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Higher positive lymph node ratio indicates poorer distant metastasis-free survival in adenoid cystic carcinoma patients with nodal involvement



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ABSTRACT

Objective: Extensive studies have been conducted to analyze adenoid cystic carcinoma (ACC) in the head and neck region. No research has been published focusing on ACC patients with cervical lymph node (LN) metastasis. The aims of current investigation were to summarize the clinical characteristics of ACC patients with LN metastasis (ACC-LNM) and to identify prognostic factors for tumor-related outcomes.

Material and methods: A retrospective review was conducted with respect to ACC patients with nodal involvement between 2000 and 2013. The clinical variables and outcomes of these special cases were recorded and further analyzed. Metastasis-free survival and overall survival rate were calculated using the Kaplan–Meier method, and the log-rank test and Cox regression analysis were applied to identify the prognostic factors.

Results: A total of 47 patients (34 male and 13 female) 32–77 years of age (mean: 54.6 years; median: 54 years) were analyzed in the current protocol. The recurrence-free survival (RFS), distant metastasis-free survival (MFS), and overall survival (OS) rate in all patients were 90.1%, 55.6%, and 60.1%, respectively. In univariate analysis, T stage, positive LN ratio, LN-involved section, and extracapsular spread were strongly associated with poorer MFS rate. The predictive roles of LN-involved section and surgical margin on the OS rate were also identified. In multivariate analysis, positive LN ratio and surgical margin were predictors for MFS and OS rate, respectively.

Conclusions: Positive LN ratio was strongly associated with distant metastasis. Comprehensive treatment should be performed in ACC patients with higher positive LN ratios. In addition, ideal surgical margin should be achieved to acquire better overall survival rate.

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1. Introduction

Adenoid cystic carcinoma is a type of high-grade malignant tumor of salivary gland origin, and it accounts for approximately 1% of all head and neck malignancies, 10–15% of all salivary neoplasms, and about 30% of minor salivary gland tumors (Spiro et al., 1974). ACC has distinctive biological behaviors compared with other

malignancies, with the typical features of slow growth, high propensity to neurovascular invasion, high frequency of distant metastasis (DM), especially in the lung, and long-time survival with tumor (Bhayani et al., 2012). It is infrequent to see loco-regional and cervical lymphatic metastasis in ACC patients, with a general incidence of approximately 10% reported in previous works (Min et al., 2012). Therapeutic neck dissection will be performed in patients with clinical or radiological bases to suspect metastasis. In order to find occult positive lymph nodes or to improve the survival rate, an elective neck dissection might be implemented even in the absence of metastasizing signs (Amit et al., 2014a,b,c; Ettl et al., 2014). Positive LN has been associated with poorer survival rate compared with the rates in patients without lymphatic disease (Amit et al., 2014a,b,c; Min et al., 2012). Predictive factors for survival, such as postoperative radiotherapy, tumor site, TNM stage, histological

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subtype, and surgical margin, have been extensively discussed in general ACC patients (Li et al., 2011; Agarwal et al., 2008; Van et al., 2013). To our knowledge, there is no study concerning the prognostic analysis on ACC patients with LN metastasis (ACC-LNM) thus far. The objectives of the current research were to report the outcomes of ACC-LNM and to identify related prognostic factors. The investigators hypothesized that there existed at least one facet that could be manipulated by surgeons to improve outcomes of ACC-LNM patients. The specific aims were 1) to make a portrait of the clinical characteristics of ACC-LNM; 2) to report the outcomes (local recurrence, distant metastasis, and tumor-related death); and 3) to identify the predictors for ACC-LNM patients.

2. Material and methods

2.1. Study design and sample

To address the research purpose, the investigators designed and implemented a retrospective study, which was approved by the Ethics Committee of Shanghai 9th People's Hospital. The study population was composed of all patients presenting to the Oral and Maxillofacial Surgery Department of Shanghai 9th People's Hospital for evaluation and management of adenoid cystic carcinoma from 2000 to 2013. In our department, therapeutic neck dissection was performed in the patients with clinical or radiological suspicions of metastasis. In order to find occult positive lymph node or to improve the survival rate, an elective neck dissection might be implemented even in the absence of metastasizing signs. To be included in this study, patients had to meet the following criteria: 1) ACC patients who had undergone supraomohyoid neck dissection (SOND) and radical neck dissection (RND); 2) ACC patients diagnosed with LN metastasis following neck dissection; 3) patients who had received surgery and following adjuvant therapy at our institution; and 4) patients with complete documentation of treatments and follow-up. Patients were excluded as study subjects if they met the following exclusion criteria: 1) ACC patients who had undergone section I dissection, through which occult LN could not be detected; 2) patients without LN involvement; and 3) presence of a presurgical distant metastasis. Data were acquired from the electronic database of our hospital, collected and sorted mainly by one doctor, and identified by two other doctors to ensure the objectivity of the documents.

2.2. Study variables

The primary predicative variables in the current study included tumor status (primary/recurrent), histological subtype (solid, cribriform, tubular, and mixture, which was composed of tubular and cribriform subtypes), T stage (judged by tumor size and adjacent extension), N stage, TNM stage, number of positive LN, positive LN ratio (percentage of positive LN in total LN with a cut-point of 1:5), LN-involved section (I/II/III/IV/V, which was designated as >2-section and ≤2-section involvement), low section (IV/V) involvement, extracapsular spread, neurovascular invasion (perineural/capillary/concurrent), surgical margin (negative/positive), neck dissection (SOND: I–III sections; RND: I–V sections), adjuvant radiotherapy, and chemotherapy. Other variables, such as gender, age at diagnosis, medical status, and course of disease were also recorded.

The outcomes of ACC-LNM included local recurrence, distant metastasis, and tumor-related death. In current research, distant metastasis and tumor-related death were designated as the outcome variables. Local recurrence was not analyzed alone because of the low number of recurrent cases. The time intervals between surgical procedures and the presence of different

outcomes were recorded. Metastasis-free survival (MFS) was defined as the time interval between ACC-LNM diagnosis and the first appearance of distant metastasis. Overall survival (OS) was defined as the time period from surgery to ACC-LNM-related death.

2.3. Statistical analysis

The follow-up interval was counted in months from the date of surgery to the date of last follow-up or death. The 5- and 10-year MFS rates (%) and OS rate (%) were calculated using Kaplan–Meier survival analysis. The prognosis-related variables were also analyzed to determine their correlation with MFS and OS via log-rank test. A p value of <0.05 was considered statistically significant and the factors within this value were sorted and then entered into Cox regression model using multivariate analysis. All statistical analysis was performed using SPSS software version 20 (SPSS Inc., Chicago, IL, USA).

3. Results

3.1. Patient characteristics prior to surgical treatment

There were 1149 patients diagnosed with ACC in the head and neck region at our institution between 2000 and 2013, and of these patients, 272 had undergone SOND and RND. Histologically confirmed LN metastasis was found in 58 patients, with an incidence of 21.3%. Of these, 11 were eliminated according to the exclusion criteria. A total of 47 patients (34 male and 13 female) from 32 to 77 years of age (mean: 54.6 years; median: 54 years) were finally analyzed in the current protocol. Systemic disease was found in 13 patients (27.7%). The majority of patients (n = 30, 63.8%) had complaints about the illness for <6 months. Eleven patients (23.4%) had recurrent ACC (Table 1). As for the primary site of ACC, 12 (25.5%) presented in the mouth floor, followed by 8 (17%) in the tongue and submandibular gland, respectively, 6 (12.8%) in the sublingual gland, 5 (10.6%) in the palate, and 8 (17%) in the parotid gland and other sites (gingiva, jaw) (Fig. 1).

3.2. Treatments and pathological characteristics

All patients received surgery plus different types of neck dissection (SOND: n = 21, 44.7%; RND: n = 26, 55.3%). The most common subtype of ACC after pathological diagnosis was the mixture type (n = 23, 48.9%), followed by tubular (n = 10, 21.3%), solid (n = 8, 17%), and cribriform (n = 6, 12.8%). Due to the specific feature of slow growth and complicated anatomic structure in the oral and maxillofacial regions, a large proportion of patients (n = 28, 59.6%) developed into stage III and IV in T classification. Twenty-six patients (55.3%) were classified as N2, and 35 patients (74.5%) were diagnosed with TNM stage 4. The number of positive LN yielded during surgery ranged from 1 to 8; the RND group had more positive LN compared with SOND group (p = 0.007) (Fig. 2). Twenty-four patients had a positive LN ratio of ≥1:5, which meant that these patients had more widespread positive LN than those with a ratio of <1:5. We also analyzed the LN distribution in the cervical region, with the finding that positive LN distribution in most patients (n = 38, 80.1%) was ≤2 sections, and only 5 patients (10.6%) had positive LN with IV/V section extension. In some cases, ACC may extend to the outside of the LN, resulting in adjacent soft tissue involvement. In our cases, LN extracapsular spread was detected in 18 patients (38.2%). As a typical feature of ACC, neurovascular invasion was easily seen. There were 18 patients (38.3%) diagnosed with perineural invasion, followed by concurrent invasion of both perineural and capillary in 14 patients (30.0%), and capillary invasion alone in 2 patients. Due to the extensive invasion,

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