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Clinical Observation

Distant metastasis and survival of adenoid cystic carcinoma after definitive treatment

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ABSTRACT

Objective: Adenoid cystic carcinoma (ACC) is an aggressive tumor and characterized by late development of distant metastases (DM). The aim of study was to analyze the clinicopathological predictors of DM in ACC and to determine survival after the development of DM.
Methods: Thirty patients with ACC treated by surgery and/or radiotherapy were included. The impact of clinicopathological factors on DM was assessed. Factors included primary site, T stage, histological growth pattern, surgical margin, perineural invasion (PNI), postoperative radiotherapy (PORT) and local recurrence. The median follow-up was 62 months (range, 3–267 months).
Results: Twenty-four patients have relapsed local and/or distant metastases. The most common pattern of tumor relapse was DM, which developed in 17 patients. The 5-year, 10-year, and 15-year disease-free survival rate was 46%, 19%, and 15%, respectively. The positive surgical margin was significantly associated with DM rate. Neither primary site, T stage, histologic growth pattern, PNI, PORT nor local recurrence influenced on DM rates. The median survival period after the detection of DM for lung metastasis alone or bone and others were 47 months and 19 months, respectively ($P = 0.03$).
Conclusions: ACC develops DM frequently even without locoregional recurrences. Only the status of surgical margins showed an association with the occurrence of DM. The survival of patients developing DM is significantly associated with the site of metastases and better in patients with lung compared to bone and other organs. A multimodality treatment approach including chemotherapy and molecular targets therapy is warranted to treat distant metastatic disease.

1. Introduction

Adenoid cystic carcinoma (ACC) is the most common malignant salivary gland tumors, accounting for about 10% of all salivary gland tumors [1], and characterized by slow growth, high propensity of perineural invasion (PNI), frequent local recurrences, and a delayed development of distant metastasis (DM) [2]. Histologically, ACC has been classified into the three subtypes such as tubular, cribriform, and solid according to its growth patterns [3]. Initial therapy for ACC of the head and neck, in general, consists of surgical resection and/or adjuvant postoperative radiotherapy (PORT), whereas chemotherapy is usually reserved for the palliative treatment of advanced local or metastatic disease. A solid growth pattern, positive resection margins, PNI, and higher tumor stages were reported adverse prognostic factors [4–6]. Even when locoregional control has been achieved, however, patients with ACC may still develop DM even a long time after their initial treatment, and some may live for more than 10 years after diagnosis of DM. Fewer studies have documented the clinical outcomes of patients after they have developed DM [7,8]. The objective of this retrospective study was to analyze the clinical and histopathologic predictors of DM in ACC and to determine survival after the development of DM.

2. Patients and methods

2.1. Patient characteristics

Thirty-five patients who had treated for ACC of the head and neck between 1972 and 2004 were retrospectively reviewed. Of these, three patients with inadequate follow-up and two patients

☆ 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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with distant metastases at the time of presentation were excluded in this study. The remaining thirty patients were included. There were 16 men and 14 women who ranged in age from 38 to 82 years, with a mean age of 59 years. Diagnostic workup for the evaluation of tumor extension included computed tomography (CT), ultrasonography, whole body bone scan, chest X-ray, and/or magnetic resonance imaging (MRI).

Tumors were retrospectively restaged using the 2009 International Union Against Cancer (UICC) TNM staging system [9]. Major salivary gland tumors were staged according to the TNM-Classification of malignant tumors. Minor salivary gland tumors were staged according to their site of origin similar to squamous cell carcinoma of the head and neck. The histologic growth patterns were classified into tubular, cribriform, or solid patterns by their predominant histological features from the biopsy or surgical specimens. The PNI and surgical margins of excision were also assessed.

The treatment philosophy of ACC in our institution was to remove the primary lesion if it seemed to be completely resectable, and the functional and cosmetic result was judged to be acceptable. PORT was indicated in patients with close or involved surgical margins, perineural invasion, or bone invasion. Chemotherapy was not routinely administered at the time of initial treatment. Patients treated with surgery alone were a subset of patients with early stage tumors located to the buccal mucosa and lip. Tumors in the major salivary glands were removed by complete gland excision. Radical resection was performed for tumors originating in the maxillary sinus or palate. Radiation therapy was delivered to the primary site using a 6-MV photon beam with dose of 2 Gy at one fraction per day, 5 days a week. The median radiation dose was 60 grays (Gy) (range, 60–73 Gy). Three-dimensional conformal techniques and intensity modulations were not applied in this study period.

2.2. Statistical analyses

All survival times were calculated from the date of the initial diagnosis. Median follow-up for all patients was 62 months (range, 3–267 months) and 79 months (range, 9–267 months) among surviving patients. The overall survival (OS), disease-specific survival (DSS), and disease-free survival (DFS) were calculated using the Kaplan–Meier method [10]. OS was defined as the time from diagnosis to the time of death or last contact. DSS was defined as the time from diagnosis to the time of death of cancer or last contact. DFS was defined as the time from diagnosis to the time of recurrence or death, whichever occurred first. For those who did not have a recurrence or die, DFS was the time until last contact. Differences between survival functions for different strata were log rank statistic. The Chi-square test or Fisher's exact test for categorical variables and the student t test for continuous variables were used to evaluate differences between groups. The *P* values of less than 0.05 were considered statistically significant. Multivariate analysis was not used because of the small number of patients within the subgroups.

3. Results

3.1. Demographic analysis

The clinical, pathological and treatment-related data of 30 patients are presented in Table 1. The tumor was located in the major salivary glands in seven patients (3 submandibular, 3 sublingual, and 1 parotid) and in the minor salivary glands in 23 patients (14 oral, 6 maxillary sinus, and 3 oropharyngeal). T classification was T1 in three patients, T2 in 11 patients, T3 in seven patients, and T4 in nine patients. There were only two patients with N positive clinically at initial presentation. Histologic examination showed that 11 (37%) of the 30 patients were solid pattern. The initial treatment consisted of surgery alone in nine patients, surgery followed by radiotherapy (RT) in 16 patients, and RT alone in five patients with contraindications for resection because of their medical comorbidities. Of the 25 patients who had surgical resections of the primary tumors no tumor was demonstrated at the surgical margins were in only 7 patients (28%). The remaining 18 patients had shown macroscopic or microscopic tumor in their surgical margins. The primary sites that had positive surgical margins were maxillary sinus or palatal primary tumors mostly. PNI was present in 17 (68%) of 25 patients in which histological specimens were available for adequate evaluation.

Table 1
Demographic and clinicopathological charactristics of patients.

Gender	
Male	16
Female	14
Age, year (mean)	38–82 (59)
Site of primary tumor	
Major salivary glands	
Submandibular	3
Sublingual	3
Parotid	1
Minor salvary glands	
Oral cavity	14
Maxillary sinus	6
Oropharynx	3
T stage	
1	3
2	11
3	7
4	9
Histologic growth pattern	
Tubular	8
Cribriform	11
Solid	11
Treatment	
Surgery	9
Radiotherapy	5
Combined	16
Surgical margins	
Negative	7
Positive	18
Perineural invasion (PNI)	
Negative	8
Positive	17
Postoperative RT (PORT)	
No	9
Yes	16

A neck dissection was performed in nine patients (30%). Two patients underwent neck dissection for clinically apparent metastases, and the remaining seven patients received an elective neck dissection for surgical convenience of primary tumor resection. Neck metastases were shown in only two patients (8%) histologically. Adjuvant PORT was given to 16 patients (64%) following histopathological assessment of the surgical specimens.

3.2. Failure patterns and survival

After completion of the treatment, 24 patients have relapsed locoregionally and/or DMs. The median time to disease recurrence was 36 months (range, 3–136 months), with 8 patients occurring more than five years from the time of diagnosis. The sites of initial relapse are shown in Table 2. The most common pattern of tumor relapse was DM alone, which developed in 17 patients (71%). Five patients (21%) had a simultaneous local recurrence and DM. The remaining two patients had local and regional recurrence each