Adenoid cystic carcinoma of the salivary glands: A 20-year review with long-term follow-up

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Abstract
The behavior of adenoid cystic carcinoma (ACC) of the salivary glands has been shown to be unpredictable in terms of local and distant spread and mortality. We retrospectively studied 35 operations in 34 patients who had had a pathologic diagnosis of ACC of the salivary glands and who had been treated over a 20-year period and followed for a minimum of 10 years. We analyzed the effect that different factors had on outcomes. The site of origin appeared to be an important factor in survival rates; survival among patients with tumors that had originated in the parotid gland was fairly good, while survival among those with tumors that originated in the minor salivary glands was significantly worse. TNM staging was another significant factor in survival. Other poor prognostic indicators were local spread, nodal positivity, distant metastasis, and local and regional recurrence. Radiation and chemotherapy did not appear to be beneficial for patients with advanced disease. We recommend radical surgery with complete resection for all patients with ACC of the salivary glands and a careful assessment of the neck in patients with minor salivary gland tumors.

Introduction
Adenoid cystic carcinoma (ACC) is a malignant neoplasm of the salivary glands. It accounts for most cases of minor salivary gland malignancies and a substantial proportion of parotid and submandibular gland malignancies. The behavior of ACC has been shown to be unpredictable. The tumor has a significant propensity for perineural spread and distant metastasis. ACC is associated with a high mortality rate, and it often recurs after prolonged periods of time. On the other hand, some patients survive for a considerable length of time even in the face of distant metastasis. Several factors have been considered indicative of a poor prognosis in patients with ACC, including an advanced tumor stage, a solid histologic type, the presence of nodal metastasis, the presence of positive margins and perineural spread. Many studies have lacked a satisfactory follow-up period, a fact that may account for the differences in prognosis among them. In an attempt to clarify some of the inconsistencies regarding the behavior of ACC, we studied a series of patients who had been followed for 10 to 30 years.

Patients and methods
From January 1970 through December 1989, 40 patients with ACC of the salivary glands were treated at the Beilinson Campus of the Rabin Medical Center in Petah-Tikva, Israel. Patients who had been treated within the previous 10 years were excluded from the study to allow for at least 10 years of follow-up.

Sufficient data for inclusion in this study were available for 34 patients—17 men and 17 women, aged 22 to 80 years (mean: 57.7). The 34 patients underwent a total of 35 operations. Most of these patients had superficial parotid lesions and they had undergone a superficial parotidectomy; those who had tumors that involved the deep lobe underwent a total parotidectomy. Preservation of the facial nerve was attempted in all cases unless the nerve was clearly involved in the cancerous process. Submandibular and minor salivary gland tumors were resected with the goal of achieving adequate margins of resection. Lymph node dissection was performed only on patients who were lymphadenopathy-positive at presentation. Follow-up ranged from 10 to 30 years (mean: 15).

We compiled data on factors that might influence survival, including TNM stage, local spread (including perineural and bone invasion), regional and distant spread, type of treat-
ment, local and regional recurrence, and distant metastasis. The impact of these factors on outcome was evaluated by multiple logistic regression, and the different categories were compared by a chi-square test performed with SigmaStat Statistical Software (SPSS; Chicago). Linear variables were analyzed by linear correlation. Kaplan-Meier curves were generated for disease-free survival.

Results
The most common sites of tumor origin were the parotid gland (35.3%) and the minor salivary glands of the hard palate (17.6%) (table 1). Prior to surgery, the most common complaint at presentation (65.7%) and the most common sign on physical examination (77.1%) was a lump in the involved gland. Other clinical complaints and physical signs were seen much less often; the most common of these were local pain and oral ulcer (8.6% each).

Of the 34 patients, 22 (64.7%) presented with early cancers (T1 or T2), and the remaining 12 (35.3%) had local or regional advanced disease (T3 or T4) (table 2). Only 4 patients (11.8%) had regional lymph node metastasis at the time of surgery (table 3), and their treatment included neck dissection. Three patients (8.8%) had distant metastasis. In light of the small numbers of patients with regional and distant metastases at presentation, the effect of metastasis on survival could not be evaluated.

Histology. Histologic subtyping was available for 21 patients, 4 of whom had predominantly solid tumors. This small number precluded us from making any histologic correlations with any of the study parameters.

Treatment. All patients underwent surgical resection of their primary tumor, with the exception of 1 patient who had a distant metastasis at presentation; this patient was treated with combined radio-and chemotherapy. Two patients underwent 2 operations each. Nineteen patients (55.9%) received adjuvant radiotherapy in addition to surgical excision; 6 of the 19 also received concomitant chemotherapy.

<table>
<thead>
<tr>
<th>Site</th>
<th>n (%)</th>
<th></th>
<th>Site</th>
<th>n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Parotid gland</td>
<td>12 (35.3)</td>
<td></td>
<td>Hard palate</td>
<td>6 (17.6)</td>
</tr>
<tr>
<td>Maxillary sinus</td>
<td>3 (8.8)</td>
<td></td>
<td>Base of the tongue</td>
<td>3 (8.8)</td>
</tr>
<tr>
<td>Floor of the mouth</td>
<td>3 (8.8)</td>
<td></td>
<td>Buccal mucosa</td>
<td>2 (5.9)</td>
</tr>
<tr>
<td>Submandibular gland</td>
<td>2 (5.9)</td>
<td></td>
<td>Oral tongue</td>
<td>1 (2.9)</td>
</tr>
<tr>
<td>Lower lip</td>
<td>1 (2.9)</td>
<td></td>
<td>Ethmoid sinus</td>
<td>1 (2.9)</td>
</tr>
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</table>

<table>
<thead>
<tr>
<th>Stage</th>
<th>Patients</th>
<th>Disease-free survival n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>T1</td>
<td>10</td>
<td>6 (60.0)</td>
</tr>
<tr>
<td>T2</td>
<td>12</td>
<td>6 (50.0)</td>
</tr>
<tr>
<td>T3</td>
<td>3</td>
<td>1 (33.3)</td>
</tr>
<tr>
<td>T4</td>
<td>9</td>
<td>1 (11.1)</td>
</tr>
</tbody>
</table>

Recurrence and metastasis. Regional recurrence occurred in 12 of the 34 patients (35.3%); 8 of these recurrences developed during follow-up. Distant metastasis developed in 15 patients (44.1%); 3 metastases were detected at presentation, and 12 developed during follow-up. All but 1 of the patients with regional recurrence and all patients with distant metastasis died of disease within 3 years of diagnosis (survival: 8.3 and 0%, respectively). All patients who presented with regional metastasis died of disease during follow-up. The mean length of time to the development of regional recurrence (10.0 yr) was similar to the mean length of time to the development of distant metastasis (9.7 yr); in both cases, the range was 1 to 30 years. Only 9 of the 20 patients (45.0%) who developed a regional recurrence or distant metastasis during follow-up did so during the first 10 years of follow-up; the remaining 11 patients (55.0%) developed the recurrence or metastasis between 10 and 20 years of follow-up.

Survival. During follow-up, 19 of the 34 patients (55.9%) died of their disease and 1 patient (2.9%) remained alive with disease. Of the remaining 14 patients, 10 (29.4%) were alive with no evidence of disease and 4 (11.8%) had died of other causes with no evidence of disease; of the latter 4 patients, 2 died 8 years following treatment and 2 died 2 years after treatment. Disease-free survival was similar to overall survival—41.2 and 32.3%, respectively (table 4).

Risk factors. Analysis of different risk factors revealed that the site and size of the tumor had a significant effect on survival, as did surgical margins:

Tumor site. Patients whose tumors originated in the parotid gland (n = 12) had a significantly better survival than those whose primary tumors arose in the minor salivary glands (n = 15) (table 5). The tumors in the remaining 7 patients had originated in the maxillary sinus, base of the tongue, or ethmoid sinus.

Tumor stage. Patients with larger tumors had a higher mortality rate (p = 0.03) (table 2). Of 9 patients who presented with T4 lesions, 8 (88.9%) died of the disease despite surgery and radiotherapy. Large tumors had a greater tendency to spread locally. Local spread (including perineural and bone invasion) was found in 11 patients,
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and it had a detrimental effect on survival regardless of
tumor stage. All 3 patients with parotid tumors who had
died of their disease had local spread.

Surgical margins. At least one positive margin remained
in 10 patients postoperatively, and 7 of these patients died
of disease. Of the 24 patients who had negative margins,
there were only 11 deaths (45.8%).

Discussion
In a study of a large series of patients with ACC, Fordice
et al reported that neither tumor site nor tumor stage had
a significant effect on survival. However, considering
the limited length of follow-up in that study (as little as 2
yr in some cases) and the tendency of ACC to recur late,
their conclusions should not be considered definitive. The
TNM stage of ACC at presentation appears to be relevant
to survival. We demonstrated a linear increase in survival
with decreasing tumor stage. We could not show a correla-
tion between nodal staging and distant metastasis because
of the small number of patients, but we did find a 100%
mortality in cases of lymphadenopathy at presentation.
Fordice et al claimed that it was nodal positivity rather
than nodal stage that is the important factor, and we tend
to agree.

Local spread developed in 12 of our patients—3 of
the 12 (25.0%) who had a parotid tumor and 9 of the 22
(40.9%) who had a minor salivary gland tumor. The greater
propensity of minor salivary gland tumors to spread in
fascial planes and nerves makes complete surgical excision
much more difficult. The main determinant of survival is
probably not the tumor site per se but the propensity for
local spread, which is highly influenced by the site and
which may result in a positive surgical margin. This is even
more apparent in cases of maxillary sinus carcinoma; in
our study, 100% of these tumors spread locally, and all
affected patients died of the disease. Spiro et al have also
suggested that local spread is a major factor in decreasing
the cure rate of patients with ACC. Aggressive primary
resection might be the only way to lower the mortality
of patients with ACC in sites of prevalent local spread.
Radiation may improve the prognosis in patients with
advanced disease. We did not find this to be meaningful in

Table 3. TNM staging of ACC of the head and neck
prior to 35 operations

<table>
<thead>
<tr>
<th>T1</th>
<th>T2</th>
<th>T3</th>
<th>T3</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>9</td>
<td>12</td>
<td>8</td>
</tr>
<tr>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1</td>
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<tr>
<td>0</td>
<td>1</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>0</td>
<td>10</td>
<td>11</td>
<td>2</td>
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<tr>
<td>1</td>
<td>0</td>
<td>1</td>
<td>0</td>
</tr>
</tbody>
</table>

* Unknown primary tumor.

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our patients, but we cannot draw any conclusions because of the selection bias—that is, patients with more advanced disease were also treated with radiotherapy. In another study, Spiro et al. reported that postoperative radiotherapy conferred no advantage, but others have shown that ACC is radiosensitive, although not necessarily radiocurable. Radiation, therefore, might still be of value both in treating (postoperatively) locally advanced disease and in treating patients who refuse surgical resection.

As expected, both regional recurrence and distant metastasis were predictors of poor survival, and aggressive treatment of recurrences did not have an effect on outcome. Treatment delivered to the neck should be tailored to the specific site of origin, as has been proposed by Garden et al. In our series, there was not even 1 case of regional recurrence among the 12 patients with parotid ACC, as opposed to 11 regional recurrences in the remaining 22 patients (50.0%). We suggest careful evaluation and follow-up examinations of the neck, including ultrasonography, in cases of ACC that originate in the minor salivary glands. Surgery should entail lymph node dissection, which can be limited to the area of maximal drainage; one such option is supraomohyoid neck dissection for oral cavity tumors. Again, we emphasize the poor prognosis of our patients with regional recurrences (survival: 8.3%), indicating the importance of prevention of regional recurrence.

In the specific case of ACC of the submandibular gland, we recommend surgical excision of the submandibular triangle as the biopsy procedure. We cannot recommend elective treatment to the neck for these patients because of the small number of patients in our study who had primary disease at that site. Obviously, more studies are needed to determine the patterns of regional spread in ACC, as well as the preferred treatment modality and the role of preventive neck dissections.

Of the 6 patients in our series who received chemotherapy, 1 had early-stage disease and survived, and the other 5 had advanced disease and died of their disease despite aggressive treatment. Thus, in contrast to findings reported by Spiro et al., we observed no advantage to adding chemotherapy to the treatment protocol for patients with advanced ACC. A similar observation was reported by Hill et al., who found that the combination of cisplatinum and 5-fluorouracil resulted in no major improvement in survival.

### Table 4. Survival and mortality according to disease status among the 34 patients

<table>
<thead>
<tr>
<th></th>
<th>Alive n (%)</th>
<th>Died n (%)</th>
<th>Total n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>With ACC</td>
<td>1 (2.9)</td>
<td>19 (55.9)</td>
<td>20 (58.8)</td>
</tr>
<tr>
<td>Without ACC</td>
<td>10 (29.4)</td>
<td>4 (11.8)</td>
<td>14 (41.2)</td>
</tr>
<tr>
<td>Total</td>
<td>11 (32.3)</td>
<td>23 (67.7)</td>
<td>34 (100)</td>
</tr>
</tbody>
</table>
or symptom control in patients with ACC.

In conclusion, the prognosis of patients whose ACC originates in the parotid gland is better than that of patients whose ACC arises in the minor salivary glands; the better outcome is attributable to the low rates of local spread and regional recurrence. Regional recurrences, which are most common in cases of ACC that arise in the minor salivary glands, carry an ominous outcome. Surgery is the preferred primary treatment, and complete resection of the tumor with negative margins is indicated. In our series, no advantage was achieved from adjuvant radiation or chemotherapy.

References

Table 5. Outcome of the 27 patients with parotid and minor salivary gland tumors

<table>
<thead>
<tr>
<th></th>
<th>Disease-free survival*</th>
<th>Disease†</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n (%)</td>
<td>n (%)</td>
</tr>
<tr>
<td>Parotid</td>
<td>9 (33.3)</td>
<td>3 (11.1)</td>
</tr>
<tr>
<td>Minor salivary glands</td>
<td>3 (11.1)</td>
<td>12 (44.4)</td>
</tr>
</tbody>
</table>

*p = 0.0005 by logistic regression with multivariate analysis.
Odds ratio: 15.0 (95% confidence interval [CI]: 1.9 to 74).
Rate ratio = 3.75 (95% CI: 1.3 to 10.9).
* Alive with no evidence of ACC or dead of another cause with no evidence of ACC.
† Dead of ACC or alive with ACC (n = 1).