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# Management of Adenoid Cystic Carcinoma of the Head and Neck: Experience of the National Cancer Institute, Egypt

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## Abstract

**Purpose:** This study presents the experience of the National Cancer Institute, Cairo University, in diagnosis and management of ACC of the head and neck.

**Methods:** This is a retrospective review of 57 patients with ACC managed during the period from January 2011 to January 2016. Data about the characteristics and management of the disease were recorded. All patients were followed up to detect the development of local recurrence and distant metastasis and their management.

**Results:** The mean age was  $45.5 \pm 15.1$ , with a female-to-male ratio of 1.5:1. The minor salivary glands were affected in 61.4% of cases. Four patients (7%) were metastatic at presentation. The main presenting symptom was swelling, followed by pain. Surgical resection was performed in 48 patients (84.2%) followed by adjuvant

radiotherapy in 36 of them. Four patients received radical radiotherapy. Treatment failed in 3 patients. Recurrences were recorded in 21 out of the 50 cured patients; 9 had locoregional recurrence, 9 had distant metastases, and 3 had both. The overall survival (OS) and disease-free survival (DFS) at three years were 79% and 57.1%, respectively. Surgical resection improved OS ( $p < 0.001$ ). Advanced T-stage, lymph node invasion, solid tumors, close or positive margins worsened OS. Adjuvant radiotherapy was associated with better DFS ( $p = 0.003$ ), while solid tumors were associated with worse DFS.

**Conclusion:** Despite aggressive management with radical surgery and adjuvant radiotherapy, recurrence affects 42% of the patients within three years. Patients with unresectable tumors have a poor prognosis. Adjuvant radiotherapy improves DFS but not OS.

**Keywords:** adenoid cystic – radiotherapy – surgery – carcinoma – neck dissection

## Introduction

Adenoid cystic carcinoma (ACC) is a rare tumor accounting for nearly 1% of all head and neck malignancies<sup>[1]</sup> and about 10% of salivary glands tumors<sup>[2]</sup>. It has also been described in many other organs, including the lacrimal glands<sup>[3]</sup>. ACC of the head and neck has a unique behavior with complicated clinical course and vague etiology<sup>[4]</sup>. It is a slowly growing, but greatly infiltrative and permeative malignancy characterized by perineural invasion and multiple local recurrences<sup>[5]</sup>. Treatment to prevent developing recurrence and metastatic disease remains a challenge. Effective therapy is not yet standardized. However, radical excision and adjuvant radiotherapy are mainly employed for loco-regional control in the early stages of ACC<sup>[4]</sup>.

## Patients and methods

This retrospective study was conducted at the Surgical Oncology Department of the National Cancer Institute (NCI), Cairo University. The study included 57 patients with ACC of head and neck treated during the period from January 2011 to January 2016. The median follow-up period was 35 months (range: 5–81 months). The study included all patients with local or metastatic ACC of the head and neck of any age and both sexes. Patients who underwent surgery outside the NCI were excluded from the study.

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The medical records for all patients were revised to extract the following data: demographic features, stage at presentation, site of the primary tumor, presenting symptoms, findings of physical examination, and results of investigations. Data about the management of tumors, including surgery, radiotherapy (RT), and systemic therapy and the results of the pathological examination of the surgical specimens were recorded. All patients were followed up to detect the development of local recurrence and distant metastasis and their management. The overall survival (OS) was calculated from the date of diagnosis to date of death or the last follow-up visit. The disease-free survival (DFS) was calculated from the date of surgery or end of radical RT till the date of recurrence (either locoregional recurrence or distant metastases), death, or last follow-up.

## Results

The age of the patients ranged from 8 to 80 years, with a mean of  $45.5 \pm 15.1$  years. Twenty-one patients (36.8%) were older than 50 years. Females constituted 59.6% of the patients (n=34). Eighteen patients (31.6%) were smokers, 11 (19.3%) were hypertensive, and 6 (10.5%) were diabetic. None of the patients reported a history of previous irradiation. Four patients (7%) were metastatic at presentation. The primary disease site is shown in **table 1**. The main presenting symptom was swelling, followed by pain. Nearly half of the cases were radiologically classified as T-stage 2.

## Management:

Forty-eight patients (84.2%) had surgical resection of the tumor, and only 13 (22.8%) had neck dissection. Adjuvant RT was administered to 36 of patients who had surgery. Also, four patients received radical RT, and 3 received palliative RT. Ten patients received chemotherapy either as adjuvant chemoradiation (n=5), concomitant with radical RT (n=1), palliative with RT (n=2), and palliative for metastatic disease (n=2). Cisplatin was the primary regimen either alone or combined with Taxotere and fluorouracil. **Table 2** shows Tumor and nodal stage, histological features, margins and perineural invasion in 57 cases of ACC. **Table 3** shows adverse events of RT in 26 patients.

In addition to the four patients who were metastatic at presentation, three more patients had persistent disease despite treatment. These three patients included one with a T4a tumor of the maxilla and two patients with T4b tumors of the maxilla and nasopharynx. Recurrences were recorded in 21 out of the 50 cured patients (42%); 9 had locoregional recurrence, 9 had distant metastases, and 3 had both **Table 4**, Nine patients underwent

resection of the recurrent lesion (including lobectomy for lung metastases); 5 of them received adjuvant RT. Two patients received palliative RT for bone metastases and locally advanced recurrence, 5 received chemotherapy and five received best supportive care.

		Frequency	Percentage
Primary Site	Major salivary glands	17	29.8
	Parotid	10	17.5
	Submandibular	5	8.8
	Sublingual	2	3.5
	Minor salivary glands	35	61.4
	Maxillary sinus	16	28.1
	Oral cavity	16	28.1
	Nasopharynx	2	3.5
	Nasal mucosa	1	1.8
	Lacrimal gland	5	8.8
Symptoms	Swelling	49	86.0
	Pain	8	14.0
	Proptosis	2	3.5
	Nasal obstruction	4	7.0
	Visual defect	2	3.5
Clinical stage at presentation	Localized disease	53	93.0
	Metastatic disease	4	7.0
Initial Tumor stage	T1	4	7.0
	T2	29	50.9
	T3	9	15.8
	T4a	13	22.8
	T4b	2	3.5
Initial Nodal Stage	N0	40	70.2
	N1	6	10.5
	N2b	8	14.0
	N2c	3	5.3

**Table 1:** Primary site of the tumor, symptoms, and initial stage of the studied group (n=57)

Pathology		Frequency	Percentage
Histological Pattern	Cribriform	27	47.4
	Solid	23	40.4
	Tubular	7	12.2
Tumor stage	T1	3	6.3
	T2	20	41.7
	T3	17	35.4
	T4a	8	16.7
Histological Grade	G1	4	7.0
	G2	43	75.4
	G3	10	17.6
Nodal stage	No neck dissection	35	72.9
	N0	8	16.7
	N1	1	2.1
	N2	4	8.3
Margin status Positive perineural invasion	Free	20	41.7
	Close	4	8.3
	Positive	24	50.0
		38	79.2

**Table 2:** Tumor and nodal stage, histological features, margins and perineural invasion in 57 cases of ACC

Type of complications	Frequency	Percentage
Mucositis	21	80.8
Conjunctivitis	4	15.4
Dysphagia	3	11.5
Oral infection	3	11.5
Xerostomia	3	11.5
Trismus	2	7.7

**Table 3:** Adverse events of RT in 26 patients

## Survival analysis:

The median follow-up period was 35 months (range: 5–81 months). At the end of the study, 21 patients died, and 21 developed recurrences out of the 50 successfully treated patients; 7 patients developed recurrence within one year, eight between 1–2 years, and six patients after two years. The median OS was 63 months. The cumulative OS at three years was 79%. DFS at three years was 57.1%. Surgical resection positively affects OS ( $p < 0.001$ ). OS worsened by T-stage 4, lymph node invasion, solid histological type, close or positive margins **Table 5**. Adjuvant RT was associated with better DFS ( $p = 0.003$ ), while solid tumors were associated with worse DFS ( $p < 0.001$ ).

Type	Frequency	Percentage
Locoregional recurrence	12	
Local	10	83.3
Nodal	2	16.7
Distant metastases	12	
Lung	5	41.7
Liver	2	16.7
Brain	3	25.0
Bone	1	8.3
Lung + Liver	1	8.3

**Table 4:** Site of recurrence in 21 patients

## Discussion

This study demonstrated that the mean age at diagnosis of ACC was 45.5 years with female preponderance. 27 patients (47.4%) were in the 5th and 6th decades. However, three patients (5.7%) were  $\leq 20$  years old. The mean age was less than other large series in the literature, reporting a mean age between 57 and 62 years<sup>[6–8]</sup>. It is known that all age groups are affected by ACC, but the higher frequency is encountered in middle-aged and older patients; the 5th and 6th decades are the most commonly affected<sup>[9]</sup>. The female to male ratio in this study was 1.5:1. Ellington et al. reported a female to male<sup>[6]</sup>. Ko et al. found a 2:1 female to male ratio<sup>[9]</sup>. On the contrary, Andrade et al. reported no gender predilection in ACC of the maxillary sinus<sup>[10]</sup>. In general, literature is inconsistent concerning sex predominance of ACC<sup>[11]</sup>.

In the current study, 61.4% of the patients had tumors of the minor salivary glands, mainly in the maxillary sinus and oral cavity. ACC is considered the most common malignant tumor of minor salivary gland<sup>[12]</sup>. Minor salivary glands were the primary site in 56% of cases in a single-center analysis of 105 cases from the Netherlands with similar proportion reported by Shultz et al.<sup>[13]</sup>. Conversely, an extensive study of 2286 primary ACCs of the head and neck found that major salivary glands were more commonly affected than minor glands<sup>[14]</sup>.

Swelling was the most common presenting symptom in this series encountered in 86% of cases, which is consistent with the literature. It has been shown that regional lymph node metastasis is generally rare<sup>[15]</sup>. However, 7% of the patients were metastatic at presentation. Usually, a small proportion of patients present with distant metastasis. Radical excision with adjuvant radiotherapy is the primary locoregional control modality of early disease stages. However, obtaining disease-free margins is generally not achieved due to

	n	No. of events	p-value
Whole group	57	21	
Age groups			
≤50 years	36	14	0.744
>50 years	21	7	
Gender			
Male	23	7	0.683
Female	34	14	
Primary site			
Lacrimal gland	5	3	0.234
Major salivary	17	3	
Minor salivary	35	15	
Surgery			
No	9	8	<0.001
Yes	48	13	
Margins			
Free	20	2	0.050
Positive + close	28	11	
Perineural invasion			
No	19	4	0.058
Yes	38	17	
Pathological grade			
Grade 1,2	47	15	0.153
Grade 3	10	6	
Histological type			
Cribriform	27	5	0.003
Solid	23	16	
Tubular	7	0	
Overall T stage			
T1+T2	26	9	0.017
T3	17	5	
T4	14	7	
Lymph nodes			
Negative	48	15	0.042
Positive	9	6	
Radiotherapy			
No	14	5	0.994
Yes	43	16	

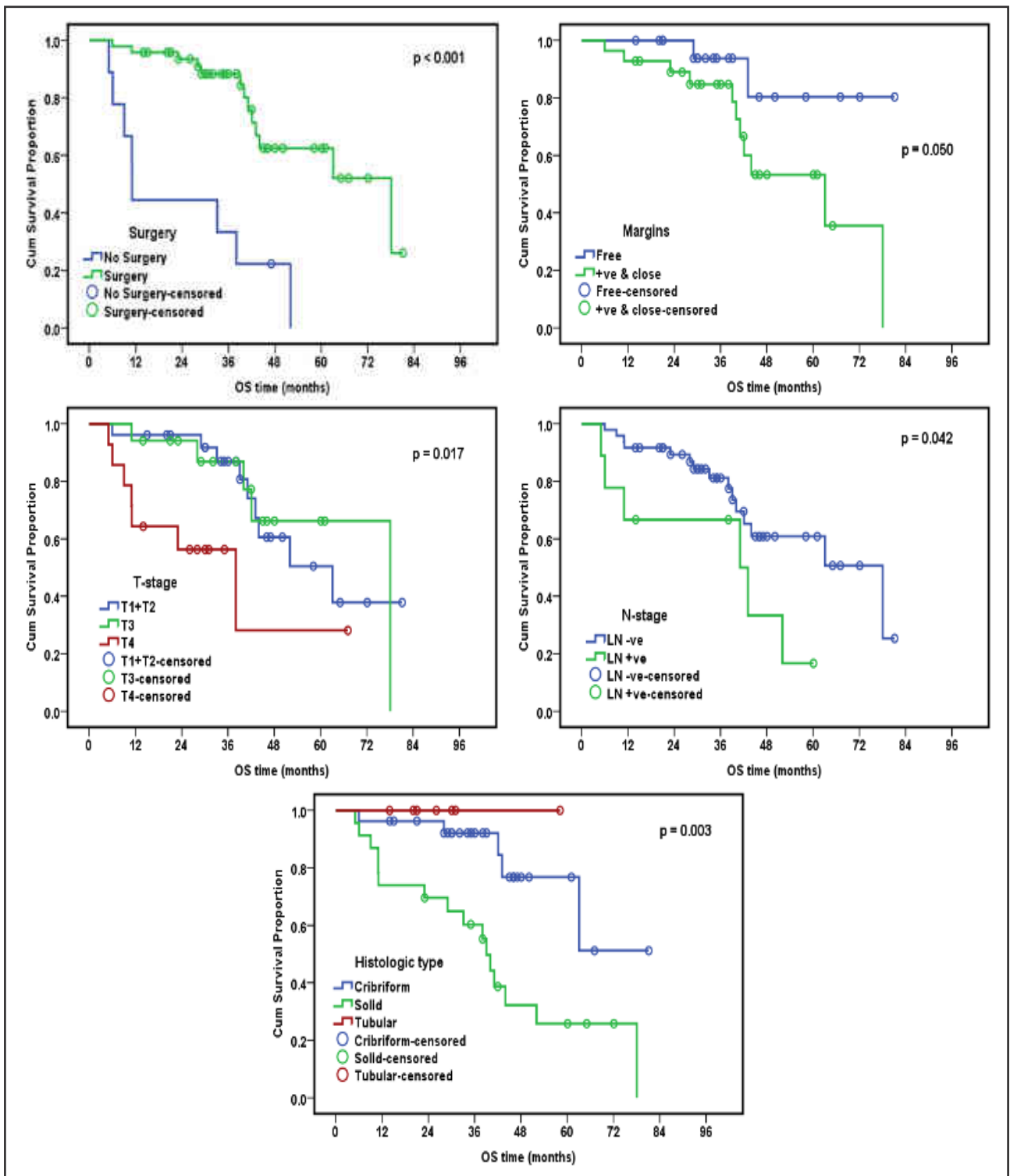
**Table 5:** OS in relation to the prognostic factors

difficult anatomical access of some lesions and frequent tendency to perineural invasion<sup>[16]</sup>. In the current study, 84.2% of the patients were managed by surgical resection; 75% of them received adjuvant radiotherapy. Only 13 patients (22.8%) had neck dissection. It is worth to note that 70% of the patients were clinically evaluated as N0 stage. Traditionally, cervical lymph node metastasis is considered uncommon in ACC. It was reported to occur in 4%–33% of patients<sup>[17–19]</sup>. Recent research found that primary tumor site, lymphovascular invasion, and T-stage were associated with nodal metastasis<sup>[20,21]</sup>. Minor salivary glands have a higher rate of neck lymph node metastases than major glands. A recent meta-analysis found a pooled frequency of cervical lymph node occult metastases of 14%. As the standard for elective neck dissection is 15–20%, it is unnecessary to be performed for all patients with ACC of the head and neck<sup>[22]</sup>. By the end of the follow-up, 21 out of the 50 cured patients (42%) developed recurrences. The number of locoregional and distant metastases were equal.

The OS and DFS at three years were 79% and 57.1%, respectively. Surgical resection positively affects OS ( $p < 0.001$ ). Adjuvant RT was associated with better DFS ( $p = 0.003$ ), but not with OS. While solid tumors were associated with worse DFS. This finding is consistent with previous studies. Adjuvant RT is recommended for patients with risk factors for recurrence as high grade, positive margins, perineural or lymph vascular invasion, and nodal metastasis<sup>[23]</sup>. However, the role of adjuvant RT remains controversial. Similar to our findings, excellent local control with surgery and postoperative RT has been reported<sup>[24–26]</sup>. However, Katz et al.<sup>[27]</sup> indicated that postoperative RT could delay rather than prevent local recurrence. In the same line, Adelstein et al.<sup>[28]</sup> suggested that RT may achieve tumor reduction, and in cases of unresectable tumors, it may be used as a palliative. ACC is considered by many authors, a clinically high-grade tumor. However, its prognostic factors are fairly variable and inconsistent across studies.

In the current study, solid tumors were associated with worse OS and DFS compared to cribriform and tubular histological types. These results are consistent with previous reports that solid tumors were related to higher recurrence, early distant metastases, and higher mortality<sup>[29]</sup>.

Other factors affecting OS in this study were advanced stage, nodal invasion, and close or positive margins. These findings are in agreement with previous studies<sup>[30]</sup>. In the head and neck, the positive surgical margin in ACC is a poor prognostic factor. However, the effect of close margins, i.e., tumor-free margins of less than 5 mm, is controversial<sup>[7]</sup>. A recent study found positive margins as

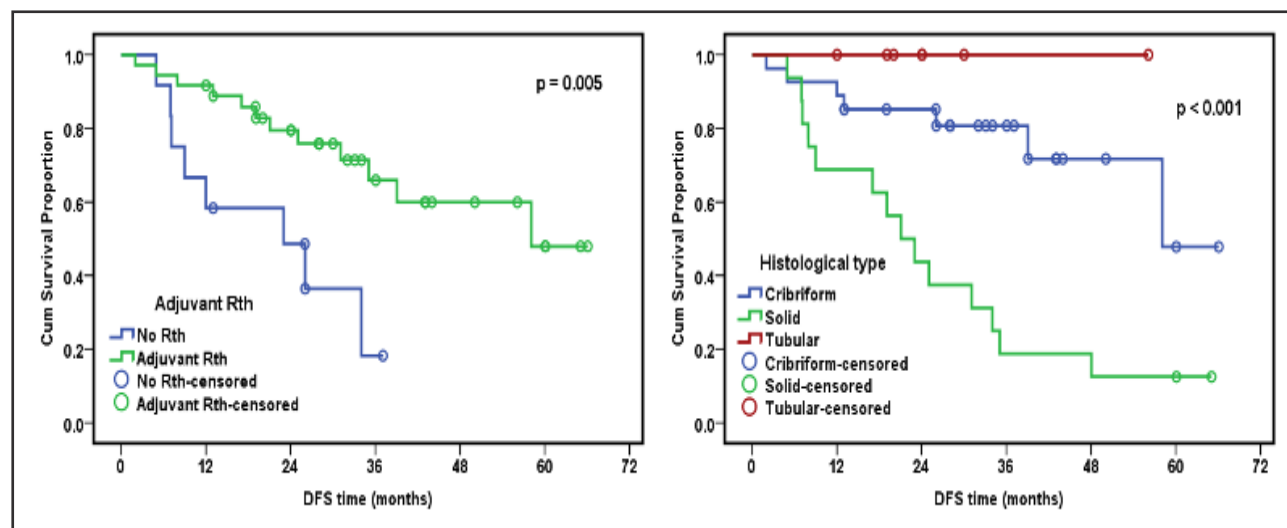


**Figure 1:** Relation of OS with surgery, condition of surgical margins, T–stage, nodal status, and histological type

an independent factor associated with worse outcome, but patients with close margin have a similar OS and DFS as those with negative margins<sup>[30]</sup>. Unfortunately, in the current study, we couldn't analyze close margin as a separate category because only 4 cases were classified as close margin.

## Conclusion

ACC of head and neck is commonly encountered in the 5th–6th decades of life with female preponderance. It affects mainly the minor salivary glands. Despite aggressive management with radical surgery and adjuvant radiotherapy, recurrence affects 42% of the patients within three years. Patients with unresectable



**Figure 2:** Relation of DFS with adjuvant RT and histological type

tumors have a poor prognosis. Adjuvant RT improves DFS but not OS. Advanced stage, lymph node invasion, solid histological type and close or positive margins worsen OS, while solid tumors were associated with worse DFS.

## Funding and Conflict of Interest

This study don't receive any fund and there is no conflict of interest

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