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Prognostic factors depicting overall survival in lesser major (submandibular, sublingual) and minor salivary gland tumors

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ABSTRACT

The purpose of this analysis is to determine the predictors of 5 year overall survival in patients with lesser major (submandibular, sublingual) and minor salivary glands cancer. A historical cohort of 97 patients with submandibular, sublingual and minor salivary glands cancer excluding sinus tumors with a median follow-up of 56.5 months was analyzed. Kaplan-Meier curves and log-rank test were used for subgroup survival analysis. Multivariate models employing Cox's proportional hazard models were used to determine the predictors of 5 year overall survival. The mean age of the cohort was 56 years. The site of involvement was submandibular in 46.39%, sublingual in 8.2% and minor salivary glands in 45.36%. The 5 year overall survival, disease-specific survival and disease-free survival were 65%, 81% and 56%, respectively. 5 year survival was 71% in patients treated with surgery alone, 67% treated with radiation only, 65% with combination of surgery and radiotherapy, and 0% for palliation ($p<0.0001$). Multivariable Cox's proportional hazard model identified site, age and treatment modality affecting 5 year overall survival. Patients with submandibular gland cancer had a greater risk of dying within the 5 year period as compared to patients with minor salivary glands cancer (HR=3.3; 95% CI=1.4-7.9; $p<0.01$). Surgery followed by adjuvant radiation had 75% protective effect on the hazard of death as compared to other treatment modalities (HR=0.25; 95% CI=0.1-0.7; $p<0.001$). Site, age and treatment modalities are important predictors of survival in small salivary gland cancer. [Turk J Cancer 2008;38(4):159-166]

KEY WORDS:

Submandibular tumors, sublingual tumors, minor salivary gland tumor, radiotherapy

INTRODUCTION

Salivary gland tumors are a histological and clinically diverse group of neoplasms, which often present significant diagnostic and management challenges. These tumors are uncommon, with an overall incidence of approximately 0.3-0.5 cases per 100,000 population per year in Canada and account for only 3% to 5% of all head and neck cancers (1). The three major salivary glands are the parotid gland, submandibular gland and sublingual gland. The parotid gland, the largest salivary glands, is found on each side of the face. Submandibular glands are smaller and are found on either side of the neck, under the tongue area. The sublingual glands are the smallest and found under the floor of the mouth and below either side of the tongue. In addition, there are about 600 to 1,000

minor salivary glands that are too small to see without a microscope. These minor salivary glands are located beneath the lining of the lips, tongue, hard and soft palate, cheeks, sinus, nose, and larynx.

Most tumors of the parotid are benign. Tumors in the minor salivary glands are usually malignant and quite rare however in submandibular gland 50% of tumors are malignant. Salivary gland cancer is characterized by a complex and diverse group of tumors with variable outcome. Assessment of various prognostic factors is very difficult due to heterogeneous biological and histological behavior of the tumor. The purpose of our study was to determine independent predictors of the 5 year overall survival in lesser major (submandibular, sublingual) and minor salivary gland cancers and their impact on clinical decision making.

MATERIALS AND METHODS

A historical cohort of 97 patients with submandibular, sublingual and minor salivary gland malignancy excluding sinus tumors registered in the Cancer Registry of the Province of Manitoba, Canada from 1970 to 2003 was reviewed. To ensure uniformity, information was collected from the medical records on a standard form covering demographics, patient and treatment related factors. Vital information was obtained from the department of epidemiology and cancer registry, CancerCare Manitoba. Clinical data was available on all patients. Of 97, 40 underwent computed tomography (CT) scan of head and neck and 10 had magnetic resonance imaging (MRI) as a part of initial work up. The AJCC staging system was used to classify tumor according to size and extension based on available clinical (n=70) or pathological information (n=27). Kaplan-Meier curves were plotted for survival analysis and log rank test was used for comparing subgroups. Patients were censored if they lived more than 60 months or died without disease within 5 years of diagnosis. Multivariate models employing Cox's proportional hazard model were used to determine the independent effect of each variable on 5 year overall survival.

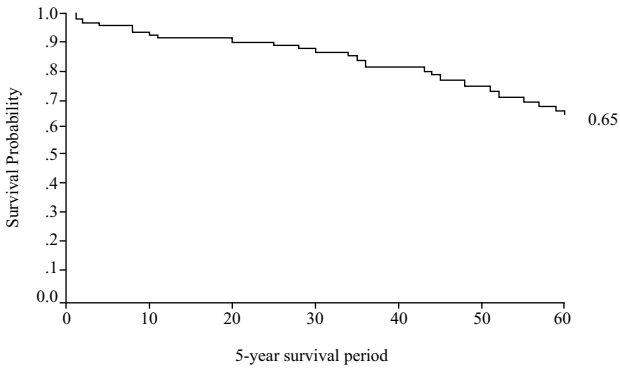

Fig 1. Overall Survival at 5 years

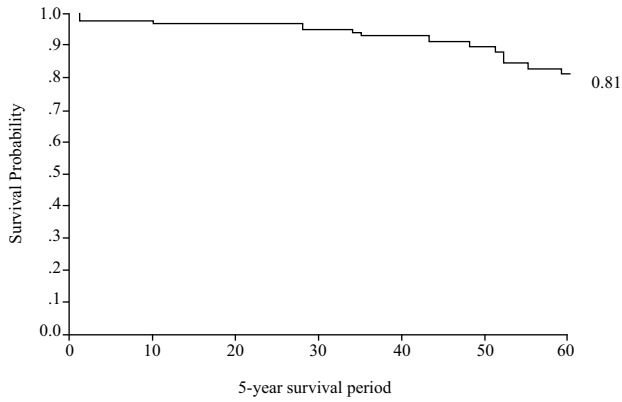

Fig 2. Disease Specific Survival at 5 years

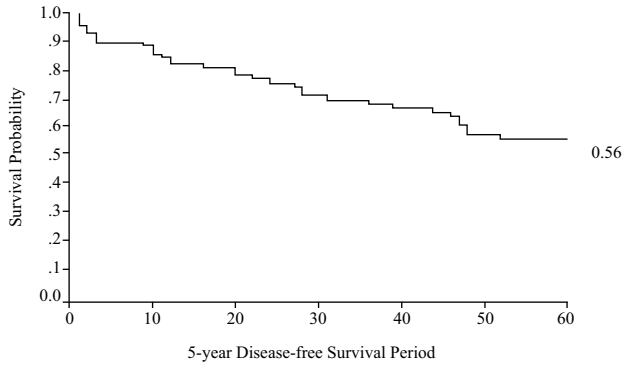

Fig 3. Disease Free Survival at 5 years

RESULTS

Base line patient characteristics are outlined in table 1. Median age at presentation was 56 years (range: 20-94) in males and 60 years (range: 7-90) in females. Fifty-five percent of patients were males in our cohort. The most common symptom was painless mass in 78 (75.66%) patients and 19 (18.43%) patients had a rapidly enlarging

Table 1
Baseline demographic and clinical characteristics

Variable	n	%
Sex		
Male	53	55
Female	44	45
Age in years		
>65 years	33	33.3
<65 years	64	66.7
Symptoms		
Painless mass	78	80.41
Painful mass	19	19.58
TNM		
T1	52	53.60
T2	31	31.9
T3	11	11.3
T4	3	3.09
N+	8	8.7
AJCC Stage		
Stage I	47	48.45
Stage II	26	26.80
Stage III	12	12.3
Stage IV	12	12.3
Prognostic score		
0	54	55.7
1	30	30.9
2	11	11.3
3	2	2.1
Differentiation		
Well differentiation	40	41.23
Moderate differentiation	24	24.74
Poor differentiation	33	34.02
Margins		
Margins close	11	11.3
Margins involved	24	24.74
Margin negative	62	63.12
Treatment		
Surgery	36	37.1
Surgery and Radiotherapy	56	57.7
Supportive care	2	2.06

painful mass. The mean size of the mass was 3.5 (±2.4) cm. Sixty percent of patients had symptoms for less than 6 months duration. The gland site was submandibular in 45 (46.39%) patients, sublingual in 8 (8.2%) and minor salivary gland in 44 patients (45.36%). The majority of tumors in minor salivary gland were seen in hard palate, soft palate, buccal mucosa and larynx. Histology for all sites included mucoepidermoid carcinoma (20.6%), acinic cell carcinoma (6.2%), adenoid cystic (35%), adenocarcinoma (16.5%), carcinoma expleomorphic adenoma (8.2%), squamous carcinoma (4.1%), myoepithelial carcinoma (5.2%) and other histology (4.1%) (Table 2).

Staging investigations included blood work, chest X-ray in all patients, CT scan of the head and neck in 40 patients, MRI of head and neck in 10 patients and CT scans of the chest and/or abdomen in twenty patients of the cohort. Fifty-two (53.60%), 31 (31.9%), 11 (11.3%) and 3 (3.09%) patients had T1, T2, T3 and T4 disease, respectively. Only 1.1% of the patients had distant metastasis at presentation. Forty-seven (48.45%), 26 (26.80%), 12 (12.3%) and 12 (12.3%) patients had Stage I, II, III and IV disease, respectively. In stage IV most of the patients had locoregionally advanced disease. Eight (8.7%) patients had clinically neck node metastases at presentation.

Ninety-two patients 94.84%) were treated with curative intention whereas 5 (5.15%) patients were treated with palliative intent. Thirty-six (37.1%) patients received surgery as the sole modality of treatment, 56 (57.7%) patients underwent surgery and postoperative adjuvant radiation. Adjuvant radiation was used for the following

Table 2
Distribution of histological types

WHO Type	n	%
Mucoepidermoid carcinoma	20	20.6
Acinic cell carcinoma	6	6.2
Adenoid cystic carcinoma	34	35
Adenocarcinoma	16	16.5
Carcinoma expleomorphic adenoma	8	8.2
Myoepithelial carcinoma	5	5.2
Squamous	4	4
Other	4	4

reasons: locally advanced tumor, nerve involvement, extra capsular spread of nodes and positive margins. Three (3.1%) patients received radiation with a palliative intent in view of comorbidities, unresectable disease or low performance status. Two patients (2%) chose supportive care only. The most frequent surgery at first presentation was local excision in 90% patients and 27 (27.8%) patients underwent neck dissection. Sixty-two (63.91%) patients had clear resection margins, 11 (11.3%) patients had close and 24 (24.74%) patients had involved margins. Fifty patients (50%) received ≤50 Gray of radiation and 50 (50%) received >50 Gray.

The median follow-up was 56.5 months. Thirty-five (36.08%) patients had recurrence. Twelve (34.24%) patients had recurrent disease locally in submandibular gland, 14 (40%) had distant metastasis mainly in lung followed by liver and bone, 1 patient (2.8%) had neck nodes and 8 patients (22.8%) in hard palate, respectively. The majority of recurrences were seen in patients with adenoid cystic histology (51.42%), followed in decreasing order by other histologies adenocarcinoma (11.4%), mucoepidermoid (8.5%), acinic cell carcinoma (2.8%), carcinoma ex pleomorphic adenoma (5.7%), squamous carcinoma (5.7%) and other histology (14.2%). The majority of recurrences with adenoid cystic histology may be due to the fact that this was the most common histology on presentation. Recurrence varied by T stage with 15% in T1, 25% in T2, 28% in T3, 32% in T4, respectively.

Overall survival (OS) at 5 years was 65%; fifty-eight percent in females versus 69% in males. Disease free survival was only 56% and disease specific survival (DSS) at 5 years was 81%. Patients with poorly differentiated tumor, moderately differentiated tumor and well differentiated tumor on pathology report had 5 year OS of 41%, 63% and 78%, respectively (p <0.0517). In patients with T1 disease OS at 5 years was 69% whereas in patients with T2, T3 and T4 it was 61%, 50%, 67%, respectively (p=0.7178). 5 year OS was 65% for Stage I disease, 67% for Stage II disease, 56% for Stage III disease and 42% for Stage IV disease (p=0.3410). Patients with negative neck nodes had a higher 5 year OS of 66% as compared to only 33% in patients with positive nodes (p=0.6906). Table 3 enumerates the 5 year overall survival probabilities for each category of the risk factors examined in the univariate analysis. The variables that were either statistically significant (p<0.05) or marginally significant for OS (p<0.10) were tested in the multivariable Cox's proportional hazard model. Patients 65 years or older had over three folds the hazard of death within five years as compared to younger patients, p <0.0024 (HR=3.4; 95% CI 1.5-1.7.4), submandibular vs. minor salivary gland tumor, p <0.0073 (HR=3.3; 95% CI=1.4-7.9), surgery and postoperative adjuvant radiation versus other treatment

Table 3
5 year overall survival probabilities by major demographic and clinical variables

Variable	5 year OS probability	P value
Sex		
Male	69	0.3609
Female	58	
Age		
<65 years	77	0.0034
>65 years	43	
Gland involvement		
Submandibular gland	53	0.0687
Other salivary glands	75	
AJCC Stage		
I	69	
II	67	0.3410
III	56	
IV	42	
Neck dissection		
+	62	0.8438
-	66	
Treatment		
Surgery	71	
Surgery and Radiation	65	0.0000
Radiation	67	
Supportive care	0	
Margin		
Margin clear	65	
Margin close	89	0.2627
Margin involved	56	

modalities including surgery alone and patients who were treated with palliative intent (n=5), p<0.0002 (HR=0.25; 95% CI=0.1-0.7). In this model we controlled the effect of age, site and prognostic score on 5 year overall survival. Patients with submandibular gland cancer had three folds the hazard of death within 5 year period as compared to patients with other salivary gland cancer (HR=3.3; 95% CI=1.4-7.9). None of the staging system significantly predicted 5 year survival in the multivariate models in this study group (Table 4). We formulated an additive pathological prognostic score based on presence or absence of various pathological factors such as differentiation, lymphatic or vascular invasion and perineural invasion. Each parameter if present got score of 1. The computed prognostic score showed a negative survival trend with increasing score from 0-3: however the trend was not statistically significant in univariate analysis. It was explored in the multivariate Cox's hazard model and we found that higher score doubled the hazard of death for each point above zero p<0.01 (HR=2.1; 95% CI=1.2-3.8).

DISCUSSION

In literature very few authors have evaluated submandibular gland, sublingual and minor salivary glands tumors together as one entity. However in 1979, Batsakis (2) called this group as minor and lesser major salivary glands tumor. In our study we have followed the same nomenclature. The submandibular and sublingual glands are collectively called lesser major glands and rest of tumors are enumerated under minor salivary gland tumors. Our study confirms that clinically the main presenting symptom is painless mass and is quite consistent with the literature (3). Adenoid cystic was the most frequent histology in our patient population and is also a consistent finding in the literature (4). Early stage salivary gland tumors are usually curable by adequate surgical resection alone. The prognosis is more favorable when the tumor is in a major salivary gland; the parotid gland is most favorable, then the submandibular gland; the least favorable primary sites are the sublingual and minor salivary glands (5). Large bulky tumors or high-grade tumors in parotid cancers carry a poorer prognosis and may best be treated by surgical resection combined with postoperative radiation therapy while as in minor salivary gland neoplasms it depends mainly on site and histological grade (6). For high-grade or larger (≥4 cm) tumors, a more extensive resection may be necessary along with neck dissection (7). Surgical resection usually includes an adequate cuff of normal tissue around the tumor. Involvement of bone (mandible or maxilla) requires an appropriate palatectomy or mandibulectomy (8).

In Spiro's (9) review of previously untreated minor salivary gland neoplasm's, the 5 year survival for malignant neoplasms was 73%, 10 year survival was 56%, 15 year survival was 46% and the 20 year survival was 35% for patients treated with surgery. This data was compared to a similar cohort of patients with major salivary gland neoplasms and no difference in survival was found. Patients with sinus primaries had a significantly lower overall survival rate compared to patients with oral lesions at 10 years. Spiro also divided minor salivary gland malignancies into two groups: low-grade neoplasms including low-grade mucoepidermoid carcinoma, low grade adenocarcinoma, and acinic cell carcinoma; and high-grade malignancies including malignant mixed tumor, high grade mucoepidermoid tumors, high grade adenocarcinoma and adenoid cystic carcinoma. Patients with low-grade histologies had a significantly better survival rate over twenty

Table 4
Cox's proportional hazard model predicting 5 year overall survival

Variable	HR	95% CI	P value
Age	3.3	1.004-1.055	0.0240
Submandibular vs. other salivary glands	3.4	1.5-7.4	0.0024
Prognostic score (0-3) per point	2.1	1.2-3.8	0.0050
Surgery and radiation vs. surgery alone	0.25	0.1-0.7	0.0002

years. Low grade lesions had a 93% survival at 10 years compared to high grade tumors with a 42-58% survival at 10 years (10).

In our data the 5 year overall survival probability was better in well differentiated tumors as compared to poorly differentiated tumors but it did not reach the statistical significance. However the differentiation in our data is purely as per pathology report which is different from what Dr. Spiro has used.

Minor salivary gland cancers tend to have a worse outcome than those involving the major salivary glands, particularly adenoid cystic cancers. In a 20-year review of 21 patients treated for minor salivary gland malignancy in a single institution, it was found that mucoepidermoid tumors were more common in the oral cavity and adenoid cystic carcinomas in the sinonasal tract (p=0.002). Outcome was variable with sinonasal and adenoid cystic carcinoma having a poorer outcome. Kaplan-Meier curves showed that oral tumors had a higher probability of long term survival. Radical surgery with reconstruction and post-operative adjuvant radiotherapy was effective in achieving loco-regional control. There were no local recurrences within 5 years and three after 5 years. Five patients developed metastatic disease within 10 years and a further two after 10 years. Late recurrences occurred and survival was mainly determined by the presence of systemic disease (11). A benefit for adjuvant radiation in high-risk cases was suggested in another series of 128 patients with malignant intraoral minor salivary gland tumors who were treated with either surgery alone (n=59) or surgery followed by postoperative radiation (n=32); the remainder were either unresectable or refused surgical treatment. Radiation was administered to patients with close or positive surgical margins or metastatic cervical lymphadenopathy. Although local recurrence rates were the same or slightly higher in the radiated patients, the fact that this group was selected for radiation based upon poor prognostic features led the authors to postulate a beneficial effect of radiation. The five year survival rates were similar in the two groups (86 versus 88 percent, respectively) (12). The effect of radiation therapy on minor salivary gland neoplasms was retrospectively studied in a group of 160 patients at MD Anderson Cancer Center in 1994 by Garden et al. (13). The group recommends the use of radiation in patients with perineural invasion, positive margins, high-grade histology, recurrence, and in patients with neck disease. Microinvasion of small unnamed nerves is not an indication for radiotherapy. They recommend a dose of 60 gray in 2 gray per fraction over 6 weeks. Treatment should commence as soon as possible after surgery. In the mid 1980's when high-grade lesions were treated only by surgery recurrence rates were reported to be as high as 50%. In this series only 12% had a local recurrence, while 36% of patients relapsed with distant metastasis. External beam radiation has been shown to increase local control in unresectable and inoperable lesions.

Our study is the first in literature to demonstrate that patients with primary neoplasm in submandibular gland do worse compared to patients with minor salivary gland tumors. In literature so far the most frequent encounter has been the opposite. Our data also concurs with the fact that radiation combined with surgery has a protective effect on hazard of death as compared to other modalities. This has been discussed in length in study by Dutch Head and Neck Oncology Cooperative Group (14). Although minor salivary gland neoplasms are infamous for late recurrence, 70% of recurrences appear within 2 years. Paranasal sinus lesions are particularly prone to recurrence, as are adenoid cystic carcinomas, adenocarcinoma, and pleomorphic adenomas excised without an adequate margin. There are reports of local recurrence developing over 20 years after initial treatment.

With regards to metastasis, in Spiro's (15) series of 378 patients who had carcinomas of the minor salivary glands, at least 19% developed distant spread with the likelihood significantly increased if the neck was clinically positive at presentation. The incidence of distant metastasis for adenoid cystic carcinoma is reported to be between 25%-50%; the most frequent sites being the lung and bone. With adenoid cystic carcinoma, surgical excision of isolated pulmonary metastasis is indicated due to its indolent nature.

Prospective trials of adjuvant chemotherapy for resected minor salivary gland tumors have not been conducted, and the few small retrospective series do not con-

sistently support benefit. Thus, the routine use of adjuvant chemotherapy cannot be justified unless in the setting of a clinical trial. The role of systemic chemotherapy in the management of salivary gland cancers is limited to disease that is metastatic or locally advanced and unresectable.

Clinicopathological data have demonstrated correlations between poor clinical outcomes and the expression of molecular markers such as mutated p53 protein and vascular endothelial growth factor (VEGF) in salivary gland cancers. Recent studies have also evaluated the epidermal growth factor receptor family including erbB1/EGFR and erbB2/HER2 as potential therapeutic targets. While the prognostic significance of EGFR overexpression has not been well defined, overexpression of the HER2 oncoprotein has been associated with biological aggressiveness and poor prognosis in most series. Given the suboptimal response rates, duration of response, and toxicity of conventional chemotherapy, a better understanding of the biology of salivary gland malignancies will lead to improved prognostication and treatment. With the emergence of molecular targeted therapy, these tumors become an optimal candidate for trials of investigational drugs and established drugs for new indications (16). Suen and John (17) performed a multicenter review of patients who had received systemic 5-Flurouracil, cisplatin and or adriamycin based chemotherapy for advanced salivary gland tumor. The overall response in the series was only 42%.

Fast neutron beam radiation therapy or accelerated hyper fractionated photon beam therapy are shown effective in unresectable tumors. The Radiation Therapy Oncology Group in United Sates and Medical Research Council of Great Britain compared the efficacy of neutron therapy vs. conventional radiation in a randomized, clinical trial. Disease free and overall survival seems to be favorable with fast neutron therapy (18). Clinical trials are appropriate, and should be considered whenever possible.

Radiotherapy (RT) combined with local hyperthermia or concomitant chemoradiotherapy may play a role in the treatment of some locally advanced or recurrent salivary gland tumors, but experience is limited and thus are experimental approaches. Combining photons with carbon ion therapy is promising, but clinical experience is limited (19). Other technical improvements in RT delivery such as three-dimensional conformal RT or intensity modulated RT hold promise for increasing rates of tumor control while minimizing toxicity (20). There is sparse data regarding brachytherapy in salivary gland tumors of the hard and/or soft palate that had been excised. In this study all patients had close or involved margins. Six were treated with a dental applicator alone, two with an applicator and additional I-125 seeds in tubes and one with an implant alone. The applicator consists of two layers of plastic made from a dental impression enclosing a predetermined number of I-125 seeds, 9-39, glued to one surface and a layer of ash metal to protect the tongue. It was inserted 1-3 months post-operatively and delivered 35-62 Gy, median 56 Gy, at 5-7 mm depth over 58-156 h, median 120 h, at 0.26–0.67 Gy/h, median 0.45 Gy/h. With median follow-up of 50 months there were no recurrences. So, brachytherapy is an effective way of delivering postoperative radiotherapy to the hard and soft palate salivary gland tumors that have been incompletely excised or have unfavorable histology. Local control is excellent, treatment time is short and morbidity is minimal (21).

CONCLUSIONS

Despite the diverse variety of malignant salivary tumors, it is possible to identify patients with significant adverse prognostic characteristics, which can be detected clinically. In conclusion, this historical cohort study has elucidated factors such as advanced age, tumor site; treatment modality can predict 5 year survival in minor, sublingual and submandibular salivary gland tumors. With respect to optimum treatment for these cancers, multicentric prospective randomized studies are needed.

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References

1. National Cancer Institute of Canada, Statistics Canada: Canadian Cancer Statistics 2004, Toronto, Canada, 2004.
2. Batsakis JG. Neoplasm's of the minor and "lesser" major salivary glands. Tumors of the head and neck. 2nd ed. Baltimore: Williams and Wilkins, 1979;76-99.
3. Anderson JN Jr, Beenken SW, Crowe R, et al. Prognostic factors in minor salivary gland tumors. Head Neck 1995;17:480-6.
4. Loyola AM, de Araújo VC, de Sousa SO, et al. Minor salivary gland tumors: a retrospective study of 164 cases in a Brazilian population. Eur J Cancer B Oral Oncol 1995;31B:197-201.
5. Spiro RH. Salivary neoplasm's: Overview of a 35 year experience with 2,807 patients. Head Neck Surg 1986;8:177-84.
6. Koul R, Dubey A, Butler J, et al. Prognostic factors depicting disease specific survival in parotid gland tumors. Int J Radiation Oncology Biol Phys 2007;68,3:714-8.
7. Granick MS, Solomon MP, Hanna DC. Management of Benign and Malignant Salivary Gland Tumors. In: Georgiade GS, Riefkohl R, Levin LS, editors. Georgaide Plastic, Maxillofacial, and Reconstructive Surgery. 3rd ed. Baltimore, MD: Williams & Wilkins, 1997;155-65.
8. Hoffman H, Funk G, Endres D. Evaluation and surgical treatment of tumors of the salivary glands. In: Thawley SE, Panje WR, Batsakis JG, Lindberg RD, editors. Comprehensive management of head and neck tumors. 2nd ed. Philadelphia: WB Saunders, 1998;1147.
9. Spiro RH, Koss LG, Hajdu SI, Strong EW. Tumors of minor salivary origin: a clinic pathologic study of 492 cases. Cancer 1973;31:117-29.
10. Spiro RH, Thaler HT, Hicks WF, et al. The importance of clinical staging of minor salivary gland carcinoma. Am J Surg 1991;162:330-6
12. Strick MJ, Kelly C, Soames JV, et al. Malignant tumours of the minor salivary glands--a 20 year review. Br J Plast Surg 2004;57:624-31.
13. Garden AS, Weber RS, Ang KK, et al. Postoperative radiation therapy for malignant tumors of the minor salivary glands. Cancer 1994;73:2563-9.
14. Terhaard CHJ, Lubson H, Rasch CR, et al. The role of radiotherapy in the treatment of malignant salivary gland tumors. Int J Radiat Oncol Biol Phys 2005;61:103-11.
15. Spiro RH, Thaler HT, Hicks WF, et al. The importance of clinical staging in minor salivary gland carcinoma. Am J Surg 1991;162:330-6.
16. Rizk S, Robert A, Vandenhooft A, et al. Activity of chemotherapy in the palliative treatment of salivary gland tumors: review of the literature. Eur Arch Otorhinolaryngol 2007:264:587-94.
17. Suen JY, Johns ME. Chemotherapy for salivary gland cancer. Laryngoscope 1982;92:235-9.
18. Laramore GE, Krall JM, Griffin TW, et al. Neutron versus photon irradiation for unresectable salivary gland tumors: final report of an RTOG-MRC randomized clinical trial. Int J Radiat Oncol Biol Phys 1993;27:235-40.
19. Schulz-Ertner D, Nikoghosyan A, Didinger B, et al. Therapy strategies for locally advanced adenoid cystic carcinomas using modern radiation therapy techniques. Cancer 2005;104:338-44.
20. Nutting CM, Rowbottom CG, Cosgrove VP, et al. Optimisation of radiotherapy for carcinoma of the parotid gland: a comparison of conventional, three-dimensional conformal, and intensity-modulated techniques Radiother Oncol 2001;60:163-72.
21. Stannard C, Hering E, Hough J, et al. Post-operative treatment of malignant salivary gland tumours of the palate with iodine-125 brachytherapy. Radiother Oncol 2003;3:307-11.