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Original Article

The effect of first line chemotherapy on adenoid cystic carcinoma of breast

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Abstract: Objective: There is no consensus on the use of chemotherapy for patients with adenoid cystic carcinoma of the breast to date. The aim of this retrospective study was to assess the effect of first line chemotherapy on ACC of the breast. Methods: Twenty (0.22%) cases of ACC of the breast were treated in our center between January 2005 and December 2015; 16 of which received 8 cycles of epirubicin based regimen followed by a taxane based regimen neoadjuvant chemotherapy (NAC). The clinical and pathological response of ACC to chemotherapy was investigated and compared with 64 invasive ductal carcinoma (IDC) patients. Results: All 16 cases of ACCs of the breast were ER, PR and HER2 negative, while 2 ACCs had axillary metastasis. Sonographic response in all ACCs showed stable disease (SD) as compared to those in 15 of 64 IDCs ($P<0.01$). After surgery, the pathological response in 13 ACCs was Miller and Payne (MP) grade I as compared to that in one IDC ($P<0.01$). After a median follow-up of 77 months, the 10-year disease-free survival (DFS) was 81.3% in ACCs and 83.4% in matched IDCs ($P=0.938$). The 10-year breast cancer-specific survival (BCSS) was 77.8% in ACCs and 87.7% in matched IDCs ($P=0.745$). Conclusion: ACCs of the breast has a good prognosis. ACC patients were not responsive to chemotherapy.

Keywords: Adenoid cystic carcinoma, breast, neoadjuvant chemotherapy

Introduction

ACC of the breast is a rare subtype of primary breast cancers, accounting for <0.2% of all the breast cancers [1, 2]. ACC is often a triple-negative breast cancer usually characterized as an indolent cancer with favorable outcomes [3, 4]. Surgery with or without radiotherapy is the most recommended treatment. Whether or not chemotherapy should be used in ACC patients is still controversial. We found that 3%-66% of breast ACCs patients received adjuvant chemotherapy in previous studies [4-7]. Because of the rarity of the tumor, there was lack of high-level evidence to demonstrate that ACC patients treated without chemotherapy were not worse off than those with chemotherapy. Furthermore, when distant metastases occurred, chemotherapy was the only systemic treatment used, because of its triple negative subtype. It is necessary to find the real effect of chemotherapy on ACC patients. NAC is the most direct method to test drug sensitivity, and according to previous studies, postoperative pathological evaluation is a good surrogate to survival outcomes of non-specific triple negative breast cancer. Therefore, we retrospectively reviewed the ACC and matched IDC patients who received NAC, and compared the differences in response of chemotherapy and survival outcome between these two groups.

Patients and methods

Study patients

This retrospective study was approved by the review board of Beijing cancer hospital. We reviewed all breast cancer patients between January 1, 2005 and December 1, 2015, with a total of 8,946 breast cancer patients that were treated at our center, 20 (0.22%) patients had ACC, 16 of whom received NAC. The clinicopathological characteristics of 16 ACC patients were retrospectively reviewed and compared with 64 IDC patients (grade 1 or 2) These ACCs and IDCs samples were reviewed by a pathologist with more than 8 years of experience in breast pathology.

Table 1. Characteristics of ACCs and matched IDCs

Characteristics	ACCs (N=16)	1:4 matched IDCs (N=64)
Age (years)	54.6 (35-77)	58.2 (40-78)
<50	7 (43.7%)	28 (43.7%)
≥50	9 (56.3%)	36 (56.3%)
Tumor size	2.3 (1.2-5.7)	2.5 (1.5-5.4)
T1	7 (43.7%)	28 (43.7%)
T2	8 (50%)	32 (50%)
T3	1 (6.3%)	4 (6.3%)
ER		
Negative	16 (100%)	64 (100%)
PR		
Negative	16 (100%)	64 (100%)
HER2		
Negative	16 (100%)	64 (100%)
LN		
Positive	2 (12.5%)	8 (12.5%)
Negative	14 (87.5%)	56 (87.5%)
Chemotherapy regimen		
4 cycles CEF3w followed by 4 cycles Tq1w	16 (100%)	64 (100%)

Treatment

All of the 16 ACC and 64 IDC patients underwent 8 cycles of NAC. The chemotherapy regimens consist of 4 cycles cyclophosphamide 600 mg/m^2 plus epirubicin 90-100 mg/m^2 plus fluorouracil 600 mg/m^2 every 21 days (CEF q3w), followed by 4 cycles paclitaxel 80 mg/m^2 at days 1, 8, 15 (Tq1w). After completion of NAC, patients either received breast-conserving surgery (BCS) or mastectomy accordingly, and those with positive axillary nodes proved by sentinel lymphnode biopsy (SLNB) or fine needle aspiration (FNA) received subsequent axiliary lymph node dissection (ALND). Patients who underwent BCS received subsequent whole breast radiation.

Clinical and pathological response evaluation

The clinical response of primary tumor after NAC was evaluated by ultrasound (US), which was classified according to the World Health Organization criteria [8]. Complete response (CR) was defined as complete resolution of all the known disease. Partial response (PR) was defined as ≥50% reduction in perpendicular diameters of breast tumor without progression of any lesion or appearance of any new disease and stable disease (SD) as a <50% reduction or a <25% increase. Surgical specimens after NAC were evaluated using MP classification [9]. MP grade 1: no change or reduction in individual malignant cells. MP grade 2: up to 30% loss of tumor cells. MP grade 3: between an estimated 30% and 90% reduction in tumor cells. MP grade 4: >90% disappearance of tumor cells. MP grade 5: complete disappearance of invasive cancer.

Statistical methods

Besides 16 ACC patients, we also reviewed 64 IDC (grade 1 or 2) patients who were treated during the same period, and all these 64 IDCs were matched with TNM stage, age of diagnosis, ER, PR, HER2 expression, and NAC regimen in a 1:4 ratio. The clinical and pathological response of NAC, surgery, radiotherapy, other treatment details and survival outcome were compared between two groups. We used the chi-square or Fisher's exact test for categorical variables, and the log-rank test for survival. Disease-free survival (DFS) was defined as the length of time from the date of diagnosis to the date of first recurrence, or death. Breast cancer-specific survival (BCSS) was defined as the length of time from the date of diagnosis to the date of death due to breast cancer. Statistical analysis was performed using SPSS (version 15.0). For all analyses, a *P*-value of <0.05 was considered to be statistically significant.

Results

The characteristics of patients and tumors were described in **Table 1**. A total of 16 ACC patients who received NAC were recruited in this study. The mean age at diagnosis was 54.6±12.8 (range, 35-77) years. The mean tumor size was 2.3±1.2 (range, 1.2-5.7) cm. ER, PR, and HER2 were negative in all 16 patients. Two (12.5%) patients presented lymph node metastasis, one proved by SLNB and the other proved by FNA, both of them underwent

Table 2. Treatment details of ACCs and matched IDCs

	ACC (N=16)	IDC (N=64)	*P*-value
Axillary staging			0.75
FNA	1 (6.3%)	5 (7.8%)	
SLNB	15 (93.7%)	59 (92.2%)	
Breast operation			0.50
BCS	9 (56.3%)	30 (46.9%)	
Mastectomy	7 (43.7%)	34 (53.1%)	
Axillary node clearance			0.67
Yes	2 (12.5%)	8 (12.5%)	
No	14 (87.5%)	56 (87.5%)	
Sonographic response			<0.01
uSD	16 (100%)	15 (23.4%)	
uPR	0 (0%)	29 (45.3%)	
uCR	0 (0%)	20 (31.3%)	
Pathological response			<0.01
MP Grade I	13 (81.3%)	1 (1.6%)	
MP Grade II	3 (18.7%)	5 (7.8%)	
MP Grade III	0 (0%)	28 (43.7%)	
MP Grade IV/V	0 (0%)	30 (46.9%)	
Adjuvant irradiation			0.50
Yes	9 (56.3%)	30 (46.9%)	
No	7 (43.7%)	34 (53.1%)	

Abbreviations: ACC, adenoid cystic carcinoma; IDC, invasive ductal carcinoma; FNA, fine needle aspiration; SLNB, sentinel lymph node biopsy; BCS, breast conserving surgery.

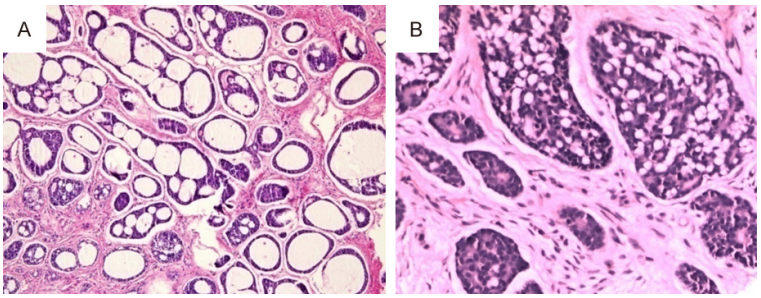

Figure 1. Morphological features of ACC before and after NAC. A. HE (hematoxylin and eosin, ×100) of ACC before NAC. B. H&E (×400) of ACC after NAC with a pathological response of MP grade 1.

subsequent axillary lymph node dissection (ALND).

The differences between ACCs and IDCs after NAC were compared. Except for the response to NAC, no significant difference was observed in other treatment details between the two groups (**Table 2**). Sonographic response in all ACC patients and 15 (23.4%) IDCs was ultrasound stable diseases (uSD) (P<0.01). While pathological response in 13 (81.3%) ACCs was MP grade I, and 3 (18.7%) ACCs were MP grade II, significantly worse than the pathological responses in IDCs, only one (1.6%) IDC was MP grade I and 5 (7.8%) IDCs were MP grade II (P<0.01) (**Figure 1**).

The median follow-up time was 77 (range, 22-184) months for all patients. The details of all the first events were shown in **Table 3**. One lung metastases and 1 axillary metastasis in ACC patients were recorded. These two patients received subsequent palliative chemotherapy. The 10-year DFS was 81.3% [95% confidence interval (CI): 57-99.9%] in ACCs and 83.4% (95% CI: 72.2-94.6%) in matched IDCs (P=0.938) (**Figure 2**); while the 10-year BCSS was 77.8% (95% CI: 50.6-99.9%) in ACCs and 87.7% (95% CI: 76.9-98.5%) in matched IDCs (P=0.745) (**Figure 3**).

Discussion

ACC of the breast is extremely rare among primary breast cancers with specific clinicpathological features. Twenty ACCs of the breast (0.22% of all invasive breast cancers) were identified in our center during the study time, a bit higher than that of a previous study (≤0.2%) [1, 2]. The ACCs of the breast usually presented with the absence of the expression of ER, PR, and HER2, and previous studies showed that only 0-30% ACCs were ER/PR-positive [3, 4, 6, 10]. In this study, all 16 ACCs were triple-negative, consistent with the previous findings. The axillary lymph node metastasis rate was 12.5% among these patients, similar with that reported in other studies (0-8%) [2, 10, 11].

There is no controversy in surgery and radiation therapy in ACC patients. Jodim Coates et al reviewed the Surveillance, Epidemiology, and End Results (SEER) database, 376 ACC patients were included in the study, they found that

Table 3. Details of the first events of ACC and IDC patients

Tumor type	Tumor size	ER	PR	HER2	Nodal stage	NAC	MP grade	Surgery	Time to recurrence (months)	Recurrence site
ACC	2.2	-	-	-	-	CEF3w+Tq1w	1	Mastectomy	35	Lung
ACC	2.1	-	-	-	-	CEF3w+Tq1w	1	Mastectomy	31	Axillary node
IDC	2.6	-	-	-	-	CEF3w+Tq1w	2	BCS	24	Axillary node
IDC	5.4	-	-	-	+	CEF3w+Tq1w	3	Mastectomy	74	Chest wall
IDC	3.7	-	-	-	-	CEF3w	2	BCS	47	Death
IDC	4.1	-	-	-	+	CEF3w+Tq1w	3	BCS	32	Lung
IDC	3.2	-	-	-	-	CEF3w+Tq1w	3	Mastectomy	48	Chest wall
IDC	2.8	-	-	-	-	CEF3w+Tq1w	1	Mastectomy	67	Death
IDC	3.8	-	-	-	-	CEF3w+Tq1w	1	Mastectomy	11	Liver
IDC	3.3	-	-	-	-	CEF3w+Tq1w	3	BCS	69	Axillary node

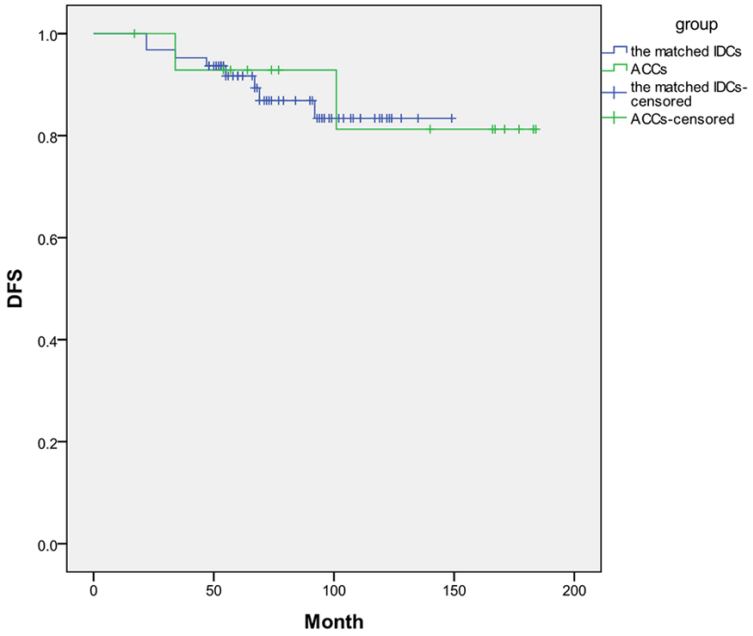

Figure 2. Disease free survival (DFS) and Breast cancer specific survival (BCSS).

adjuvant radiation therapy after BCS for ACC patients improved both BCSS and overall survival (OS) [10]. Two other retrospective cohort studies also proved the benefit of the radiation therapy [4, 12]. All 16 ACC patients in this study underwent BCS with radiation therapy or mastectomy. ALND is only considered in patients with positive lymph nodes [2]. SLNB was performed in 93.7% (15 of 16) ACCs in our study, and only 12.5% patients received ALNB because of proved lymph node metastasis.

The main disagreement about the treatment of ACCs is whether to use chemotherapy or not. In total, 3%-66% of the breast ACCs patients received adjuvant chemotherapy in previous studies [4-7]. What caused such a disagreement? Possibly because ACCs were usually triple negative with a good prognosis. Many studies reported an outcome in patients with ACC with 5-year overall survival exceeding 90% [3-6, 10, 13]. Triple negative subtype in IDCs always comes with the worst prognosis, and this subtype is an independent indicator for the majority of breast cancer patients to use chemotherapy. There was lack of high level evidence to demonstrate the effect of chemotherapy on ACC patients because of its rarity. NAC and pathological evaluation after NAC might show us this effect.

NAC was widely used in triple-negative IDC patients, and the response to NAC had been proposed as a surrogate for predicting long-term survival. Our retrospective data was critical to the effect of chemotherapy on ACCs. The first line chemotherapy for triple negative IDCs was epirubicin or doxorubicin based regimen followed by taxane based regimen. In the current study, 16 ACCs received NAC for 8 cycles CEF q3w followed by Tq1w. The sonographic response of all ACCs was uSD as compared to only 23.4% in IDCs ($P<0.01$). Moreover, a similar significant difference was observed in pathological response, 81.3% ACCs were MP grade I, 18.7% ACCs were MP grade II, and no ACC was MP grade III-V, compared to 9.4% IDCs who were MP grade I or II and 90.6% IDCs who were MP grade III-V ($P<0.01$). MP grade I is defined

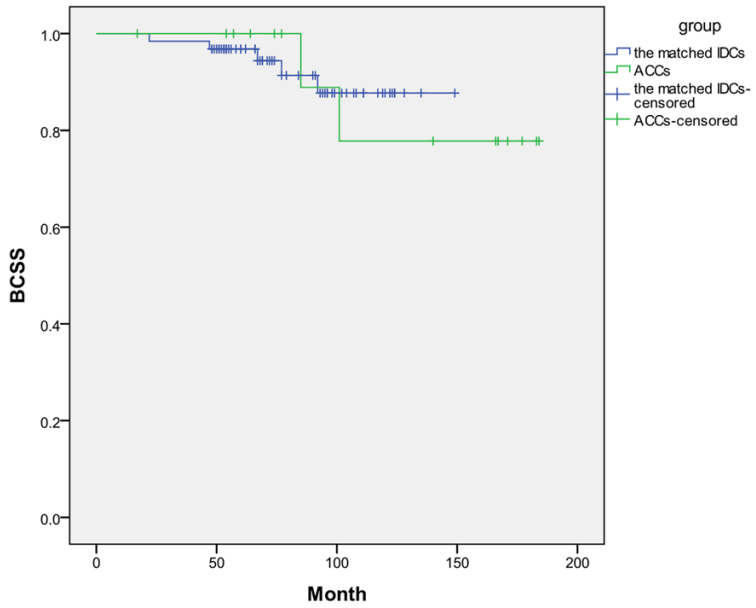

Figure 3. Breast cancer specific survival (BCSS).

as no change or alteration to individual malignant cells and no reduction in overall cellularity; and it is a rare response of invasive breast cancer to chemotherapy. In a prospective randomized clinical trial at our center, only 5.1% of patients had a pathological response of MP grade I to NAC, and none of them presented triple-negative subtype [14]. On the other hand, 81.3% of ACC patients had a pathological response of MP grade I, which was direct evidence for the response of ACCs to first line chemotherapy.

For IDC patients, MP grade V is usually related to superior prognosis of breast cancer, while MP grade I is related to poor prognosis. In the current study, although the majority of ACC patients had a pathological response of MP grade I, the 10-year DFS was 81.3% and BCSS was 77.8%. Comparing to ACCs, only one IDC patient was MP grade I and 46.9% IDC patients were MP grade V, and the 10-year DFS was 83.4% and 10-year BCSS was 87.7%, respectively. There was no significant difference of survival outcome that could be found in the two groups. Two matched pair studies with large samples showed similar results, there was no significant difference in both BCSS and OS as compared to ACC patients and matched IDC patients [15, 16]. However, these two studies didn't mention the effect of systemic therapy on ACCs. In the current study, all the IDC patients with a recurrence or metastasis had a pathological response of MP grade I, II, or III, but no recurrence or metastatic patients was MP grade IV or V, which was the same as reported previously. For I ACC patient, all of them were MP grade I or II, but only 2 presented metastasis. The pathological response of ACC to NAC did not seem to be related to worse DFS and BCSS.

Furthermore, when distant metastases occur, chemotherapy is presently the preferred choice. At present, we can only rely on the experience of treating metastatic ACCs of the salivary glands. In a systemic review about the systemic therapy in the management of metastatic ACCs of the salivary glands, partial objective response was observed in patients who received paclitaxel, gemcitabine, cisplatin and doxorubicin based regimens [17]. Whether these regimens in ACCs of the breast are effective is not clear, we have little experience of the effect of chemotherapy on breast ACCs.

Since ACC is a rare type of primary breast cancer, larger studies are limited to databases and meta-analyses. Our research provided direct evidence that ACCs of the breast weren't responsive to first line chemotherapy. This finding support the consensus of St. Gallen 2011, ACCs didn't require any adjuvant cytotoxic treatment, except for node positive patients [18]. Furthermore, when distant metastases occurs, epirubicin or taxane based regimen may not be the first choice for the patients.

In conclusion, ACCs of the breast had a good prognosis. ACC patients were not responsive to chemotherapy, and the pathological responses of ACC weren't related to long-term survival directly.

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Disclosure of conflict of interest

None.

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