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ORIGINAL ARTICLE

Clinicopathological Review and Survival Characteristics of Adenoid Cystic Carcinoma

Fariba Binesh · Ali Akhavan · Omid Masumi · Abbas Mirvakili · Nasim Behniafard

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Abstract To study the clinical characters, the outcomes of treatments and the factors affecting treatment results of adenoid cystic carcinomas at Shahid Sadoughi Hospital and Shahid Ramazanzadeh radiotherapy center, Yazd, Iran. The clinical data of 31 patients with adenoid cystic carcinoma of any anatomic site diagnosed over an 8 year period (2004–2012), were investigated retrospectively. Data regarding patients' characteristics, pathological features and follow-up were obtained from patients records. Survival rate, local recurrence and distant metastasis were analyzed using Kaplan–Meier method. Prognosis factors were analyzed by Log-rank test and Cox regression. The study included31 patients with adenoid cystic carcinoma. The mean age at presentation was 50.2 ± 24.8 years. There were 11 (35.5 %) males and 20 (64.5 %) females with a female predilection (M:F = 0.55:1). Parotid gland was the most common site (8/31, 25.7 %) followed by submandibular gland (7/31, 22.6 %). Perineural invasion was detected in 67.7 % of the cases. Positive surgical status was reported in 48.4 % of the specimens. Metastasis was detected in 25.8 % of the patients and the most common site of distant metastasis was lung. Overall survival rates at 2, 5, and 7 years were 95, 75, and 57 % respectively. Margin status showed significant effect on survival (P value = 0.01). Positive surgical margin is an important factor affecting the prognosis of the patients with adenoid cystic carcinoma. Surgery with negative surgical margin is the first choice of treatment for the patients with adenoid cystic carcinoma. Our findings show that the prognosis of patients with adenoid cystic carcinoma in our center is fair.

Keywords Adenoid cystic carcinoma · Survival · Clinicopathology

F. Binesh (✉)
Department of Pathology, Shahid Sadoughi University of Medical Sciences, Yazd, Iran
e-mail: binesh44@yahoo.com

A. Akhavan
Department of Radiotherapy, Isfahan University of Medical Sciences, Isfahan, Iran

O. Masumi · N. Behniafard
Otorhinolaryngology research center, Shahid Sadoughi University of Medical Sciences, Yazd, Iran

A. Mirvakili
Department of Otolaryngology, Shahid Sadoughi University of Medical Sciences, Yazd, Iran

Introduction

Adenoid cystic carcinoma (ACC) is generally a slow-growing but highly malignant neoplasm with a remarkable capacity for recurrence. It accounted for 4.4 % of all salivary gland tumors and 11.8 % of malignant salivary gland neoplasms [1]. It affects a wide age range (9–103 years) with a peak incidence in the fifth to seventh decades, but it is very rare in children [1]. ACC commonly occurs in the major and minor salivary glands of the head and neck. Other sites include the lungs, breasts, lacrimal glands, and skin [2].Compared to other malignancies, ACC tends to grow more slowly. Thus, patients often do well in the short-term but long-term prognosis remains guarded and most succumb to the disease within 10–15 years. Late recurrences and distant metastases remain a challenge. Owing to the slow growth rate of the tumor, there is much controversy regarding the treatment of ACC. However, surgery remains the mainstay of management with or without radiotherapy. Distant metastasis frequently

develops, mainly in the first 5 years post treatment. Local recurrences often develop even later on, warranting long term follow up of these patients. Long-term follow-up is essential regardless of the site because ACC is prone to undergo late recurrence and metastasis [3]. Most patients eventually develop distant metastases, mainly in the lungs and bone, despite the local control of the tumor. The occurrence of bone metastasis usually corresponds to rapid tumor dissemination and death of the patient, whereas lung metastases demonstrate a less aggressive clinical course [4]. The purpose of the current study is to report our experience with ACC, the relevant clinicopathological, prognostic factors and also to determine how surgical resection affect the recurrence, time of recurrence, and long-term survival of these patients.

Materials and Methods

This study was approved by the Ethics Committee of Shahid Sadoughi University of Medical Sciences. In this retrospective project, the medical records of cancer patients were reviewed from 2004 to 2012 and the medical charts of all **patients** diagnosed with ACC treated at Shahid Sadoughi Hospital and Shahid Ramazanzadeh Radiotherapy center, Yazd, Iran were retrieved. Variables recorded were the hospital patient registration number, date, name, age, sex, address, topography, presence or absence of perineural invasion, resection margins, node status, treatment protocol, overall survival, and time for recurrence for each subject according to the clinical data provided in their medical charts and patients follow up via phone.

Recurrence was defined as a need for additional surgery after primary tumor excision. Statistical analysis was performed with SPSS 17.0 (SPSS Inc., Chicago, IL). Survival was estimated using the Kaplan–Meier method. Univariate and multivariate logistic regression analysis was used to determine any correlation between patient-related factors and postoperative outcomes.

Results: A total of 33 patients with ACC were treated between September 2004 and September 2012, with 31 patients meeting the necessary inclusion criteria. The age at diagnosis ranged from 18 to 99 years, with a mean age of 50.2 ± 24.8 years. There were 20 women and 11 men. The primary tumor site is given in Table 1. Tumor diameter ranged 12–45 mm with a mean diameter of 24.8 ± 10 mm. Information was available regarding the state of the surgical margins at microscopic level for 26 patients, of whom 16 had tumor-free margins (51.6 %) and 10 had affected margins (48.4 %). The presence of perineural invasion (PNI) was also analyzed in 29 patients, of whom 21 (67.7 %) had microscopic PNI compared to 8 (25.8 %) who did not. 5 (19.2 %) patients had evidence of cervical lymph node metastasis at the time of diagnosis. 4 (12.9 %) patients gave up surgery on initial diagnosis and 27 (87 %) patients underwent primary surgical excision of their tumors. Chemotherapy was given to 4 (12.9 %) of the patients. 24 (77.4 %) of the cases had received radiotherapy. 8 (25.8 %) had evidence of distant metastasis. The most common site of distant metastasis was lung, followed by liver and bone. At the time of the study, 18 patients were alive. There were 4 deaths due to ACC, 1 death owing to unrelated cause and the remaining were lost to follow-up. The average survival for our patients was 85.6 ± 8.6 months (95 % CI 68.8–102.5 months). The overall survival (OS) rates at 2,5, 8 years were 95, 75, 57 % respectively. As it is shown in Fig. 1 at 0–82 months the OS had decreased and then had not. Male patients had decreased OS compared with female patients (70.3 vs. 98.3) although this difference failed to reach statistical significance (P value = 0.21).There was no difference in OS between the age group 18–49 and 50-99 years (P value = 0.97). Survival was worse in all intervals for patients presenting with lymph node metastasis (0 % at 87 months) but again this difference failed to reach statistical significance (P value = 0.73).Regarding PNI, as it is shown in Fig. 2, OS in patients without PNI is longer till 45 months but after that it reaches to zero which is owing to small sample size. 48.4 % of the cases had positive surgical margin. OS in patients with positive surgical margins was 42 months less than patients with negative surgical margins (P value = 0.01) (Fig. 3). The overall recurrence rate among the patients was 33.3 % with a mean recurrence time of 65.4 months in the age group 18-49 years and 60 months in the age group 50-99 years. After recurrence OS dropped until 55 months and then remained constant. There was no association between recurrence, age (P value = 0.66), gender (P value = 0.65), PNI (P value = 0.54), node metastasis (P value = 0.65) and positive surgical margin (P value = 0.42). Since majority of the patients in this study underwent radiation therapy (RT) we were unable to evaluate the relationship between OS, recurrence and RT. When the OS was compared regarding the origin of the tumor, patients with parotid, sabmandibular gland and bronchus tumors had the best survival (all patients were alive) and patients with trachea and maxillary sinuses tumors had the worst survival.

Discussion

This retrospective study was to evaluate the relevant clinicopathological, recurrence rate and OS in ACC patients at two institutions in Yazd, Iran. Adenoid cystic carcinoma is a rare tumor. Because of the rarity of this tumor, a small

Table 1 Shows the primary tumor site

Tumor site	Number	Percent
Parotid gland	8	25.7
Submandibular gland	7	22.6
Trachea	3	9.7
Bronchus	3	9.7
Maxillary sinus	3	9.7
Others	7	22.6[a]
Sum	31	100

[a] Others include nasopharynx, lip, palate, tongue and larynx

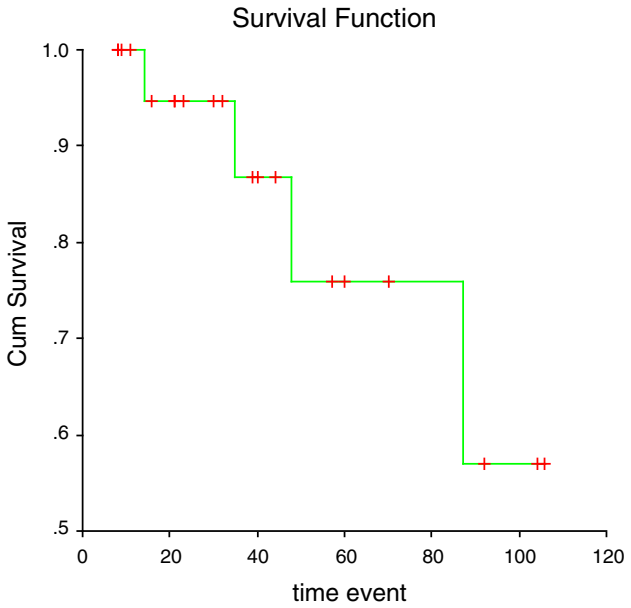

Fig. 1 Shows overall survival in patients with ACC

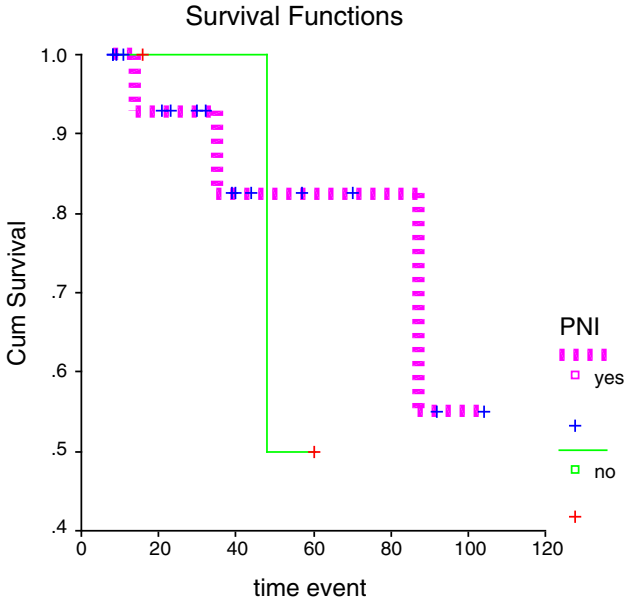

Fig. 2 Reveals overall survival according to perineural invasion

number of patients would be expected. The current study included 31 patients with ACC of any anatomic site diagnosed over an 8 year period (2004–2012). The patient population in one review was reported to range from 10 to 96 years [5]. In the current study the age at diagnosis ranged from 18 to 99 years, with a mean age of 50.2 ± 24.8 years. Gender predilection is an inconsistent feature in the literature with some authors reporting a male predominance and others finding a female or no gender predilection [6, 7]. We found a female predilection (M:F = 0.55:1). These gender differences indicate that there may be a hormonal influence accounting for biological behaviors of ACC. Up to 50 % of these tumors occur in the intraoral minor salivary glands usually in the hard palate [8]. However in the present study major salivary glands were affected more. Consistent with other study the most affected major salivary gland was the parotid gland [9]. It seems that compared to other malignancies, ACC tends to grow more slowly. Thus, patients often do well in the short-term but long-term prognosis remains guarded and most succumb to the disease within 10–15 years. Although the 5-year survival rate is high, 10- and 15-year survival markedly decreased. Hence, it is classified as "high risk" by the World Health Organization [10]. The overall survival of the present study was approximately the same as, much better or less than those reported in the other studies [7, 11–14]. The differences between their data and the present study were evaluated in terms of the following: (1) the outcome for patients with ACC is site dependent [15]. In our study the majority of patients had a major salivary gland ACC which has a better outcome, likely related to surgically wider tumor-free margins, (2) it seems females had better survival outcomes, there were more females in our study (3) treatment modalities are different in different studies, (4) race might play a role, (5) the social and economic position should not be ignored in medical behavior. Given the rare nature of this malignancy we can only attempt to identify trends; it is not possible to arrive at statistically significant conclusions. None of the variables were analyzed in relation to the survival of the disease, except for the surgical margin, showed a statistically significant relationship to it, although differences in survival can be appreciated in connection to some of these variables, such as lymph node involvement & perineural invasion. Consistent with studies by Gomez et al. [14,] and Agnes Oplatek [16] who demonstrated decreased survival in patients with cervical nodal metastasis, our data showed a decrease in survival, too. Whereas isolated lymph node involvement without distant metastasis may not have significantly altered survival in some studies, [17] lymph node involvement is a risk factor for subsequent distant

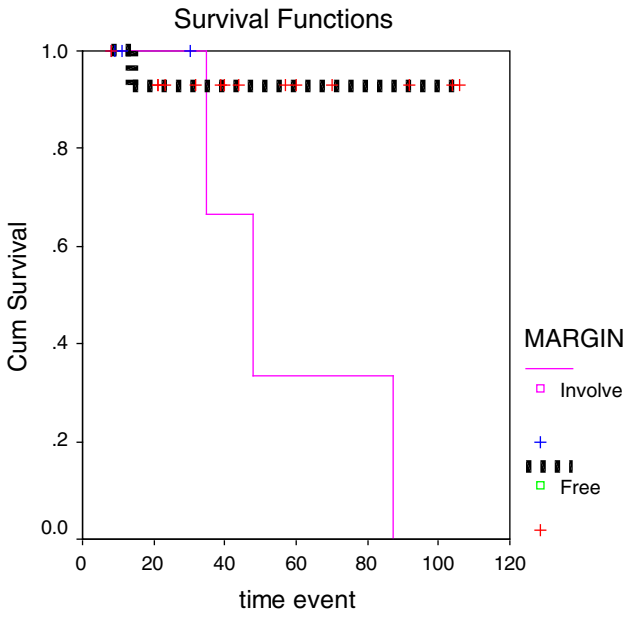

Fig. 3 Shows overall survival regarding surgical margin

metastasis [9]. The findings of the present study are concordant with those from other study [16] confirming the important impact of tumor site at diagnosis.ACC is well-known for its indolent growth but common recurrence. The overall recurrence rate among our patients was 33.3 %. The clinical course of ACC is characterized as distant metastasis; one study found that 20 % of patients developed distant metastases over the course of their follow-up [17]. Patients who were diagnosed with early-stage disease and without local recurrence of the primary tumors could also develop distant metastases [18].In one series, rate of distant metastasis was reported as 47.8 % with mean time to distant metastasis reported as approximately 5 years [19].In the current study 8 (25.8 %) patients had evidence of distant metastasis. Additionally, we did not find that increased age was associated with increased recurrence rate or overall survival which is in contrast with other study [20]. Jones et al. [21] reported that males with primary adenoid cystic carcinomas of the head and neck had a significantly better prognosis than females, while our results indicated that females had a better disease-specific survival. Consistent with other study positive surgical margin was a strong prognostic factor [9].Meanwhile, one study showed the adequacy of surgical resection did not seem to influence overall survival or recurrence rate [16]. It should be noted that a relatively high number of patients with microscopically positive margins in our and in other studies show the difficulty in determining the extension of the resection of this tumor. Furthermore, it is usually difficult for the pathologist to assess these margins in surgical specimens that are from complicated anatomical structure resections, and retraction after fixation is another problem. As a result, it is necessary to emphasize the importance of frozen section to guarantee the surgical borders of the tumor. Our study revealed that the presence of perineural invasion is associated with a decreased overall survival, although the difference was not significant. This result is in line with other study that indicates this as a negative prognostic factor [9], although there is also another study that does not find this relationship [7] which is why it is still controversial. Radical excision by surgery has been the primary treatment option. However, the extensive local infiltrative and perineural spread related to this malignancy often cause difficulty to achieve high tumor control. The effect of adjuvant radiation therapy on survival in patients with ACC is much debated. One study revealed that adjuvant radiotherapy after standard complete surgical resection was effective [22]. One recent study showed neutron radiation therapy achieved excellent 5-year local control [23]. Since majority of the patients in this study underwent RT we were unable to evaluate the relationship between OS, recurrence and RT. The role of chemotherapy for adenoid cystic carcinoma is still controversial [24].

In conclusion ACC is relatively rare and it may result in recurrence even many years post-diagnosis. Close follow up of all patients for recurrence and metastasis is essential, although no formal guidelines exist regarding the most appropriate mode and duration of follow up. Greater knowledge of the biological behavior of these carcinomas would help us to improve the outcome of the patients. Our results showed surgery with negative surgical margin is the first choice of treatment for the patients with adenoid cystic carcinoma.

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Conflict of interest None.

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