features of carcinoma of the major salivary glands treated with surgery and postoperative therapy were studied. Surgery and PORT is an effective combined modality therapy for major salivary gland carcinoma with over 90% compliance and <20% recurrence. Early treatment with postoperative radiotherapy may increase the survival rate in major salivary gland carcinoma patients. Long term survival could not be evaluated in this study due to poor follow up. Studies with larger patient population and longer follow up are needed to correlate outcome and disease characteristics. Newer therapy including chemotherapy and targeted therapy should be explored particularly for patients with recurrent and metastatic disease.

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