

## Case series



# Adenoid cystic carcinoma of the breast

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## Adenoid cystic carcinoma of the breast

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## Abstract

*Adenoid cystic carcinoma (ACC) is a rare histological form of the breast cancers. Due to the rarity of this type of carcinoma, the therapeutic management strategy still controversial. A retrospective study reporting data concerning five patients with breast ACC diagnosed between 1993 and 2017. Cases were reviewed for age at diagnosis, clinical, radiological and histological tumour presentation, type of treatment and treatment outcomes. Out of a total of 3066 breast cancer patients, 5 patients had breast ACC (0.1%). The median age at diagnosis was 46 years (range 26-57 years). A palpable mass was the common presenting symptom in all cases. No patient had clinical evidence of regional lymph node*

*metastases and staging investigations showed no evidence of metastatic disease. All patients underwent primary surgery with ipsilateral axillary lymph node dissection in 3 cases. Adjuvant chemotherapy was performed in two patients and postoperative radiotherapy in all cases. Tamoxifen-based hormonal therapy was administered in an only patient who had positive hormonal receptors. After a median follow-up of 107 months, the overall mean survival was 106.8 months and the average disease-free survival was 97.8 months. Breast ACC has a low propensity for local recurrence after excision despite triple negative nature. Since the frequency of axillary lymph node metastases is very low, we suggest that lymphadenectomy is to be avoided in this type of tumour. Adjuvant radiotherapy remains a standard treatment after conservative surgery.*

## Introduction

Adenoid cystic carcinoma (ACC) is a rare histological form that occurs mainly in the salivary glands. Other sites have also been reported including the cervix, skin, aerodigestive tract, breast and Bartholin's glands with an incidence of 0.1% of all breast cancers [1,2]. The ACC of the breast affects on the whole women between the fifth and sixth decade of life but can be observed in women between 19 and 94 years [1,3,4]. Due to the rarity of this type of carcinoma, the diagnostic and prognostic features as well as the therapeutic management guidelines have not been clearly established. Unlike extra-mammary ACC, breast ACC is usually a localized neoplasm. It has mostly an excellent prognosis and it is a slow growing tumour often without any lymph node involvement [5]. This study aims at detailing the epidemiological, anatomoclinical and prognostic particularities; analyzing therapeutic results and reviewing the literature to determine the best treatment for this form of carcinoma.

## Methods

This retrospective study reports data concerning five patients with breast ACC diagnosed and treated in the department of oncology radiotherapy of the Habib Bourguiba university hospital, Sfax, Tunisia, between 1993 and 2017. Cases were reviewed for age at diagnosis, clinical, radiological and histological tumour presentation, type of treatment and treatment outcomes (overall survival and disease free survival). All tumours were classified according to the 7<sup>th</sup> edition of the TNM / UICC 2009 classification of breast cancers. For patients treated before 2009, staging was updated from previous clinical descriptions to fit the new classification. Follow-up was calculated from the date of the histological diagnosis. All data have been updated on 12/31/17.

## Results

Out of a total of 3066 breast cancer patients, only 5 patients had breast ACC (0.1%). The majority of patients (n=4) were less than 50 years old with a median age at diagnosis of 46 years (range 26-57 years). Three patients had no prior family history of breast cancer or personal history of breast malignancies. A palpable mass was the common presenting symptom in all cases. No patient had clinical evidence of regional lymph node metastases at the time of the initial treatment. Preoperative ultrasound-mammography was performed in all cases. An opacity with circumscribed margins and homogeneous density was observed in the majority of cases (n=3). Diffuse microcalcifications were associated in only one case. Staging investigations were performed and showed no evidence of metastatic disease. The tumour was classified T2 in the majority of cases (n = 4) (Table 1).

All patients underwent primary surgery, consisting of mastectomy in 4 patients and lumpectomy in one patient. Ipsilateral axillary lymph node dissection was performed in 3 cases which revealed negative in all cases. The Bloom Richardson grade

was I in three cases and II in one patient. Hormonal receptor status was assessed in all cases and was negative in 4 patients. The analysis of HER-2 expression was carried out in three patients and was negative in all cases. The complementary immunohistochemical study to identify other markers was conducted in two patients (Table 2). Adjuvant chemotherapy was performed in two patients. Postoperative radiotherapy was indicated in all cases. The average radiotherapy dose was 56 Gy in standard spreading and fractionation (range 50-66 Gy). A hormonal therapy for 5 years was performed in the only case of ER/EP+ disease. After a median follow-up of 107 months, 4 patients were alive, in complete remission. Only one patient had pulmonary, hepatic and cerebral distant metastases 10 months after the end of radiotherapy. Mean overall survival and mean recurrence-free survival were each 106.8 months (range 57-156.5 months). Mean distant metastases-free survival was 97.8 months (range 21-156.5 months).

## Discussion

ACC of the breast represents approximately 0.05 to 0.1% of breast cancers [3,6]. Although it is a predominantly female carcinoma, a few cases have been reported in men [4,7]. The average age is 61 years, but this type of carcinoma can be seen even in patients between 19 and 94 years old [1,4,6]. It is exceptionally observed in premenopausal women [3]. In our series the patients were younger with a median age of 46 years and the majority were premenopausal. The most common presenting symptom is a well-circumscribed palpable mass within the breast and often located behind the nipple or in the upper outer quadrants [1,8,9]. Imaging characteristics are nonspecific and may suggest benign breast diseases. On mammography, the disease can present as a lobulated mass with circumscribed or irregular margins. Calcifications are rarely observed. Ultrasound features are those of a regular or irregular, heterogeneous or hypoechoic solid mass [1,9]. This is in agreement with our

results: there was an opacity with circumscribed margins and homogeneous density in the majority of cases (n=3). Diffuse microcalcifications were associated in only one case. ACC of the breast is usually defined as a triple negative carcinoma. Though triple negative breast cancers are aggressive forms, breast ACC, has a slow growth with an excellent prognosis [4]. In our series, hormonal receptor status was negative in 4 patients and HER-2 expression was negative in all cases. The complementary immunohistochemical study to identify other markers was performed in two patients: it was negative in both cases for C-kit, positive for E-cadherin in one case and positive for P63 in the other. According to Mastropasqua *et al.* the nuclear immunoreactivity of the breast ACC for C-kit, E-cadherin and P63 was 95%, 90% and 85%, respectively [10]. Grading of breast ACC is based upon the proportion of cystic and solid cell components as applied to its salivary counterpart: the tumour is classified grade 1 in case of absence of solid components; grade 2 when it contains less than 30% of solid components; and grade 3 if the solid component accounts for more than 30% of tumor volume [11].

ACC does not typically spread via the lymphatic route, and consequently, regional lymph nodes are rarely involved, representing only 0.8% (according to Sumpio *et al.*) [12], 1.7% (as stated by Arpino *et al.*) [4] and 6.7% (on the authority of McClenathan *et al.*) [1]. There were no cases of axillary lymph node metastasis in our study. The optimal treatment of breast ACC is still controversial. There is no standard for the surgical treatment. The indications are similar to those of breast carcinomas. Retrospective studies reported high rates of local relapses after conservative breast surgery: Sumpio *et al.* showed that among 8 patients with local recurrence, 6 underwent lumpectomy [12]. In Leeming *et al.* study, 9 (37%) of 24 patients treated with conservative surgery had local recurrence [13]. Since the frequency of axillary lymph node metastases is very low, some authors suggest that lymphadenectomy is to be avoided in this type of tumour. The sentinel lymph node technique seems to be a good option for

some patients [14]. The benefit of adjuvant radiotherapy after conservative surgery of breast carcinomas was proven with a 10-year local recurrence risk reduction of 15.4% for N- and 21.2% for N+ and a benefit in terms of specific survival of around 8.5% at 15 years [15]. Three trials showed that elderly patients with good-prognosis breast cancer without nodal involvement and hormone receptors may not benefit from adjuvant radiotherapy after conservative surgery, in terms of local control [16-18]. However, there were no subgroup studies based on histological types. Despite the excellent prognosis and the rarity of this histological entity, radiotherapy remains a standard treatment after conservative surgery of breast ACC.

Although many authors recommend adjuvant chemotherapy combining cyclophosphamide, anthracyclines and 5-fluorouracil, in patients with high-grade breast ACC and/or lymph node or distant metastases, its benefit for this type of breast cancer is still controversial. Arpino *et al.* suggested that there would be no difference in survival between patients who received postoperative chemotherapy and those who did not receive chemotherapy [3]. Given the rarity of this type of histological breast cancer and its triple negative nature, the benefit of hormonal therapy has not been studied. In our study, surgical treatment consisted of radical mastectomy in 4 patients and conservative surgery in a one patient. Axillary ipsilateral dissection was performed in 3 patients. Adjuvant chemotherapy was administered in two patients and postoperative radiotherapy was indicated in all cases. Tamoxifen-based hormonal therapy was administered for 5 years in the only patient who had positive hormonal receptors. Although it is most often a triple negative cancer, ACC of the breast has a favourable prognosis with a local recurrence rate of about 3-18% and 5-year survival rates >90% [5,19]. In another 40-year institutional journal, Millar *et al.* reported a 10-year local recurrence rate of 31%, a 5-year and a 10 year overall survival of 88% and 75%, respectively [4] (Table 3). However, distant metastases and late

recurrences may happen, suggesting a longer-term follow-up. The most common metastatic site is the lung followed by the bones, liver and kidneys [20]. After a median follow-up of 107 months, the overall mean survival was 106.8 months and the average disease-free survival was 97.8 months.

## Conclusion

Breast ACC is a rare histological form of breast cancers. The clinico-radiological appearance may suggest benign breast disease. It is generally a triple negative carcinoma but has a slow growth with an excellent prognosis. In the absence of prospective studies, there are still no standards for the treatment of breast ACC. Larger studies would better define an optimal strategy for the management of this type of cancer and improve disease free survival.

### *What is known about this topic*

- *Adenoid cystic carcinoma is a rare histological form of the breast cancers;*
- *Due to the rarity of this type of carcinoma, the therapeutic management strategy still controversial.*

### *What this study adds*

- *Breast adenoid cystic carcinoma has a low propensity for local recurrence after excision despite triple negative nature;*
- *Since the frequency of axillary lymph node metastases is very low, lymphadenectomy is to be avoided in this type of tumour;*
- *Despite the excellent prognosis, adjuvant radiotherapy remains a standard treatment after conservative surgery.*

## Competing interests

The authors declare no competing interests.



## Authors' contributions

All the authors contributed to the conduct of this work. All authors also state that they have read and approved the final version of the manuscript.

## Tables

**Table 1:** patients' characteristics and clinical features of the tumours

**Table 2:** pathological features of tumours

**Table 3:** a review of the literature survival outcomes of breast ACC

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**Table 1:** patients' characteristics and clinical features of the tumours

Patient	Age (years)	Sex	Site	Menopausal status	Tumoral site	Clinical symptoms	TNM* classification
1	26	F	Right breast	Premenopausal	UOQ	Palpable mass	T4b N0 M0
2	57	F	Right breast	Postmenopausal	UOQ	Palpable mass + pain	T2 N0 M0
3	46	F	Left Breast	Premenopausal	LIQ	Palpable mass	T2 N0 M0
4	49	F	Right breast	Premenopausal	RN	Palpable mass	T2 N0 M0
5	41	F	Right breast	Premenopausal	UOQ	Palpable mass	T2 N0 M0

\*: 7th edition of the TNM / UICC 2009 classification of breast cancers. OQ: union of outer quadrants, LIQ: lower inner quadrant, RN: retro-nipple, F: female

**Table 2:** pathological features of tumours

Patient	Histological tumour size (cm)	Margins	SBR Grade	VI	PNI	ER	PR	HER-2	c-kit	P63	E-cadhine
1	4.5	Negative	2	-	-	-	-	-	-	-	+
2	2.5	Negative	2	-	-	+	+	-	NP	NP	NP
3	4	Negative	1	-	-	-	-	NP	-	+	-
4	1	Negative	1	-	-	-	-	NP	NP	NP	NP
5	5.4	Negative	1	-	-	-	-	-	NP	NP	NP

PNI: Perineural Invasion, VI: Vascular Invasion, NP: Not Performed, ER: Oestrogen Receptor, PR: Progesterone Receptor

**Table 3:** a review of the literature survival outcomes of breast ACC

Study	Period of the study	Number of patients	Treatment	Survival
Arpino <i>et al.</i>	1970-1998	28	BS: 78.6% BS + adjuvant RT : 21.4% <b>Type of BS : M :</b> 78.5% CS : 21.5%	5-year OS : 85% 5-year DFS : 100% 10-year DFS : 93.8%
Millar <i>et al.</i>	1960-2000	19	BS: 52.7% BS + adjuvant RT : 47.3% <b>Type of BS : M :</b> 47.3% CS : 52.7%	5-year OS : 88% 10-year OS : 75% 5-year DFS : 82% 10-year DFS : 46%
Li <i>et al.</i>	1973-2008	696	BS: 67.7% BS + adjuvant RT : 30.7%	<b>localized stages:</b> SS 5ans : 96.8% SS 10 ans : 94% <b>Loco-regionally advanced stages:</b> 5-year SS : 78.5% 10-year SS : 75.4% <b>Metastatic stages:</b> 5-year SS : 15.9% 10-year SS : 15.9%
Ghabach <i>et al.</i>	1977-2006	338	BS: 70% BS + adjuvant RT : 30%	5-year OS : 98.1% 10-year OS : 94.4%
Khanfir <i>et al.</i>	1980-2007	61	BS: 34% BS + adjuvant RT : 66% <b>Type of BS : M :</b> 33% CS : 67%	5-year OS : 82% 10-year OS : 74% 5-year DFS : 94% 10-year DFS : 86%
Our study	1993-2018	5	BS + adjuvant RT : 100% <b>Type of BS : M :</b> 80% CS : 20%	Mean OS : 106.8 mois Mean DFS : 97.8 mois

BS: breast surgery, M: mastectomy, CC: conservative surgery, RT: radiotherapy, OS: overall survival, SS: specific survival, DFS: disease-free survival.