Journal of Oral and Maxillofacial Surgery, Medicine, and Pathology 27 (2015) 337–343

Contents lists available at ScienceDirect

Journal of Oral and Maxillofacial Surgery, Medicine, and Pathology

journal homepage: www.elsevier.com/locate/jomsmp

Clinical Observation

Long-term treatment outcomes and prognostic features in adenoid cystic carcinoma of the head and neck

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ARTICLE INFO

Article history:
Received 4 August 2014
Received in revised form
18 September 2014
Accepted 24 September 2014
Available online 6 November 2014

Keywords:
Adenoid cystic carcinoma
Head and neck cancer
Surgery
Radiation therapy
Survival analysis

ABSTRACT

Purpose: The aim of this study was to identify independent predictors of outcome and to characterize the patterns of failure in a long-term, single-institution experience with the management of adenoid cystic carcinoma (ACC) of the head and neck using survival analyses.
Patients and methods: We investigated prognostic factors, such as gender, age, primary tumor site, TNM stage, treatment modalities, perineural invasion, metastases, surgical margins, histological grade, cervical lymph node metastasis, and postoperative RT spread through 86 cases of ACC diagnosed by Seoul National University Dental Hospital (SNUDH) from 1984 to 2013. The overall survival and disease-free survival were evaluated. Survival rates were predicted and Kaplan–Meier's survival curves were generated for each factor. Cox proportional hazard models were used for multivariate survival analysis.
Results: Survival analysis shows that overall survival (OS) at 5 years, 10 years, and 20 years was 75%, 55%, and 41%, respectively. Disease-free survival (DFS) at 5 years, 10 years, and 20 years was 58%, 44%, and 28%, respectively. Univariate analysis revealed that age, primary tumor site, histological subtype, clinical stage, cervical lymph node metastasis, and presence of distant metastasis were significant predictors while perineural invasion, margin involvement, and gender did not demonstrate statistical difference between the treatment groups. Our multivariate analysis revealed that advanced clinical stage (stages III and IV), distant metastasis, and age over 60 years were independent significant prognostic factors.
Conclusions: Recurrence and metastasis were the main cause of treatment failure of ACC in head and neck. T stage, age, primary tumor site, histologic type, cervical lymph node metastasis, and distant metastasis were the independent prognostic factors of ACC in head and neck. Radical surgery and reasonably postoperative radiotherapy were the main treatment strategy.

1. Introduction

Adenoid cystic carcinoma (ACC) accounts for less than 1% of all head and neck malignancies and approximately 10% of all salivary neoplasm [1]. ACC is characterized by insidious local growth, high incidence of perineural invasion, infrequent regional metastases, and frequent development of local recurrences despite aggressive surgical resection. Although 5-year survival rates are relatively high and lymph node metastases are rare, the disease is difficult to manage because of its indolent nature and the propensity for distant metastases, particularly to the lung.

The combination of surgery and postoperative radiation therapy has enabled us to improve locoregional control of disease, but the prolonged clinical course, spanning decades, has made it difficult to determine whether the treatment option affects survival. Some authors have reported an increased local control of the disease with combined surgical and radiotherapy treatments [2]. However, other studies were not able to demonstrate a significant effect for postoperative radiotherapy [3,4]. Recent study reported that the incidence of cervical lymph node metastasis in ACC is approximately 10% [5]. The incidence of cervical lymph node metastasis and the association between the presence of lymph node metastases and the overall survival rate of ACC is unclear. Therefore, the advisability of an elective neck treatment in these patients is inconclusive. Several studies showed that advanced clinical stage and solid histological subtype are relevant prognostic factors associated with survival of the patients [2–4]. Evidence of nerve invasion

☆ Asian AOMS: Asian Association of Oral and Maxillofacial Surgeons; ASOMP: Asian Society of Oral and Maxillofacial Pathology; JSOP: Japanese Society of Oral Pathology; JSOMS: Japanese Society of Oral and Maxillofacial Surgeons; JSOM: Japanese Society of Oral Medicine; JAMI: Japanese Academy of Maxillofacial Implants.

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http://dx.doi.org/10.1016/j.ajoms.2014.09.011
2212-5558/

was found to be a significant prognostic factor by some, while others found no impact on survival or an adverse prognosis when there was clinical evidence of nerve involvement alone [6,7].

The aim of this study was to identify independent predictors of outcome and to characterize the patterns of failure in a long-term, single-institution experience with the management of ACC of the head and neck.

2. Patients and methods

Between 1984 and 2013, 86 patients with primary ACC at head and neck were treated at the Department of Oral and Maxillofacial Surgery, Seoul National University Dental Hospital (SNUDH). Patient records were reviewed and the following data were collected: gender, age, primary tumor site, TNM stage (retrospectively staged according to UICC, 7th edition classification), treatment modalities, perineural invasion, metastases, surgical margins, histological grade, cervical lymph node metastasis, and postoperative RT. Clear margin was defined as a tumor-free margin ≥5 mm. A close margin meant a tumor-free margin of >1 and <5 mm. A margin was considered positive in case of tumor-free margin <1 mm [8]. According to the histological typing of salivary gland tumors by WHO, all cases were histologically reviewed to confirm the diagnosis and the tumors were classified as tubular, cribriform or solid [9]. Postoperative radiotherapy was indicated in the presence of margin involvement, perineural invasion, multiple lymph node metastasis and advanced stage disease. However, despite clinical factors, in cases of patient refusal for radiotherapy or poor general status, exceptions were made and postoperative radiotherapy was not performed. Also, when a clear resection margin was achieved there were cases where postoperative radiation was not performed even when there was evidence of perineural invasion or in advanced stage disease. In patients with clinical evidence of nodal metastases, we performed therapeutic neck dissection. However, elective neck dissection was not routinely performed for patients without neck adenopathy in our cohort.

The anatomical distribution of the ACCs is shown in Table 1.

This study was carried out under the approval of the Institutional Review Board of School of Dentistry, Seoul National University, Seoul, Korea.

2.1. Statistical analysis

The Kaplan–Meier analysis and log rank test were used to assess univariate factors and disease-free survival. Overall survival was calculated from the date of the first treatment (surgery, radiotherapy or chemotherapy) or first consultation (for the untreated cases) until the date of death from any cause and was censored at the last follow-up at which the patient was known to be alive. Disease-free survival (DFS) was calculated from the date the treatment ended to the date of disease recurrence and was censored at the earliest of the date of the last follow-up or the date of death before recurrence. Cox proportional hazard models were used for multivariate survival analysis. All statistical analyses were performed with using the software package IBM SPSS Statistics 19 (IBM, New York, USA).

Table 1
Distribution of primary tumor site.

Site	Number of cases (%)
Parotid gland	3 (3.5)
Submandibular gland	9 (10.5)
Sublingual gland	7 (8.1)
Maxillary sinus	8 (9.3)
Palate	40 (46.5)
Floor of mouth	5 (5.8)
Lip	4 (4.7)
Buccal mucosa	10 (11.6)
Overall	86 (100)

Table 2
Patient demographics and clinical characteristics.

Gender		
Male	37	43.0%
Female	49	57.0%
Age	23–86 years (median 50.0 years)	
<40	18	20.9%
41–60	50	58.2%
>60	18	20.9%
Clinical stage (TNM)		
I	9	10.5%
II	27	31.4%
III	12	14.0%
IV	38	44.1%
Histological subtype		
Cribriform	51	59.3%
Tubular	19	22.1%
Solid	16	18.6%
Surgical margins		
Clear	21	24.4%
Close	3	3.5%
Positive	20	23.3%
NR	42	48.8%
Perineural invasion		
Yes	26	30.2%
No	19	22.1%
NR	41	47.7%
Treatment modality		
Surgery + RT	46	53.5%
Surgery only	35	40.7%
RT only	5	5.8%
Distant metastasis		
M0	26	30.2%
M1	24	28.0%
NR	36	41.8%

3. Results

Of the 86 patients diagnosed as having ACC of the head and neck included in this study, 37 were male (43%) and 49 female (57%), giving a male–female ratio of 1:1.32. The median age of this population was 50.0 years (range 23–86 years), the median follow-up time was 160.44 months (range 3–348 months). During this period, 58.1% of patients developed a recurrence. In Table 2 details of the demographic, tumor, and treatment-related data are shown.

3.1. Overall and disease-free survival rates

Mean survival in our cohort was 12.3 years. Life-time table analysis shows that overall survival (OS) at 5 years, 10 years, and 20 years was 75%, 55%, and 41%, respectively. Disease-free survival (DFS) at 5 years, 10 years, and 20 years was 58%, 44%, and 28%, respectively. Fig. 1 shows the life-time table curves for the OS and DFS rates.

3.2. Age

With respect to age, the DFS at 5 years and 10 years for patients with age <40 was 73.4% and 65.3%, respectively, while the DFS for patients with age over 60 at 5 years and 10 years was 19.3% and 0%, respectively ($p = 0.026$, Fig. 2).

3.3. Clinical stage

According to the UICC classification, 9 cases belonged to stage I, 27 cases to stage II, 12 cases to stage III, and 38 cases to stage