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ORIGINAL ARTICLE

Treatment and clinicopathologic predictors for adenoid cystic carcinomas of the head and neck

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Summary

Purpose: *To retrospectively evaluate the management and clinicopathologic predictors of outcome of adenoid cystic carcinoma (ACC) patients treated and followed at our Department.*

Methods: *Data on 41 patients treated between 2000 and 2006 at the University of Istanbul, Institute of Oncology, were reviewed. Factors affecting recurrence, distant metastasis and survival were evaluated.*

Results: *There were 22 (53.6%) major salivary and 19 (46.3%) minor salivary gland tumors. Eighteen patients (43.9%) had solid histologic type tumor. Twenty-one (51%) patients had perineural invasion and 28 (68.2%) high grade tumors. Sixteen (39%) patients had stage I disease, 12 (29.1%) stage II and 13 (31.5%) stage III. Thirty-two patients (78.4%) had radical and 9 (21.9%) partial resection. Thirty-one patients (75.6%) received adjuvant postoperative radiotherapy (RT). Eight patients (19.5%) suffered locoregional relapse and 9 (21%) distant metastases. Two patients (4.8%) died from ACC and 7 (17%) from other causes.*

The median follow-up was 48 months (range 24-60). Disease free survival (DFS) at 2 and 3 years were 78% and 58%, respectively. Overall survival (OS) at 2 years and 3 years were 87% and 80%, respectively. Median time to locoregional relapse and distant metastasis was 28 and 32 months, respectively. Seven of 9 patients with distant metastasis had solid tumor subtype. Distant metastasis occurred more frequently in patients with tumors of major salivary glands (66%). Sites of distant metastasis were lung alone (n=5), bone alone (n=2) and 2 patients had both lung and bone metastasis.

There was no statistically significant relationship between clinical T stage and solid histology with locoregional relapse ($p > 0.05$). Surgical resection type and perineural invasion were significant prognostic factors for locoregional relapse ($p=0.03$). T stage ($p=0.001$), grade ($p=0.02$) and solid histology ($p=0.003$) were prognostic factors associated with DFS.

Prognostic factors associated with OS were grade ($p=0.001$), clinical T stage ($p=0.02$), solid histology ($p=0.01$), radical excision ($p=0.04$) and perineural invasion ($p=0.001$).

Conclusion: *ACC is a neoplasm in which early diagnosis is important because it is a slow-growing tumor producing diffuse invasion. Distant metastasis and locoregional relapse can be predicted by solid histologic subtype, high grade, type of surgery, perineural invasion and tumor stage. The most frequent sites of metastasis are lung and bone.*

Key words: adenoid cystic carcinoma, distant metastasis, prognostic factors, recurrence, treatment, survival

Introduction

ACC is a malignant tumor that arises from the secretory epithelial cells of salivary glands of the head and neck and accounts for less than 1% of all head and neck malignancies and approximately 10% of all salivary neoplasms [1-3]. ACC has been characterized by slow growth, multiple local recurrences, and delayed development of distant metastasis [2,4]. Distant metastasis of ACC occurs more frequently than regional lymph node metastasis [1,5,6]. ACC develops most often in the major salivary glands and the submandibular gland, and less frequently in the sublingual and parotid glands [4,6]. Other rare locations include the aerodigestive tract, lacrimal glands and adnexal skin glands. Most ACC patients are in their 5th and 6th decade of life, and females are affected more than males [1,4,6]. Three histological subtypes of ACC are known: cribri-

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form, tubular and solid. The solid subtype is the most aggressive one [3,4]. Perineural invasion is characteristic of these tumors and occurs in up to 60% of the cases [7]. Cervical metastasis is rare and occurs in only 8-13% of the patients [6,8,9]. Distant metastasis may occur in up to 50% of ACC patients during the course of the disease, with lungs and bones being the most common sites [8,10]. Tumor stage, prevalence of perineural invasion, tumor size, extent of surgery, and RT have been identified as important prognostic factors for outcome in patients with ACC [8,9].

In patients who have resectable tumors, complete resection is considered. Locoregional control rates of 95% generally are obtained with complete resection and adjuvant RT.

In this study we retrospectively evaluated the management and the clinicopathologic predictors of outcome of ACC patients treated and followed at the Institute of Oncology, Istanbul University, Medical Faculty.

Methods

From January 2000 to December 2006, 41 patients with ACC of head and neck were treated at the Istanbul University, Oncology Institute. Patients were classified according to their clinical stage (American Joint Committee on Cancer Staging System). All patients had preoperative computed tomography (CT) scans to determine the tumor's local extent. Preoperative diagnosis was made on histological samples taken by either FNA or incisional biopsy.

All of the patients underwent surgery; 33 (78.4%) of them had radical resection, 9 (21.9%) partial resection and 31 (76%) received postoperative adjuvant RT.

The type of surgery was planned based on the primary tumor site and included partial or total maxillectomy, parotidectomy and transoral resections. Patients with cervical nodal disease underwent neck dissection according to the level of nodal involvement, thus ranging from radical to selective neck dissection. Positive or narrow margins, perineural invasion or more aggressive histological subtypes (generally the solid type) were the criteria for deciding to utilize postoperative RT.

Statistical analyses

Statistical analyses were performed using SPSS -16 version for Windows. Cumulative survival and distant metastasis rates were calculated using the Kaplan-Meier method and the differences were assessed by the log-rank test. P-values < 0.05 were considered statistically significant.

Results

The patient clinical characteristics are summarized in Table 1.

The majority of the patients were female (n=23; 56%) with median age of 46 years (range 29-72). Patients were observed for 24-60 months (median 48). For major salivary gland tumors, 9 patients (21.9%) had stage I disease, 5 (12.1%) stage II, and 8 (19.5%) stage III. For minor salivary gland tumors, 7 patients (17%) had stage I, 7 (17%) stage II, and 5 (12%) stage III.

Twenty-one patients had tumors that showed perineural invasion. Tumors were located in the major salivary glands in 22 patients (53.6%), of which 5 were in the parotid and 17 in the submandibular glands.

Table 1. Characteristics of patients, therapy and disease

Characteristics	*Patients, n*	*%*
Age (years)		
< 45	19	46.3
≥ 45	22	53.6
Sex		
Male	18	43.9
Female	23	56
Symptom duration (months)		
<12	28	68.2
≥12	13	31.7
Primary treatment		
Surgery	41	100
RT	31	75.6
Surgery+RT	31	75.6
Surgery		
Radical	33	80.4
Nonradical	9	21.9
Stage		
I-II	28	68.2
III-IV	13	31.7
Sites of recurrence		
Locoregional	8	19.5
Distant metastasis	9	21
Histologic type		
Tubular	12	29.5
Solid	18	43.9
Cribriform	11	26.8
Histologic grade		
I	14	34.1
II	10	24.3
III	17	41.4
Perineural invasion		
Positive	21	51.2
Negative	20	48.7
Resection margin		
Positive	8	19.5
Negative	33	80.4

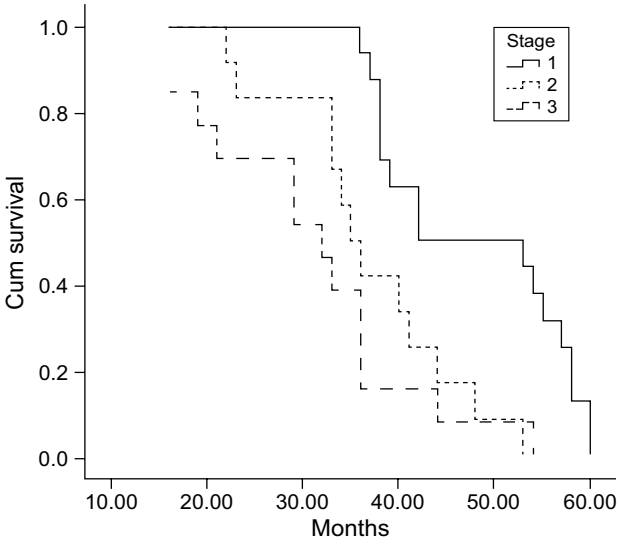

Figure 1. Overall survival according to stage (p= 0.02).

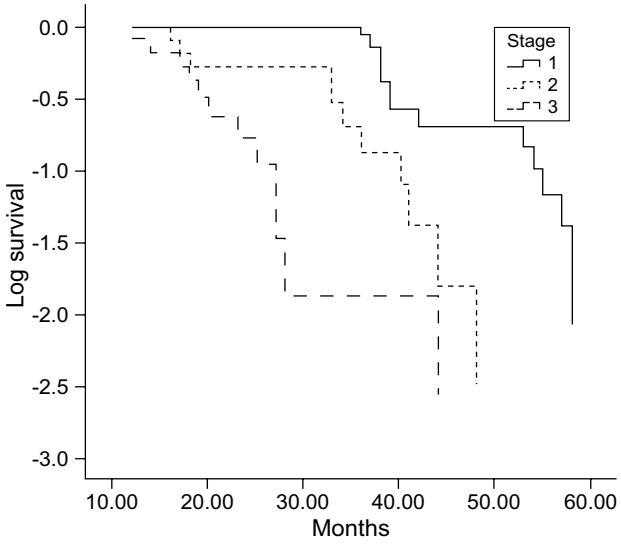

Figure 2. Disease free survival according to stage (p=0.0001).

Nineteen patients (46.3%) had minor salivary gland tumors. Resection margins: 8 close surgical margins (3 in submandibular tumors and 5 in minor salivary gland tumors). Seventeen patients recurred, 8 (19.5%) with locoregional disease. Distant metastasis was observed in 9 (21%) patients. Median time to locoregional relapse and distant metastasis was 28 and 34 months, respectively. Two patients had lung and bone metastasis, 5 lung alone and 2 bone alone metastasis. DFS rates at 2 and 3 years were 78% and 58%, respectively. OS rates at 2 and 3 years were 87% and 80%, respectively. Stage was statistically important factor for DFS and OS (Figures 1,2). There was no significant difference in DFS rates with regard to age, sex, duration of symptoms, tumor site, and extent of surgical resection. No statistically significant relationship was found between clinical T stage and solid histology with locoregional relapse (p >0.05). On the contrary, surgical resection type and perineural invasion were statistically significant prognostic factors for locoregional relapse (p=0.03). T stage (p=0.001), grade (p=0.02) and solid histology (p=0.003) were prognostic factors associated with DFS. The prognostic factors associated with OS were grade (p=0.01), clinical T stage (p=0.02), solid histology (p=0.01), radical resection (p=0.04) and perineural invasion (p=0.001) (Table 2).

Table 2. Prognostic factors concerning local recurrence, distant metastasis, DFS and OS (p-values)

Variable	*Locoregional relapse*	*Distant metastasis*	*DFS*	*OS*
Age (years) (<50 vs. ≥50)	0.071	0.696	0.132	0.345
Histological grade (poor vs. well)	0.051	0.042	0.022	0.011
Perineural invasion (present vs. absent)	0.031	0.122	0.072	0.001
Stage (I+II vs. III)	0.322	0.011	0.001	0.020
Tumor size (cm) (<3 vs. ≥3)	0.242	0.041	0.001	0.020
Histologic type (solid vs. other)	0.271	0.081	0.003	0.010
Primary site (minor vs. major)	0.212	0.543	0.073	0.552
Resection margin (positive vs. negative)	0.032	0.651	0.281	0.041

DFS: disease free survival, OS: overall survival

Discussion

ACCs are malignant neoplasms originating from both the minor and major salivary glands, characterized by slow growth, diffuse invasion and potential to produce distant metastases, mainly to the lungs and bones [1]. ACCs show a high propensity for perineural spread along the involved peripheral nerves. Tumor stage, perineural spread, histologic type, grade, extent of surgery, and RT have been identified as important prognostic factors for outcome [1,3,6,11]. In this series of 41 patients we analyzed factors such as age, sex, symptom duration, tumor site, primary therapy modalities, extent of surgical resection, clinical stage, histologic grade, perineural invasion and surgical margins. There was a female predominance among the cases, which was similar to the observation of several authors [1,4,6]. Most ACCs occurred in minor salivary glands and, when present in the major salivary glands, the submandibular gland was the one most frequently affected. According to the literature, the primary treatment of ACC is surgery with negative margins [1,2,4,5]. In the present series, for parotid tumors, superficial parotidectomy was the standard procedure for stage I disease. Total parotidectomy was done when there was clinical invasion or suspicion of local invasion.

Negative margins are always possible for T1 and T2 submandibular gland tumors and selective neck dissection for salivary gland tumors is controversial in N0 cases and is of little benefit to these patients [12,13]. For ACC of minor salivary glands transoral resection with free margins is possible in all T1 and T2 lesions.

CT scans were carried out in order to determine the tumor stage more precisely and plan the most proper surgical intervention. Surgical margins were analyzed and, when close or positive, RT was indicated. Adjuvant RT was used for cases of T3 tumors, even when the margins were free of disease. The portals were wide and encompassed all nerve routes because of the tendency ACC to show perineural invasion.

Distant metastasis has been known as a factor affecting survival of patients with ACC, similarly as in other malignant tumors. Tumor size greater than 3 cm, locoregional recurrence and cervical node involvement were reported to be highly predictive of distant metastasis [3,6]. Patients with solid subtype ACCs developed distant metastasis most rapidly and frequently. Of note, there was no significant difference in the development of distant metastasis with regard to the adequacy of surgical margins. In our study there was no significant difference in DFS rates by age, sex, symptom duration, tumor site, and extent of surgical resection. Grade 3 disease, perineural invasion and close surgical margins were associated with local recurrence and distant metastasis. OS was influenced by histologic growth pattern, tumor stage and the presence of metastasis. These findings are similar to those found in the literature.

Conclusion

ACC shows locally aggressive behavior and a high rate of local recurrence and distant metastasis, especially when perineural invasion, high histologic grade and stage III are present. RT is important treatment after surgery with close margins, high grade tumors and perineural invasion. Long-term follow-up is needed because local recurrence and distant metastasis may occur late, especially among high-risk patients.

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