RESEARCH ARTICLE

Ten Year Experience with Surgery and Radiation in the Management of Malignant Major Salivary Gland Tumors

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Abstract

Background: Despite being rare in incidence, malignant tumors of major salivary glands show diverse histological variation. There are limited data on major salivary gland tumor management and outcome from Pakistan. The objective of this study was to share our experience with management of malignant tumors of major salivary glands. Materials and Methods: Patients who received treatment at Shaukat Khanum Cancer Hospital and Research Center from July 2002 to June 2011 with an underlying diagnosis of a major salivary gland malignancy were included. Patient characteristics and treatment modalities were assessed. Local, regional and distant failures were determined. Disease free survival (DFS) and overall survival (OS) were calculated using Kaplan Meier curves and the Log rank test was used to determine statistical significance. Univariate and multivariate analyses were performed using Cox proportional hazard regression. Results: The parotid gland was the primary site of origin in 104 (80%) patients. Mucoepidermoid carcinoma (43%) and adenoid cystic carcinoma (24%) were the most common histological types. Surgery followed by adjuvant radiation remained the mainstay treatment modality with 81 (62%) patients. Nineteen (15%) patients were treated with surgery alone and 30 (23%) patients with locally advanced surgically inoperable tumors received radiation only. Forty one (32%) patients failed the treatment (local 12, regional 11, locoregional 5, distant 13). The expected 5 year DFS and OS were 65% and 74% respectively. On multivariate analysis, grade was the only independent predictor of DFS and nodal involvement was the only independent predictor of overall survival. Conclusions: Employing existing standards of treatment, comparable survival can be achieved in Pakistani population with major salivary gland malignancies as elsehwere in the world.

Keywords: Salivary gland tumor - survival - surgery - radiation

Asian Pac J Cancer Prev, **15 (5)**, 2195-2199

Introduction

Malignant tumors of major salivary glands are rare and represent only 3%-6% of all head and neck (Pinkston and Cole, 1999) cancers (Spiro, 1986). Around 80% of salivary gland tumors arise from parotid gland of which 20-30% are malignant (Matsuba et al., 1985). Submandibular gland carcinoma accounts for 15-20% malignant tumors of major salivary glands (North et al., 1990; Vander Poorten et al., 1999). These tumors affect all age groups but are more common in later life. Mucoepidermoid carcinoma (MECa) is the most common malignant tumor of parotid gland, whereas adenoid cystic carcinoma (ACCa) represents the most frequent histological type of submandibular and minor salivary gland tumor (Spiro and Dubner, 1990). Surgery remains the primary treatment modality in management of malignant tumors of major salivary gland. In the past, these tumors were considered radiation resistant and tumor bulk was thought to be responsible for this under achievement (Spiro et al., 1975; Terhaard et al., 2005). Vikram et al. (1984) demonstrated effective use of radiation therapy in locally advanced tumors. This lead to widespread acceptance of radiotherapy in surgically inoperable tumors and resulted in effective palliation and disease control. The clinical presentation and treatment options used in management of patients with salivary tumors in Pakistan remains under reported. The number of patients with malignancy in these studies is small, follow up minimal and survival not determined (Malik, 2007; Musani et al., 2008; Shah et al., 2013). The objective of this study was to report clinical profile, treatment modalities and survival in patients with malignant tumors of major salivary gland in Pakistan.

Materials and Methods

Head and neck database at Shaukat Khanum Memorial Cancer Hospital and Research Center was accessed to collect data on patients treated radically for malignant tumors of major salivary glands from July 2002 to June 2011. Patients had fine needle aspiration cytology (FNAC) or biopsy (incision/excision) performed at an outside

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medical facility and were diagnosed with malignancy on slide review at our institute. Patients who presented with metastatic disease or were treated with palliative intent were excluded from the study.

All patients were staged according to American Joint committee on Cancer 6th edition for salivary gland tumors. Baseline investigations and imaging including MRI of face/neck and X ray chest were performed in all patients prior to initiation of treatment. Surgery was the mainstay treatment modality in all operable cases. Post-operative radiotherapy was offered if one or more of the following factors were present; high grade disease, T3-T4 tumor, nodal positivity and/or positive margins. In post-operative setting 60 Gy in 30 fractions was the standard radiotherapy protocol. The regimen was increased up to 66 Gy in 33 fractions in patients with high-grade tumors, positive margins and or pathologically node positive disease. Patients rendered inoperable due to advanced tumor or underlying medical condition were treated with radiation alone. In radiation alone group, clinically node negative patients were treated with 50 Gy in 20 fractions while clinically node positive patients were treated with 60 Gy in 30 fractions. Redo surgery was performed in operable cases with residual disease on restaging MRI scan done six weeks after the date of surgery. Other indications for redo surgery included presence of gross disease on clinical exam, positive margins and piece meal excision of the tumor. Facial nerve or its branches were sacrificed if patients demonstrated pre-operative signs and symptoms of facial nerve weakness, if the nerve was grossly infiltrated with tumor intra-operatively or an iatrogenic injury to the nerve in previously operated patient was present which required redo surgery. Patients were followed periodically on three and four monthly basis for first two years, six monthly in third and fourth year and annually thereafter.

Significant events included date of recurrence, date of last follow up, date of completion of treatment and date of diagnosis. Statistical analyses were performed on SPSS version 19. Kaplan Meier curves were used to determine Disease free survival (DFS) and Overall Survival (OS) while Log rank test was used to determine statistical significance for different variables. Patients who received radiation alone were excluded from disease free survival analysis and only overall survival was calculated for this group. Overall survival was calculated by subtracting date of last follow up from date of diagnosis. Disease free survival was calculated by subtracting date of recurrence from date of diagnosis. Univariate and multivariate Cox regression analysis was performed to determine independent predictors of survival.

Results

Patient characteristics

A total of 130 patients with major salivary gland tumors received treatment during the study period. Median age at presentation was 41 (8-75) years while median follow- up was 33 (1-126) months. Mucoepidermoid carcinoma was the most common underlying malignancy in 43% patients followed by adenoid cystic carcinoma in 24% patients. The most common primary site was parotid in 80% patients followed by submandibular gland in 17%. A total of 53 patients had their first surgery elsewhere. Tumor size stage could not be determined in 52 patients. This group represented patients with incomplete histopathological information on submitted reports. Locally advanced tumors (T3-T4) were present in 31% patients and 24% tumors were high grade. Nodal enlargement at presentation was seen in 18% patients at presentation. Table 1 demonstrates patient characteristics.

Treatment modalities

Sixty two percent patients were treated with surgery followed by post-operative radiotherapy (PORT). Patients treated with either surgery or radiation alone comprised 15% and 23% of the study group respectively. Thirty three percent patients underwent subtotal parotidectomy. Fifteen patients underwent neck dissection alongside excision of primary. Re do surgery was performed in 19% patients. Table 2 demonstrates various treatment modalities used.

Local, regional and distant failures

Table 3 represents local, regional and distant failures in patients who underwent either surgery alone or surgery followed by adjuvant radiation. All patients who failed locally had an underlying parotid tumor and surgery with adjuvant radiotherapy was the most commonly employed treatment modality in these patients. Two patients out of nineteen who underwent surgery alone relapsed and both of them were local failures. Similarly all patients who failed regionally had primary parotid malignancy and underwent surgery followed by PORT. Mucoepidermoid carcinoma was the most common underlying malignancy

Table 1. Patient Characteristics (N=130)

		No.	(%)
Age (years) (Median, Range)		41, 8-75	
Follow up (months)		33, 1-126	
Age	<40	64	49
	>40	66	51
Gender	Male	74	57
	Female	56	43
Histology	Mucoepidermoid Carcinoma	56	43
	Adenoid cystic Carcinoma	31	24
	Adenocarcinoma	14	11
	Squamous cell Carcinoma	6	5
	Pleomorphic ex Carcinoma	1	1
	Myoepithelial Carcinoma	3	2
	Carcinosarcoma	4	3
	Undifferentiated Carcinoma	11	8
	Acinic cell Carcinoma	4	3
Salivary gland	Parotid	104	80
	Submandibular	22	17
	Sub lingual	4	3
Grade	Low	39	30
	Intermediate	21	16
	High	31	24
	Un Known	39	30
Clinical T stage	T x	52	40
	T 1	13	10
	T 2	24	19
	T 3	8	6
	T 4	33	25
Clinical N stage	Node negative	106	82
	Node positive	24	18

in patients who failed locally or regionally with 7 (50%) patients. A total of 15 patients developed distant metastasis with lungs in 5, bone in 4, brain in 3 and liver metastasis in 3 patients.

Survival and prognostic factors

Expected 5 year Disease free survival was 65%. Disease free survival was significantly different with respect to tumor grade and nodal involvement. Patients who received radiation as the only treatment were excluded from DFS analysis and overall survival in these patients was 32%. Expected 5 year Overall survival was 74% for the whole group. Overall survival was significantly different with respect to age, gender, grade, tumor size and nodal involvement as shown in Table 4.

Table 5 represents the univariate and multivariate cox analysis of significant variables for disease free and overall survival. Grade was the only independent predictor of disease free survival. Poorly differentiated tumors were more likely to recur when compared with well differentiated tumors (HR: 4.4, CI: 1.5-12.64 p=0.006). For overall survival, nodal involvement was the only independent predictor of outcome and the risk of death was significantly increased in patients with nodal involvement (HR: 3.6, CI: 1.2-10.6, p=0.01).

Table 2. Treatment Modality

Treatment Modality	No	(%)
Treatment modality		
Surgery	19	15
Surgery+Radiation therapy	81	62
Radiation therapy	30	23
Surgical procedure performed		
Sublingual gland excision	3	3
Submandibular gland excision	7	7
Superficial parotidectomy	20	20
Subtotal parotidectomy	33	33
Radical parotidectomy	22	22
Sub lingual excision+ND	1	1
Sub mandibular gland excision+ND	2	2
Superficial parotidectomy+ND	3	3
Subtotal parotidectomy+ND	5	5
Radical parotidectomy+ND	4	4
Re do surgery		
Yes	19	19

Discussion

The current study provides insight to the clinical presentation, management and survival of patients with malignant tumors of major salivary gland in Pakistan. Clinico-pathological variables, treatment options and survival outcome were comparable to published

Table 3. Expected 5 Year Disease Free and Overall Survival with Respect to Clinic Opathological Variables

Prognostic factor		5 year Disease free survival (%)	p value	5 year Overall survival	p value
Age	<40	74	NS	90	0.03
	>40	56		75	
Gender	Male	60	NS	65	<0.0001
	Female	70		90	
Tumor grade	Well	78	0.002	92	<0.0001
	Mod	74		87	
	Poorly	28		50	
Margins	Positive	72	NS	93	NS
	Negative	52		70	
Peri neural invasion	Positive	63	NS	100	NS
	Negative	74		90	
Clinical T stage	T1-T2	70	NS	87	<0.0001
	T3-T4	52		50	
	Tx	60		95	
Clinical N stage	N0	68	0.008	82	<0.0001
	N+	40		52	

Table 4. Local, Regional and Distant Failures in Patients Who Underwent Surgery Alone or Surgery Followed by Adjuvant Radiation

		Age	Sex	Primary	Histology	Stage	Treatment	Redo	Time to failure (months)
Local Failures	1	39	M	Parotid	Adenoid cystic carcinoma	T2N0	S	No	40
	2	39	F	Parotid	Acinic cell carcinoma	TXN0	S	No	7
	3	60	F	Parotid	Adenocarcinoma	T1N0	S --> RT	Yes	40
	4	23	M	Parotid	Mucoepidermoid carcinoma	T1N0	S --> RT	Yes	7
	5	36	F	Parotid	Sarcoma (NOS)*	T4N0	S --> RT	No	19
	6	26	M	Parotid	Mucoepidermoid carcinoma	T1N0	S --> RT	Yes	31
	7	33	F	Parotid	Mucoepidermoid carcinoma	TxN0	S --> RT	No	2
	8	68	M	Parotid	Squamous cell carcinoma	T2N0	S --> RT	No	28
Regional failures	1	35	F	Parotid	Myoepithelial carcinoma	T2N0	S --> RT	-	27
	2	20	F	Parotid	Mucoepidermoid carcinoma	TxN0	S --> RT	-	32
	3	44	M	Parotid	Mucoepidermoid carcinoma	T4N0	S --> RT	-	40
	4	60	M	Parotid	Mucoepidermoid carcinoma	TxN0	S --> RT	-	12
	5*	55	M	Parotid	Adenoid cystic Carcinoma	TxN0	S --> RT	-	40
	6*	64	F	Parotid	Mucoepidermoid carcinoma	T4N2B	S --> RT	-	15
Distant failures	1	45	M	Parotid	Carcinoma NOS	T1N0`	S --> RT	-	52
	2	46	M	Parotid	Adenocarcinoma	TxN0	S --> RT	-	30
	3	20	F	Sublingual	Adenocarcinoma	T2N2b	S --> RT	-	4
	4	55	F	Sub lingual	Adenoid cystic carcinoma	T3N0	S --> RT	-	65
	5	48	M	Submandibular	Adenoid cystic carcinoma	TxN1	S --> RT	-	15
	6	68	M	Submandibular	Adenoid cystic carcinoma	TxN2B	S --> RT	-	4
	7	33	F	Parotid	Adenoid cystic carcinoma	TxN0	S --> RT	-	14
	8	26	M	Parotid	Adenoid cystic carcinoma	TxN0	S --> RT	-	42

Table 5. Univariate and Multivariate Analysis for Independent Predictors of Disease Free and Overall Survival

	Univariate	Multivariate		
	p value	p value	HR	CI
Disease free survival				
Grade	0.01	0.006	4.4	1.5-12.6
Nodal involvement	0.01	0.09	2.2	0.8-5.8
Overall survival				
Age	0.04	0.4	1.5	0.4-4.7
Gender	0.03	0.9	0.9	0.3-3
Grade	0.005	0.1	3.1	0.7-13
Tumor size	NS	-	-	-
Nodal involvement	<0.0001	0.01	3.6	1.2-10.6

reports from other parts of the world. Mucoepidermoid carcinoma was the most common malignancy and surgery with adjuvant radiation was the most common treatment modality. A unique feature of the present study was the number of patients referred after primary surgery elsewhere with incomplete pre-operative staging information and surgical violation of salivary gland drainage fields. Limitations of the study were its retrospective design and missing information for some important clinicopathological variables.

Majority of studies in literature have shown MECa, ACCa and adenocarcinoma as the most common histology affecting major salivary glands (Terhaard et al., 2004; Etit et al., 2012). This histopathological distribution was comparable with the present study. Though FNAC is a readily available, low morbid and cost effective method of diagnosis in major salivary malignancy; the histological diversity of these tumors makes role of FNA controversial (Spiro, 1986; Schlakman and Yousem, 1993; Garden et al., 1997; Brennan et al., 2010). In terms of imaging, MRI remains the radiological tool of choice for assessment of deep lobe parotid tumors, patterns of infiltration and imaging of para-pharyngeal spaces while computed tomography (CT) is most effective when bony erosion is suspected (Armstrong et al., 1992; Burke et al., 2011). Role of ultrasound is limited to patients with superficial swellings of parotid and submandibular gland. All patients in the present study had undergone FNAC, incisional or excisional biopsy of salivary gland elsewhere. MRI of head and neck was performed in all patients for staging and CT scan in rare cases where bony erosion was suspected.

Surgery remains the mainstay treatment option in the management of malignant tumors of major salivary glands with radiotherapy employed in adjuvant setting in presence of poor prognostic factors. Published data on management of salivary tumors in the literature consists of retrospective studies with no randomized trials to our knowledge. Previously, malignant tumors of major salivary glands were considered insensitive to radiotherapy but recent studies have demonstrated benefits of radiotherapy not only in adjuvant setting but also in primary treatment for locally advanced inoperable tumors. Factors like low growth fraction and long doubling times have been linked to favorable results of radiation in salivary gland malignancy. Armstrong et al. (1992) in their 50 year retrospective review on management of malignant tumors of major salivary glands showed that 14% (67/474) patients had clinically node positive disease at presentation and 12% had clinically occult pathologically positive nodal disease. Around 29% regional failures were observed in patients who did not receive adjuvant radiation in pathologically node positive patients. They concluded that elective neck dissection should not be recommended in salivary gland tumors given the low frequency of occult neck disease and adjuvant radiotherapy should be considered in pathologically node positive patients (Armstrong et al., 1992). Similarly importance of PORT was demonstrated in a matched pair analysis with improvement in 5-year determinate survival of stage III-IV tumors receiving PORT (51.2%) in comparison to surgery alone group (9.5%) (Armstrong et al., 1990). In pathological node positive patients, 5-year determinate survival was 48.9% in PORT group and 18.7% in surgery alone group. In the present study, neck dissection was performed only in 15 patients with clinically positive lymph nodes and operable primary tumor. PORT was given to more than 80% patients and expected 5 year DFS was 65%.

Radiotherapy is an established treatment option for advanced inoperable salivary gland tumors. Various studies have reported disease control ranging from 20% to 50% at 5 years (Fitzpatrick and Theriault, 1986; Terhaard et al., 2004; Bhide et al., 2009). A ten year study on management of malignant tumors of parotid gland treated at Royal Marsden, showed 5 year OS survival of 68% (Bhide et al., 2009). Patients treated with radiotherapy alone in the same study had a disease free survival of 29% at two years. Fitzpatrick and Theriault in their experience of over 20 years, showed a cause specific survival of 63% at 5 years, with 59% survival in patients treated with surgery alone and 73% in patients treated with surgery followed by PORT. They concluded that combined modality treatment is superior to surgery alone (Fitzpatrick and Theriault, 1986). In the present study expected 5 year OS was 76% with 62% patients receiving combined modality treatment which is comparable to most recent studies on outcomes of major salivary tumors (Ali et al., 2013). For patients treated with radiation alone OS was 32%.

T stage, lymph node status, age and grade of the tumors remain the most important prognostic variables for salivary gland malignancy (Spiro, 1986; Hocwald et al., 2001; Lima et al., 2005; Koul et al., 2007). Some studies have also demonstrated perineural invasion as an independent predictor of survival (Garden et al., 1997; Hocwald et al., 2001). Paralleling the results of previously reported studies; grade was an independent predictor of DFS while nodal involvement was an independent predictor of overall survival in the current study.

Recently, a study looked at pathological distribution of salivary tumors in northern Iran (Jaafari-Ashkavandi et al., 2013a). Out of 366 patients included, less than 20% had malignant tumors. Adenoid cystic carcinoma was the most common histology and parotid gland was the most common site of involvement. Treatment and survival was not discussed but a novel diagnostic marker was described in a separate paper (Jaafari-Ashkavandi et al., 2013b). Similarly in another study, out of 392 patients who underwent surgery for salivary gland tumors, 125 had

malignant etiology. Parotid was the most common site and adenoid cystic carcinoma was the most common malignant tumor. (Shishegar et al., 2011). Similar results have been reported elsewhere (Luksic et al., 2011). To our knowledge the present study is the first study published from Pakistan demonstrating expected 5 year disease free and overall survival in significant number of patients treated for tumors of major salivary gland malignancy. Majority of patients received multimodality treatment and comparable results thus achieved highlight the effectiveness of surgery and adjuvant radiation for this rare malignancy. Due to small number of patients affected with salivary gland malignancy, randomized trials to determine the most suitable treatment in these patients are difficult. It is important that patients undergo meticulous pre-operative staging that can best help in making treatment decisions.

References

Ali S, Sarhan M, Palmer FL, et al (2013). Cause-specific mortality in patients with mucoepidermoid carcinoma of the major salivary glands. *Ann Surg Oncol*, **20**, 2396-404.

Armstrong JG, Harrison LB, Spiro RH, et al (1990). Malignant tumors of major salivary gland origin. A matched-pair analysis of the role of combine surgery and postoperative radiotherapy. *Arch Otolaryngol Head Neck Surg*, **116**, 290-3.

Armstrong JG, Harrison LB, Thaler HT, et al (1992). The indications for elective treatment of the neck in cancer of the major salivary glands. *Cancer*, **69**, 615-9.

Bhide SA, Miah A, Barbachano Y, et al (2009). Harrington KJ, Newbold K, Nutting CM. Radical radiotherapy for treatment of malignant parotid tumours: a single centre experience 1995-2005. *Br J Oral Maxillofac Surg*, **47**, 284-9.

Brennan PA, Davies B, Poller D, et al (2010). Fine needle aspiration cytology (FNAC) of salivary gland tumours: repeat aspiration provides further information in cases with an unclear initial cytological diagnosis. *Br J Oral Maxillofac Surg*, **48**, 26-9.

Burke CJ, Thomas RH, Howlett D (2011). Imaging the major salivary glands. *Br J Oral Maxillofac Surg*, **49**, 261-9.

Etit D, Ekinci N, Tan A, Altinel D, Dag F (2012). An analysis of salivary gland neoplasms: a 12-year, single-institution experience in Turkey. *Ear Nose Throat J*, **91**, 125-9.

Fitzpatrick PJ, Theriault C (1986). Malignant salivary gland tumors. *Int J Radiat Oncol Biol Phys*, **12**, 1743-7.

Garden AS, el-Naggar AK, Morrison WH, et al (1997). Postoperative radiotherapy for malignant tumors of the parotid gland. *Int J Radiat Oncol Biol Phys*, **37**, 79-85.

Hocwald E, Korkmaz H, Yoo GH, et al (2001). Prognostic factors in major salivary gland cancer. *Laryngoscope*, **111**, 1434-9.

Jaafari-Ashkavandi Z, Ashraf MJ, Moshaverinia M (2013). Salivary gland tumors: a clinicopathologic study of 366 cases in southern Iran. *Asian Pac J Cancer Prev*, **14**, 27-30.

Jaafari-Ashkavandi Z, Najvani AD, Tadbir AA, et al (2013). MCM3 as a novel diagnostic marker in benign and malignant salivary gland tumors. *Asian Pac J Cancer Prev*, **14**, 3479-82.

Koul R, Dubey A, Butler J, et al (2007). Prognostic factors depicting disease-specific survival in parotid-gland tumors. *Int J Radiat Oncol Biol Phys*, **68**, 714-8.

Lima RA, Tavares MR, Dias FL, et al (2005). Clinical prognostic factors in malignant parotid gland tumors. *Otolaryngol Head Neck Surg*, **133**, 702-8.

Lukšić I, Virag M, Manojlović S, Macan D (2012). Salivary gland tumours: 25 years of experience from a single institution in Croatia. *J Craniomaxillofac Surg*, **40**, 75-81.

Matsuba HM, Thawley SE, Devineni VR, Levine LA, Smith PG (1985). High-grade malignancies of the parotid gland: effective use of planned combined surgery and irradiation. *Laryngoscope*, **95**, 1059-63.

Malik KA (2007). Parotid gland tumors: A six years experience. *Pak J Surg*, **23**, 133-135.

Musani MA, Sohail Z, Zafar S, Malik S (2008). Morphological pattern of parotid gland tumours. *J Coll Physicians Surg Pak*, **18**, 274-7.

North CA, Lee D, Piantadosi S, et al (1990). Carcinoma of the major salivary glands treated by surgery or surgery plus postoperative radiotherapy. *Int J Radiat Oncol Biol Phys*, **18**, 1319-26.

Pinkston JA, Cole P (1999). Incidence rates of salivary gland tumors: results from a population-based study. *Otolaryngol Head Neck Surg*, **120**, 834-40.

Spiro RH, Huvos AG, Strong EW (1975). Cancer of the parotid gland, A clinico-pathology study of 288 primary cases. *Am J Surg*, **130**, 452-9.

Spiro RH (1986). Salivary neoplasms: overview of a 35-year experience with 2807 patients. *Head Neck Surg*, **8**, 177-84.

Spiro RH, Dubner S (1990). Salivary gland tumors. *Curr Opin Oncol*, **2**, 589-95.

Schlakman BN, Yousem DM (1993). MR of intraparotid masses. *AJNR Am J Neuroradiol*, **14**, 1173-80.

Shah SA, Riaz U, Zubair M, Saaiq M (2013). Surgical presentation and outcome of parotid gland tumours. *J Coll Physicians Surg Pak*, **23**, 625-8.

Shishegar M, Ashraf MJ, Azarpira N, et al (2011). Salivary gland tumors in maxillofacial region: a retrospective study of 130 cases in a southern Iranian population. *Patholog Res Int*, **2011**, 934350.

Terhaard CH, Lubsen H, Rasch CR, et al (2004). Dutch Head and Neck Oncology Cooperative Group (2004). Salivary gland carcinoma: independent prognostic factors for locoregional control, distant metastases, and overall survival: results of the Dutch head and neck oncology cooperative group. *Head Neck*, **26**, 681-92.

Terhaard CH, Lubsen H, Rasch CR, et al (2005). Dutch Head and Neck Oncology Cooperative Group (2005). The role of radiotherapy in the treatment of malignant salivary gland tumors. *Int J Radiat Oncol Biol Phys*, **61**, 103-11.

Vander Poorten VLM, Balm AJM, Hilgers FJM, et al (1999). Prognostic factors for long term results of the treatment of patients with malignant submandibular gland tumors. *Cancer*, **85**, 2255-64.

Vikram B, Strong EW, Shah JP, Spiro RH (1984). Radiation therapy in adenoid-cystic carcinoma. *Int J Radiat Oncol Biol Phys*, **10**, 221-3.