The Breast 66 (2022) 40–48

Contents lists available at ScienceDirect

The Breast

journal homepage: www.journals.elsevier.com/the-breast

Prognosis stratification and postoperative radiation therapy utilization in adenoid cystic carcinoma of the breast

Di Zhang [1], Lixi Li [1], Fei Ma [*]

National Cancer Centre/National Clinical Research Centre for Cancer/Cancer Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing, 100021, China

ARTICLE INFO

Keywords:
Breast
Adenoid cystic carcinoma of the breast
Partial mastectomy
Postoperative radiation therapy
Nomogram
Surveillance
Epidemiology
And end results database

ABSTRACT

Purpose: Adenoid cystic carcinoma of the breast (ACCB) is a rare malignancy with a favorable prognosis. Little information exists regarding the impact of postoperative radiation therapy (RT) on survival outcome in patients with ACCB. This study aimed to evaluate the clinical significance of postoperative RT in ACCB.

Methods: Data of patients with ACCB were extracted from the Surveillance, Epidemiology, and End Results database (2000–2019). Univariate and multivariable Cox regression analyses were performed to identify prognostic factors. In addition, a nomogram model was constructed and internally validated for discrimination and calibration. The value of postoperative RT was respectively accessed in each risk subgroup according to nomogram-deduced individualized score.

Results: A total of 689 eligible patients were included in the analysis. Partial mastectomy was associated with an increased risk of death compared with partial mastectomy plus postoperative RT ($P = 0.020$), but total mastectomy with or without postoperative RT was comparable ($P = 0.624$). Then, in-depth analysis was performed for patients receiving breast-conserving therapy (n = 485, the training set vs. the testing set = 340 vs. 145). Age at diagnosis, histological grade, and T stage were identified as prognostic factors for overall survival (OS) (All $P < 0.05$). A nomogram was constructed to provide predictive accuracy toward individual OS rates of ACCB and to divide patients into different risk subgroups. Notably, compared with non-RT, postoperative RT significantly improved OS in the high-risk subgroup ($P = 0.006$ for the training set, and $P = 0.013$ for the overall population) but not in the low-risk subgroup ($P = 0.807$ for the training set, and $P = 0.293$ for the overall population), suggesting that these patients may be able to exempt from postoperative RT.

Conclusion: A robust and effective nomogram was developed to predict prognosis and assist in treatment decisions in patients with ACCB undergoing partial mastectomy.

1. Introduction

Adenoid cystic carcinoma of the breast (ACCB) is a special pathological type of invasive breast cancer, which is rare in clinical practice, and its incidence is <1% of all breast malignant tumors [1]. Traditionally, triple-negative (TN) subtype has been considered as a high-risk factor, and triple-negative breast cancer (TNBC) has been regarded to have the worst prognosis [2]. Although ACCB often presents as the TN subtype, it is unique in its biologic behavior, clinical features, and therapeutic response [3]. On the one hand, ACCB has a relatively high recurrent rate because of its frequent resection margin involvement [4]; on the other hand, due to its relatively indolent biology, even if local recurrence occurs, more than half of patients can be cured with subsequent mastectomy [5]. Patients with ACCB have an excellent prognosis, with an overall survival (OS) rate of 90–95% at 5–10 years [6].

Surgical resection is generally accepted as the primary treatment; however, no definitive guidelines have been firmly established toward this pathological type of breast cancer. Previous studies have shown that

Abbreviations: ACC, adenoid cystic carcinoma; ACCB, adenoid cystic carcinoma of the breast; RT, radiation therapy; AUC, area under curve; AJCC, American Joint Committee on Cancer; C-index, Concordance index; ER, estrogen receptor; HR, hormone receptor; HER2, human epidermal growth factor receptor 2; IHC, immunohistochemical; OS, overall survival; PR, progesterone receptor; ROC, receiver operating characteristic; TN, triple-negative; TNBC, triple-negative breast cancer; SEER, Surveillance Epidemiology, and End Results database.

* Corresponding author.
E-mail addresses: irisaaron@163.com (D. Zhang), 13552075722@163.com (L. Li), drmafei@126.com (F. Ma).

[1] **Author contributions**: Di Zhang and Lixi Li contributed equally to this work.

https://doi.org/10.1016/j.breast.2022.09.003
Received 26 June 2022; Received in revised form 26 August 2022; Accepted 5 September 2022
Available online 10 September 2022

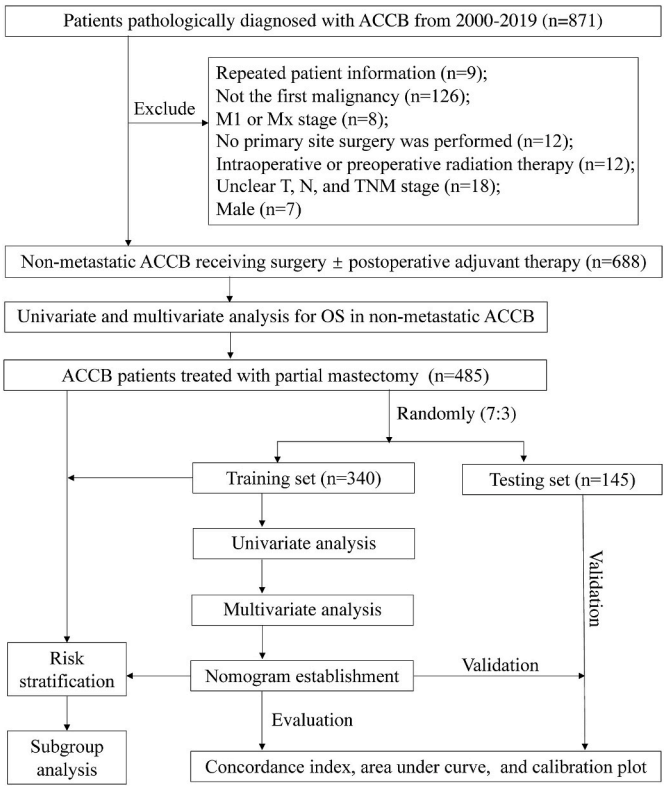

Fig. 1. The flowchart. Abbreviation: ACCB, adenoid cystic carcinoma of the breast; OS, overall survival.

postoperative RT could significantly improve survival outcomes in patients with ACCB, particularly after breast-conserving surgery [7–9]. Besides, Andrew et al. pointed that it is reasonable to consider postoperative RT in patients with negative independent predictors for the treatment of ACCB [10]. Personalized precision therapy has always been a focal topic in cancer treatment. For this rare disease with a favorable prognosis, it may be the optimal option for assessing the value of postoperative RT in therapeutic management. Based on the distinctive characteristics of ACCB, it is worth discussing whether to escalation or de-escalation treatment.

Therefore, we performed this study in a large population to comprehensively assess clinicopathological features, treatment modalities, and survival outcomes in women with ACCB. More importantly, we conducted an in-depth exploration of patients with ACCB receiving breast-conserving surgery with the aim of developing a robust nomogram to predict patient outcomes, perform risk classification, and access the value of postoperative RT. Ultimately, we hope that our findings, along with the literature reviewed, will help determine the optimal management strategies for ACCB.

2. Materials and methods

2.1. Study population

Demographics, clinicopathological features, treatment, and survival information for patients with ACCB from 2000 to 2019 were extracted in the Surveillance, Epidemiology, and End Results database (SEER). As shown in Fig. 1, patients were included if they meet the following criteria: (1) pathologically confirmed ACC, with International Classification of Oncological Diseases ICD-*O*-8200/3; (2) first malignant cancer; (3) the American Joint Committee on Cancer (AJCC) TNM stage was T1-4N0-3M0; (4) surgery of primary site was performed; (5) female breast cancer. In addition, the exclusion criteria comprised the following: (1) repeated medical information; (2) unspecific T, N, M stage; (3) M1

Table 1
General characteristic.

Characteristics	Overall population	
	n = 688	%
Race		
White	563	81.8
Black	70	10.2
Other	55	8
Marital status		
Married	395	57.4
Unmarried	266	38.7
NA	27	3.9
Primary site		
Upper-outer quadrant of breast	240	34.9
Lower-outer quadrant of breast	60	8.7
Upper-inner quadrant of breast	68	9.9
Lower-inner quadrant of breast	38	5.5
Nipple/Central portion of breast	56	8.1
Overlapping lesion of breast	162	23.5
Breast, NOS	61	8.9
Axillary tail	3	0.4
Histological grade		
I-II	452	65.7
III-IV	72	10.5
NA	164	23.8
Laterality		
Left-origin of primary	334	48.5
Right-origin of primary	354	51.5
SEER stage		
Localized	655	95.2
Regional	33	4.8
AJCC TNM stage		
I	400	58.1
II	284	41.3
III	4	0.6
T stage		
T1	404	58.7
T2	253	36.8
T3-4	31	4.5
N stage		
N0	661	96.1
N+	27	3.9
ER status		
Positive	503	73.1
Negative	132	19.2
Borderline/Unknown	53	7.7
PR status		
Positive	560	81.4
Negative	73	10.6
Borderline/Unknown	55	8
HER2 status		
Positive	338	49.1
Negative	8	1.2
Borderline/Unknown	342	49.7
Breast Subtype		
HR-/HER2-	254	36.9
HR-/HER2+	5	0.7
HR+/HER2-	82	11.9
HR+/HER2+	3	0.4
NA	344	50
Surgery method		
Partial mastectomy	485	70.5
Total mastectomy	203	29.5
Radiation therapy		
No	328	47.7
Yes	360	52.3
Treatment modality		
Partial mastectomy	400	58.1
Partial mastectomy + postoperative RT	284	41.3
Total mastectomy ± RT	4	0.6
Chemotherapy		
No	605	87.9
Yes	83	12.1

Abbreviation: SEER, Surveillance, Epidemiology, and End Results; AJCC, American Joint Committee on Cancer; NA, not available; NOS, not otherwise specified; HR, hormone receptor; ER, estrogen receptor; PR, progesterone receptor; HER2, human epidermal growth factor receptor2; RT, radiation therapy.

disease; (4) intraoperative or preoperative RT.

2.2. Variable extraction and definition

Variables were successively recorded, including age at diagnosis, race, marital status, primary tumor site, disease laterality, histological grade, SEER stage, AJCC stage (T stage, N stage, and TNM stage), immunohistochemical (IHC) results, breast subtype, surgery method, RT (yes/no), chemotherapy (yes/no), and survival outcomes. Hormone receptor (HR) consists of estrogen receptor (ER) and progesterone receptor (PR), and positive status for ER and PR were defined as $\geq$ 1% staining. Cases with human epidermal growth factor receptor 2 (HER2) IHC 3+ or IHC 2+ combined with positive result by were considered HER2 positive, while cases with HER2 IHC 0 or 1+ were considered HER2 negative. OS was the survival outcome of interest, defined as the time from the date of diagnosis to the date of death from any cause.

2.3. Statistical analyses

OS was estimated using the Kaplan-Meier method, and the log-rank test was used to compare differences between groups. Multivariable Cox regression was used to identify independent prognostic factors affecting OS. A nomogram model was developed by incorporating prognostic factors, and the discrimination and calibration were internally validated by Concordance index (C-index), time dependent receiver operating characteristic (ROC) curve and corresponding area under curve (AUC), calibration curves. All tests were two-sided, and statistical significance was set at $P < 0.05$. Statistical analyses were performed using SPSS software (version 23.0; IBM, Armonk, NY), RStudio (Version April 1, 1717©2009–2021 RStudio, PBC), X-tile software (version 3.6.1; Yale University, New Haven, USA), and GraphPad Prism software (version 8.0, Inc., United States).

2.4. Compliance with ethical standards

Due to all data in this population-based analysis can be searched from public SEER database with patient anonymity, institutional ethics committee approval and written consent were not required.

3. Results

3.1. General characteristics and treatment modalities

A total of 688 women with ACCB were identified in this analysis, with a median age at diagnosis of 61 years. The general characteristics and treatment modalities of enrolled cohort were listed in Table 1. Among them, the majority of patients were white (n = 563, 81.8%) and married (n = 395, 57.4%). Primary lesions were mostly located in the upper-outer quadrant of the breast (n = 240, 34.9%), followed by breast overlapping lesions (n = 162, 23.5%). The laterality of the lesions was roughly evenly distributed between the left and right sides (48.5% vs. 51.5%). Patients with ACCB were mainly in T1 stage (n = 400, 58.1%) and T2 stage (n = 284, 41.3%), and those without lymph node involvement were as high as 96.1%. Furthermore, more than half of the cases were histologically graded as well-moderate differentiated (n = 452, 65.7%). In addition, the negative rates for ER and PR were 73.1% and 81.4%, respectively. HER-2 status was not available in the SEER database until 2010; nonetheless, of the 346 cases with known HER-2 status, 97.7% were HER-2 negative and only 2.3% were HER-2 positive.

With regard to therapeutic options, 70.5% of patients (n = 485) underwent partial mastectomy as initial therapy, whereas the remaining 29.5% (n = 203) underwent total mastectomy. Approximately half of patients received postoperative RT (52.3% vs 47.7%), and only 12.1% received postoperative chemotherapy. The proportions of patients who underwent partial mastectomy, partial mastectomy with postoperative RT, and total mastectomy with or without postoperative RT were 21.8%, 48.7%, and 29.5%, respectively.

Table 2
Univariate and multivariable analysis of overall survival in overall cohorts.

Characteristics	Univariate	*P*	Multivariable	*P*
	HR (95% CI)		HR (95% CI)	
Age at diagnosis (year)				
≤60	1		1	
>60	4.358 (2.921–6.501)	<0.001	4.241 (2.829–6.356)	<0.001
Race				
White	1			
Black	0.965 (0.532–1.751)	0.907		
Other	0.930 (0.453–1.906)	0.842		
Histological grade				
I-II	1		1	
III-IV	2.536 (1.660–3.876)	<0.001	2.034 (1.309–3.158)	0.002
NA	0.705 (0.453–1.096)	0.121	0.646 (0.414–1.008)	0.054
Laterality				
Left-origin of primary	1			
Right-origin of primary	1.161 (0.825–1.635)	0.391		
T stage				
T1	1		1	
T2	1.453 (1.022–2.067)	0.037	1.566 (1.092–2.244)	0.015
T3-4	1.148 (0.499–2.645)	0.745	0.682 (0.268–1.737)	0.423
N stage				
N0	1		1	
N+	3.372 (1.897–5.993)	<0.001	2.51 (1.331–4.735)	0.004
ER status				
Negative	1			
Positive	0.738 (0.447–1.218)	0.235		
Borderline/ Unknown	0.721 (0.394–1.318)	0.288		
PR status				
Negative	1			
Positive	0.928 (0.532–1.621)	0.794		
Borderline/ Unknown	0.731 (0.400–1.336)	0.308		
HER2 status				
Negative	1			
Positive	5.428 (1.284–22.944)	0.021		
Borderline/ Unknown	1.372 (0.866–2.174)	0.177		
Treatment modality				
Partial mastectomy + postoperative RT	1		1	
Partial mastectomy	1.634 (1.075–2.483)	0.021	1.781 (1.156–2.745)	0.009
Total mastectomy ± postoperative RT	1.113 (0.741–1.672)	0.604	1.160 (0.761–1.768)	0.491
Chemotherapy				
No	1			
Yes	1.332 (0.849–2.090)	0.213		

Abbreviation: RT, radiation therapy; ER, estrogen receptor; PR, progesterone receptor; HER2, human epidermal growth factor receptor2; HR, hazard ratio; CI, confidence interval.

3.2. Survival and prognosis in enrolled cohorts

The median follow-up time was 8.4 years. For the enrolled cohort, the median OS was not reached, and the 3-, 5-, and 8-year OS rates were

Table 3
Baseline feature in patients with ACCB treated with partial mastectomy.

Characteristics	Overall		Training set		Testing set		*P*
	n = 485	%	n = 340	%	n = 145	%	
Age at diagnosis (year)							0.141
Median (range)	61(29–99)		62(22–99)		59(33–85)		
Race							1.440
White	394	81.24	280	82.35	114	78.62	
Black	52	10.72	38	11.18	14	9.66	
Other	39	8.04	22	6.47	17	11.72	
Histological grade							0.511
I-II	320	65.98	220	64.71	100	68.97	
III-IV	55	11.34	42	12.35	13	8.97	
NA	110	22.68	78	22.94	32	22.07	
Laterality							0.090
Left-origin of primary	229	47.22	152	44.71	77	53.10	
Right-origin of primary	256	52.78	188	55.29	68	46.90	
SEER stage							0.728
Localized	466	96.08	326	95.88	140	96.55	
Regional	19	3.92	14	4.12	5	3.45	
AJCC TNM stage							0.390
I	305	62.89	218	64.12	87	60.00	
II	180	37.11	122	35.88	58	40.00	
T stage							0.513
T1	307	63.30	220	64.71	87	60.00	
T2	171	35.26	116	34.12	55	37.93	
T3-4	7	1.44	4	1.18	3	2.07	
N stage							0.663
N0	469	96.70	328	96.47	141	97.24	
N+	16	3.30	12	3.53	4	2.76	
ER status							0.786
Positive	355	73.20	246	72.35	109	75.17	
Negative	99	20.41	71	20.88	28	19.31	
Borderline/Unknown	31	6.39	23	6.76	8	5.52	
PR status							0.211
Positive	403	83.09	276	81.18	127	87.59	
Negative	49	10.10	39	11.47	10	6.90	
Borderline/Unknown	33	6.80	25	7.35	8	5.52	
HER-2 status							0.495
Positive	257	52.99	175	51.47	82	56.55	
Negative	6	1.24	5	1.47	1	0.69	
Borderline/Unknown	222	45.77	160	47.06	62	42.76	
Radiation therapy							0.142
No	150	30.93	112	32.94	38	26.21	
Yes	335	69.07	228	67.06	107	73.79	
Chemotherapy							0.373
No	434	89.48	307	90.29	127	87.59	
Yes	51	10.52	33	9.71	18	12.41	

Abbreviation: SEER, Surveillance, Epidemiology, and End Results; AJCC, American Joint Committee on Cancer; NA, not available; ER, estrogen receptor; PR, progesterone receptor; HER2, human epidermal growth factor receptor2.

94.5%, 90.1%, and 83.1%, respectively (Supplementary Fig. 1A). Furthermore, survival analysis was performed to elucidate the effect of different treatment modality on the prognosis of ACCB, and the significance lied in partial mastectomy plus postoperative RT group and partial mastectomy alone group ($P = 0.021$) (Table 2). The 5-year OS rate of patients receiving partial mastectomy plus RT was 91.6%, which was significantly better than that of patients receiving partial mastectomy (91.6% vs. 82.5%, $P = 0.020$) but comparable to that of those receiving total mastectomy with or without postoperative RT (91.6% vs. 92.9%, $P = 0.624$) (Supplementary Fig. 1B; Supplementary Table 1).

In the multivariable analysis, after adjusting for other variables, treatment modality was still prognostic factor for OS (Table 2). Compared with patients treated with partial mastectomy plus radiotherapy, the death risk significantly increased 0.781-fold in treated with partial mastectomy ($P = 0.009$); However, no significant difference in OS was observed between patients who underwent partial mastectomy plus postoperative RT and those who underwent total mastectomy with or without postoperative RT ($P = 0.491$).

3.3. Baseline feature in patients with ACCB receiving breast-conserving treatment

As mentioned above, patients treated with partial mastectomy plus postoperative RT were identified to have favourable prognosis. To investigate which patients could benefit from postoperative RT, we conducted an in-depth analysis of these populations receiving breast-conserving therapy.

Patients were randomly assigned to the training set (n = 340) and testing set (n = 145) in a 7:3 ratio. There were no significant differences in baseline characteristics between the two sets, and the detailed results were summarized in Table 3. Most cases were localized diseased (n = 466, 96.08%), with no lymph node involvement (n = 469, 96.70%) and low histological grade (grade I-II, 65.98%). For patients who underwent partial mastectomy, the proportion of patients who received postoperative RT was relatively higher than that of patients who did not receive postoperative RT (n = 335 vs. 150, 30.93% vs. 69.07%). Because ACCB is relatively indolent, only a small percentage of patients (n = 51, 10.52%) receive chemotherapy even if they only were treated with partial mastectomy.

Table 4
Univariate and multivariable analysis of overall survival in patients receiving breast-conserving treatment.

Characteristics	Univariate	*P*	Multivariable	*P*
	HR (95% CI)		HR (95% CI)	
Age at diagnosis (year)				
≤60	1		1	
>60	5.8 (3.112–10.811)	<0.001	6.344 (3.393–11.861)	<0.001
Race				
White	1			
Black	1.523 (0.797–2.911)	0.203		
Other	1.54 (0.557–4.259)	0.405		
Histological grade				
I-II	1		1	
III-IV	2.246 (1.285–3.926)	0.005	2.116 (1.208–3.705)	0.009
NA	0.637 (0.334–1.214)	0.171	0.636 (0.333–1.216)	0.171
Laterality				
Left-origin of primary	1			
Right-origin of primary	1.312 (0.814–2.114)	0.265		
T stage				
T1	1		1	
T2	2.021 (1.261–3.237)	0.003	2.24 (1.392–3.604)	0.001
T3-4	1.992 (0.273–14.536)	0.497	1.476 (0.2–10.912)	0.703
N stage				
N0	1			
N+	3.515 (1.607–7.689)	0.002		
ER status				
Positive	1			
Negative	0.91 (0.495–1.674)	0.763		
Borderline/ Unknown	0.92 (0.394–2.148)	0.847		
PR status				
Positive	1			
Negative	1.659 (0.884–3.111)	0.115		
Borderline/ Unknown	1.115 (0.505–2.461)	0.788		

Abbreviation: NA, not available; ER, estrogen receptor; PR, progesterone receptor; HER2, human epidermal growth factor receptor2; HR, hazard ratio; CI, confidence interval.

3.4. Univariate and multivariable analysis in patients receiving breast-conserving treatment

In the training set, univariate and multivariate analyses were performed on patients treated with receiving breast-conserving treatment, and the results were shown in Table 4. Univariate analysis indicated that age at diagnosis > 60 years ($P < 0.001$), histological grade III-IV ($P = 0.005$), and T2 stage ($P = 0.002$) were closely associated with worse OS in patients with ACCB.

Furthermore, in multivariable Cox regression analysis, age at diagnosis, histological grade, and T stage were independent prognostic factor affecting OS (All $P < 0.05$). No statistical significance was obtained in race, laterality, N stage, ER status, PR status after adjusting the entire clinicopathologic variables.

3.5. Nomogram establishment and validation

All these prognostic factors selected from the above-mentioned multivariable analysis were then adopted into the nomogram model to predict the 3-, 5-, and 8-year survival probability. The nomogram model was presented in Fig. 2A.

Our nomogram model was then validated internally, with a high C-index indicating favorable discrimination (nomogram vs. SEER stage vs. TNM stage: 0.731 vs. 0.550 vs. 0.604). Likewise, the C-index of the testing set also outperforms the SEER stage (0.780 vs. 0.509) and the TNM stage (0.780 vs. 0.485).

Moreover, the 3-, 5-, and 8-year AUC of the training set were 0.772, 0.711, and 0.752, respectively (Fig. 2B). A similar trend was illustrated in the testing set, the 3-, 5-, and 8-year AUC were 0.929, 0.789, and 0.848, respectively (Fig. 2C). In addition, the calibration curves of the two sets with slopes close to 45 angles were shown in Fig. 3A and B. Reasonably, there existed an extraordinary predictive power and accuracy.

3.6. Risk stratification based on nomogram

From the curated nomogram, the prognostic score for each patient was calculated and the optimal cutoff for the prognostic score was determined. Accordingly, patients with ACCB were classified into different risk subgroups, namely low risk (n = 183, ≤101), and high risk (n = 157, >101) (Supplementary Fig. 2). Patients in the low-risk subgroup exhibited better OS compared with the high-risk subgroup (χ^2: 45.178, relative risk: 1 vs. 3.43, $P < 0.001$).

As shown in Fig. 4A, in the training set, the 3-, 5-, and 8-year OS rates of patients in the low-risk and high-risk subgroups were 96.9% vs. 89.1%, 92.1% vs. 77.5%, and 89.8% vs. 62.8%, respectively. Furthermore, the Kaplan-Meier curves in the overall population were also significantly separated, suggesting that our model can be used to effectively distinguish patients with ACCB at high risk of death (Fig. 4D). The 3-, 5-, and 8-year OS rates for patients in the low-risk subgroup were 97.9%, 94.3%, and 92.7%, respectively, whereas the 3-, 5-, and 8-year OS rates for patients in the high-risk subgroup were 91.3%, 80.4% and 67.5%, respectively.

3.7. Clinical utilization of postoperative radiation therapy

As mentioned earlier, postoperative RT can improve the prognosis of patients treated with partial mastectomy, but whether all patients require postoperative RT remains to be further explored. Next, further analysis was carried out according to different risk stratifications to assess the clinical significance of postoperative RT in patients with ACCB receiving breast-conserving surgery.

In the high-risk subgroup of the training set, an obvious difference in OS was found between patients with and without the receipt of postoperative RT ($P = 0.006$) (Fig. 3B). Compared with those who did not receive postoperative RT, patients who received postoperative RT had an absolute increase of the 3-year OS rates by 14.5%, the 5-year OS rates by 20%, and the 8-year OS rates by 20%, respectively. However, for the low-risk subgroup, no apparent difference in OS was detected among comparisons between patients receiving postoperative RT and those not receiving postoperative RT (3-year OS rate: 97.8% vs. 96.5%, 5-year OS rate: 91.0% vs. 92.7%, 8-year OS rate: 88.7% vs. 90.4%, $P = 0.807$) (Fig. 4C).

Similar trends were exhibited in the general population undergoing breast-conserving surgery. In the high-risk subgroup, patients who received postoperative RT had a significant improvement in OS compared to those who did not receive postoperative RT. The absolute value of 3-, 5-, 8-year OS rate increased by 12.2%, 15.1% and 17.1% respectively (3-, 5-, and 8-year OS rate of non-RT vs. RT: 83.3%, 70.5%, 56.3% vs. 95.5%, 85.6%, 73.4%, $P = 0.013$) (Fig. 4E). However, in the low-risk subgroup, there was no difference in OS between patients who received postoperative RT and those who did not (3-, 5-, and 8-year OS rate of non-RT vs. RT: 98.5%, 92.2%, 90.5%% vs. 97.7%, 95.2%, 93.7%, $P = 0.293$) (Fig. 4F).

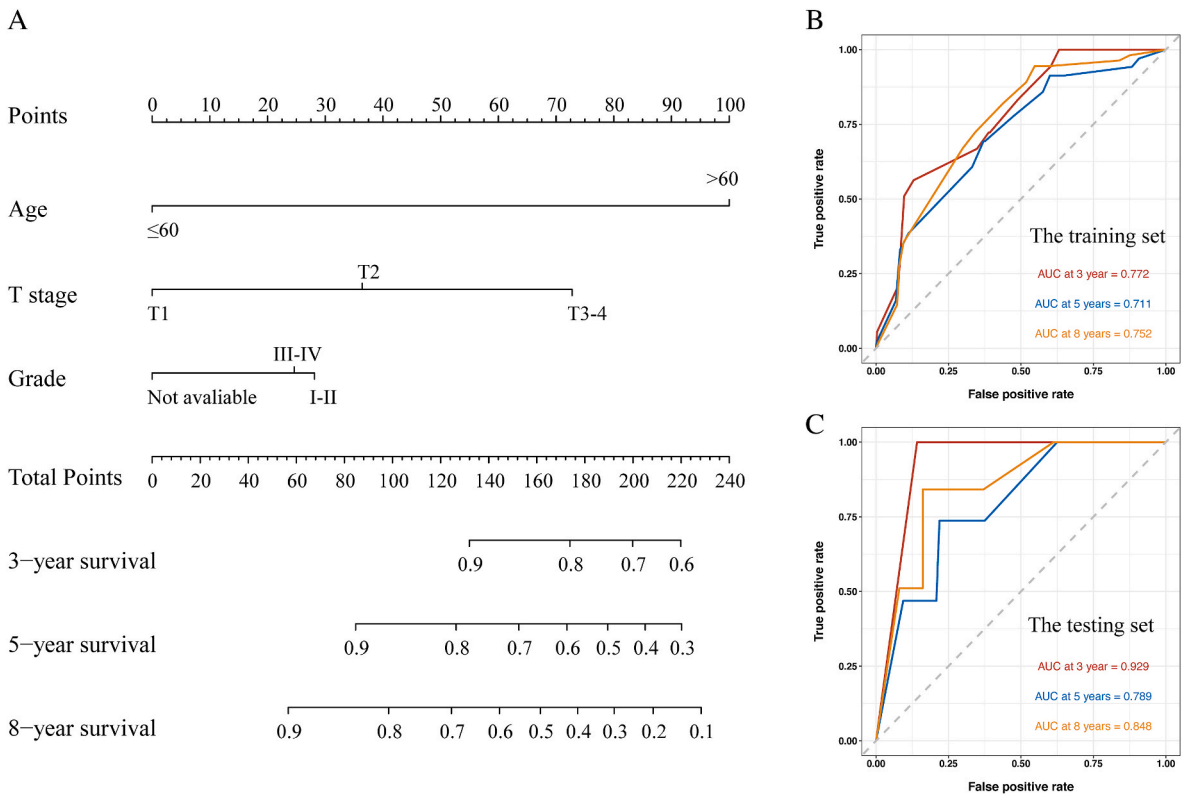

Fig. 2. Nomogram and area under curve in patients with ACCB receiving breast-conserving treatment. A. OS-nomogram in patients with ACCB receiving breast-conserving treatment; B. ROC of the nomogram for 3-, 5-, and 8-year OS prediction in the training set. C. ROC of the nomogram for 3-, 5-, and 8-year OS prediction in the testing set. Abbreviation: ACCB, adenoid cystic carcinoma of the breast; ROC, receiver operating characteristic curve; AUC, areas under the curve.

4. Discussion

Adenoid cystic carcinoma (ACC) is common in salivary glands, once called cylindroma, and rarely occurs in the breast [11,12]. ACC is a group of morphologically heterogeneous tumors that need to be differentiated pathologically from other types of breast cancer, such as invasive cribriform carcinoma [13]. It can be seen that clinicians should combine a variety of inspection methods in the process of diagnosis and treatment to avoid missed diagnosis and delay patients' treatment opportunities.

Patients with ACCB are mainly postmenopausal women. The most common clinical symptom of ACCB is a breast mass, mostly located in the upper-outer quadrant and subareolar, and mostly T1-2 lesions [14,15]. ACCB rarely has lymph node metastases, especially when the breast mass is less than 1.4 cm, and almost no axillary lymph node involvement [5,16]. Interestingly, this particular subtype of breast cancer generally does not express ER, PR and HER2. However, the prognosis of ACCB is better than that of other TNBC, which is speculated to be related to the overexpression of EGFR and MYB-NFIB fusion genes in ACC [17–20] as well as the down-regulation of genes associated with migration, proliferation and immune response [21]. All in all, ACCB has an indolent clinical behavior and a relatively favorable biological profile, and our findings were basically consistent with those reported in the literature. Notably, our study is more comprehensive and convincing because of the advantages of a larger sample size and avoiding the introduction of institution-specific treatment bias.

Previous reports on ACCB mainly described the pathological diagnosis and differential diagnosis [22,23]. The low frequency and relatively prolonged natural history of ACCB lead to difficulties in the consistency of assessment and therapeutic consensus [24]. In our study, in addition to summarizing clinical characteristics and survival outcomes, we focused on the treatment and prognosis of ACCB to provide clinical reference. Treatment modalities of ACCB usually involve resection of the primary tumor in the form of lumpectomy or mastectomy, with or without lymph node dissection [25]. Additionally, in some cases, postoperative RT was followed. Management in the previous literature suggested that breast-conserving therapy should be considered unless the primary tumor is large or with axillary lymph node metastases, in which case radical mastectomy should be performed [26].

To investigate whether breast-conserving therapy is as effective as total mastectomy in eradicating the disease, we reviewed the clinical records of a large number of patients with ACCB in the SEER database. The results showed that breast-conserving treatment including postoperative RT appeared to be equivalent to total mastectomy with or without postoperative RT in terms of survival, suggesting that both were appropriate management strategies for ACCB. Moreover, the survival rate of patients with ACCB who underwent partial mastectomy plus postoperative RT was significantly higher than those who underwent partial mastectomy. It has been commented that infiltration of ACCB into the surrounding breast parenchyma and adipose tissue may make complete resection difficult [26]; however, in this setting, the receipt of postoperative RT may be beneficial for local control and long-term survival [9,13].

Currently, postoperative RT has been widely recommended in most breast cancer treated with breast-conserving surgery. Performing postoperative RT on the breast may reduce the burden of residual microscopic lesions and decrease the possibility of hematogenous spread to a certain extent, thereby effectively improving the local control rate as well as prolonging disease-free survival and OS. However, for some patients with particular pathological types of breast cancer, especially those with ACCB with relatively indolent clinical course, the need for receiving routinely postoperative RT has not been fully determined. As mentioned above, unlike other invasive ductal carcinoma, ACCB has relatively low proliferative activity despite typically TN subtype. ACCB

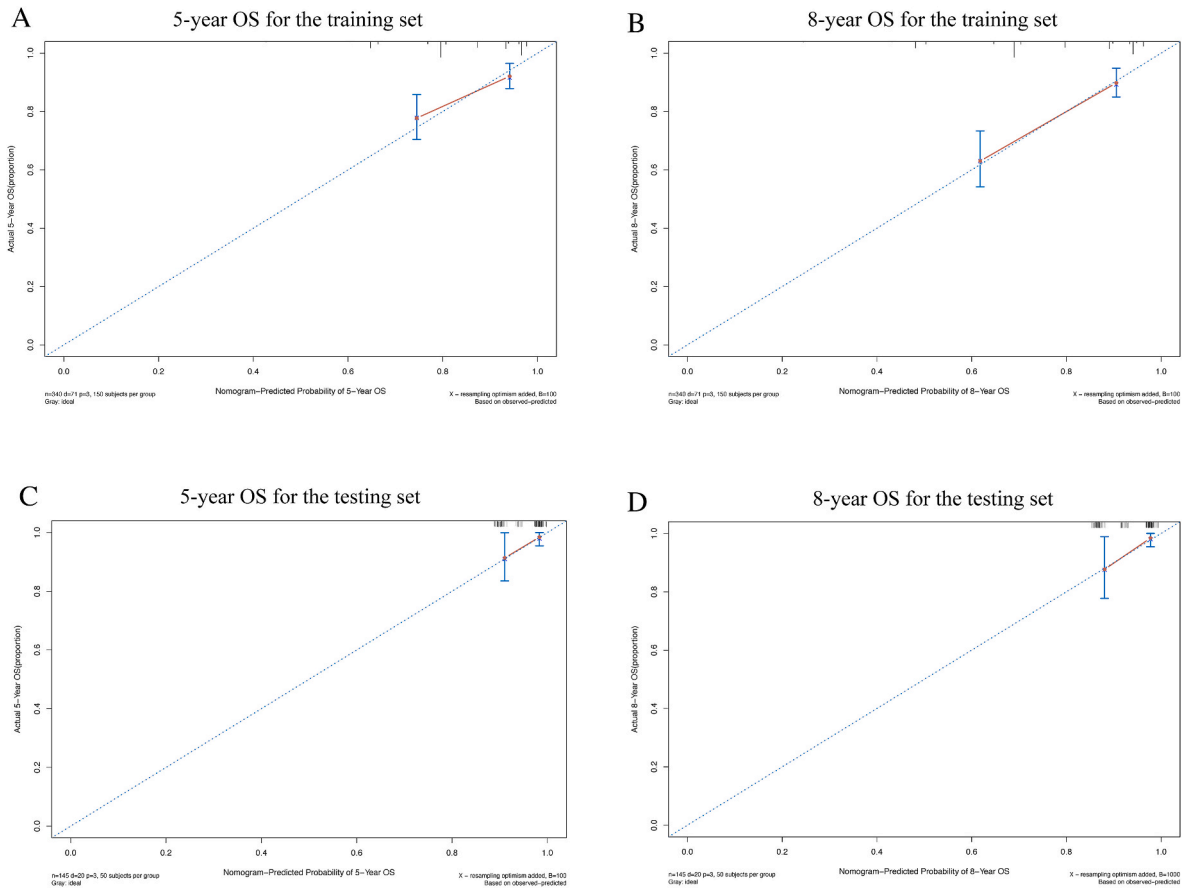

Fig. 3. Calibration plot for the prediction of 5- and 8-year OS in the training set (A–B) and the testing set (C–D). Abbreviation: OS, overall survival.

is rarely found with axillary lymph node metastasis. Besides, longer disease-free survival has been reported in patients with ACCB, with few local recurrences and/or distant metastases [27]. It is necessary for us to consider whether these patients should undergo "subtraction of treatment modality", that is, de-escalation of treatment.

In a previous single-center study spanning 20 years, all patients had surgery as primary treatment (including partial and total mastectomy), highlighting the importance of surgery but also pointing out that sentinel node excision may not be required, and postoperative RT was also not necessary. In addition, Sumpio et al. advocated simple mastectomy as primary local therapy for ACCB in view of good biological behavior [28]. In our study, further exploration was carried out on these patients undergoing breast-conserving surgery. Clinicopathological variables, including age at diagnosis, histological grade, and T stage, were identified as independent prognostic factors for OS. And then, a robust and effective nomogram were developed to predict 3-, 5- and 10-year OS in patients with ACCB. Subsequently, a risk assessment can be performed for each patient based on our nomogram model. We reasonably and innovatively proposed to divide patients into high- and low-risk subgroups with an OS nomogram score of 101 as the cut-off point, and confirmed that in the high-risk subgroup, the survival rate of patients was significantly decreased. From this perspective, physicians can tailor treatment regimens based on different risk scores. If the patient's risk score is greater than 101, it should be highly regarded, and treatment options should be considered in multiple aspects.

More importantly, we found that patients in the low-risk subgroup had comparable survival rates with or without postoperative RT, indicating that they could not did not derive additional benefit from postoperative RT. Our findings suggested that postoperative RT may not be required for all patients with ACCB undergoing breast-conserving surgery. In clinical practice, patients with low-risk scores may be able to exempt from postoperative RT, thereby reducing treatment-related side effects and treatment costs. The implementation of postoperative RT can control local tumors, but it can also cause a certain degree of damage, such as skin, mucous membrane, microvascular and other functional damage, as well as muscle fibrosis. In addition, postoperative RT will increase the length of hospitalization, not only increases the financial burden, but also has a certain risk of infection. Therefore, it is important to weigh the costs and effects when performing postoperative RT. We have reason to believe that it is reasonable to consider partial mastectomy plus postoperative RT in properly selected patients.

Despite these advantages, there are still some limitations. The SEER database lacks important information, including patient's performance status, lymph vascular invasion, and margin status, which may affect survival outcomes after ACCB. In addition, treatment intent could not be obtained due to the inherent nature of secondary data analysis. Our nomogram is expected to improve by incorporating more prognostic risk factors. Given the retrospective nature of this study, randomized controlled trials are needed to provide more convincing evidence for these results.

5. Conclusions

For patients with ACCB, partial mastectomy with postoperative RT might have comparable survival outcomes to total mastectomy with or without postoperative RT. Using the SEER database, we have successfully developed a nomogram that provides a robust and efficient method for predicting the prognosis of patients with ACCB undergoing partial mastectomy. On this basis, patients with different risk levels could be effectively distinguished, and patients who do not benefit from postoperative RT could be screened to avoid overtreatment. It is necessary to further access and validate this model using real-world sample data to

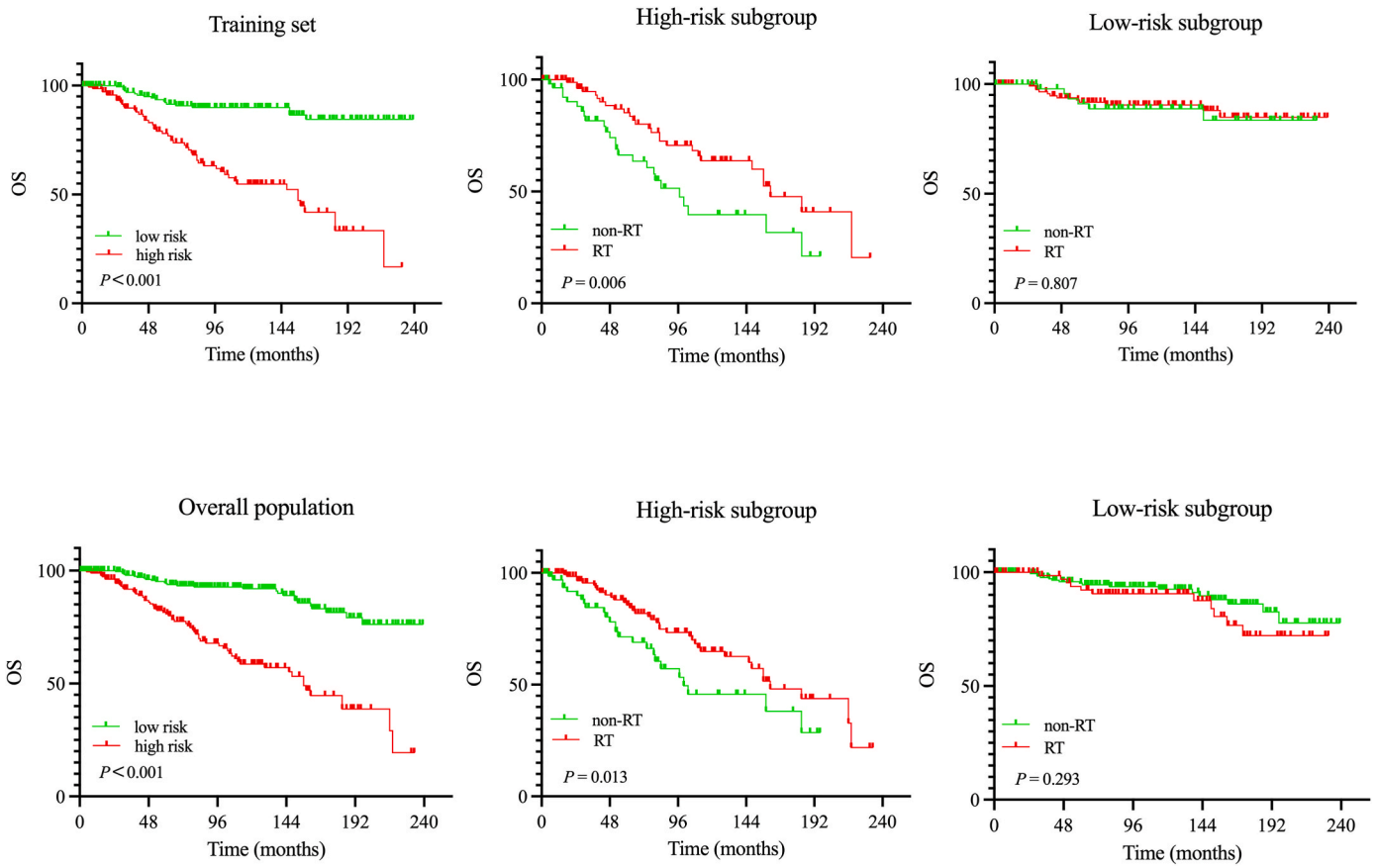

Fig. 4. The OS of patients in different risk subgroups, and differences in OS between postoperative RT and non-RT group. Abbreviation: OS, overall survival; RT, radiation therapy; non-RT, non-radiation therapy.

improve its clinical utility.

Ethics statement

Due to all data in our analysis can be searched from public SEER database with patient anonymity, institutional ethics committee approval and written consent were not required.

Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Author contributions

Fei Ma: Study concept; review of the manuscript for important intellectual content and final approval of the version to be submitted. Di Zhang: Literature review; analysis and interpretation of data; drafting of the manuscript; review of the manuscript for important intellectual content and final approval of the version to be submitted. Lixi Li: Study concept; statistical analysis; drafting of the manuscript; review of the manuscript for important intellectual content and final approval of the version to be submitted.

Data availability statement

All data can be retrieved from publicly available SEER database. These data can be found here: https://seer.cancer.gov.

Consent to publish

Due to all data in our analysis can be searched from public SEER database with patient anonymity, written consent were not required.

Declaration of competing interest

The authors declare to have no competing interests.

Acknowledgments

The authors acknowledge the open access to the database from SEER.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.breast.2022.09.003.

References

[1] Ghabach B, Anderson WF, Curtis RE, Huycke MM, Lavigne JA, Dores GM. Adenoid cystic carcinoma of the breast in the United States (1977 to 2006): a population-based cohort study. Breast Cancer Res 2010;12(4):R54.
[2] Cserni G, Quinn CM, Foschini MP, Bianchi S, Callagy G, Chmielik E, Decker T, Fend F, Kovács A, van Diest PJ, et al. Triple-negative breast cancer histological subtypes with a favourable prognosis. Cancers 2021;13(22).
[3] Wetterskog D, Lopez-Garcia MA, Lambros MB, A'Hern R, Geyer FC, Milanezi F, Cabral MC, Natrajan R, Gauthier A, Shiu KK, et al. Adenoid cystic carcinomas constitute a genomically distinct subgroup of triple-negative and basal-like breast cancers. J Pathol 2012;226(1):84–96.
[4] Hodgson NC, Lytwyn A, Bacopulos S, Elavathil L. Adenoid cystic breast carcinoma: high rates of margin positivity after breast conserving surgery. Am J Clin Oncol 2010;33(1):28–31.

[5] Arpino G, Clark GM, Mohsin S, Bardou VJ, Elledge RM. Adenoid cystic carcinoma of the breast: molecular markers, treatment, and clinical outcome. Cancer 2002;94(8):2119–27.
[6] Page DL. Adenoid cystic carcinoma of breast, a special histopathologic type with excellent prognosis. Breast Cancer Res Treat 2005;93(3):189–90.
[7] Coates JM, Martinez SR, Bold RJ, Chen SL. Adjuvant radiation therapy is associated with improved survival for adenoid cystic carcinoma of the breast. J Surg Oncol 2010;102(4):342–7.
[8] Sun JY, Wu SG, Chen SY, Li FY, Lin HX, Chen YX, He ZY. Adjuvant radiation therapy and survival for adenoid cystic carcinoma of the breast. Breast 2017;31:214–8.
[9] Khanfir K, Kallel A, Villette S, Belkacémi Y, Vautravers C, Nguyen T, Miller R, Li YX, Taghian AG, Boersma L, et al. Management of adenoid cystic carcinoma of the breast: a Rare Cancer Network study. Int J Radiat Oncol Biol Phys 2012;82(5):2118–24.
[10] Gomez-Seoane A, Davis A, Oyasiji T. Treatment of adenoid cystic carcinoma of the breast: is postoperative radiation getting its due credit? Breast 2021;59:358–66.
[11] Albores-Saavedra J, Heard SC, McLaren B, Kamino H, Witkiewicz AK. Cylindroma (dermal analog tumor) of the breast: a comparison with cylindroma of the skin and adenoid cystic carcinoma of the breast. Am J Clin Pathol 2005;123(6):866–73.
[12] Marchiò C, Weigelt B, Reis-Filho JS. Adenoid cystic carcinomas of the breast and salivary glands (or 'The strange case of Dr Jekyll and Mr Hyde' of exocrine gland carcinomas). J Clin Pathol 2010;63(3):220–8.
[13] Boujelbene N, Khabir A, Boujelbene N, Jeanneret Sozzi W, Mirimanoff RO, Khanfir K. Clinical review–breast adenoid cystic carcinoma. Breast 2012;21(2):124–7.
[14] Kleer CG, Oberman HA. Adenoid cystic carcinoma of the breast: value of histologic grading and proliferative activity. Am J Surg Pathol 1998;22(5):569–75.
[15] Ro JY, Silva EG, Gallager HS. Adenoid cystic carcinoma of the breast. Hum Pathol 1987;18(12):1276–81.
[16] Thompson K, Grabowski J, Saltzstein SL, Sadler GR, Blair SL. Adenoid cystic breast carcinoma: is axillary staging necessary in all cases? Results from the California Cancer Registry. Breast J 2011;17(5):485–9.
[17] Martelotto LG, De Filippo MR, Ng CK, Natrajan R, Fuhrmann L, Cyrta J, Piscuoglio S, Wen HC, Lim RS, Shen R, et al. Genomic landscape of adenoid cystic carcinoma of the breast. J Pathol 2015;237(2):179–89.
[18] Brill 2nd LB, Kanner WA, Fehr A, Andrén Y, Moskaluk CA, Löning T, Stenman G, Frierson Jr HF. Analysis of MYB expression and MYB-NFIB gene fusions in adenoid cystic carcinoma and other salivary neoplasms. Mod Pathol 2011;24(9):1169–76.
[19] Bell D, Roberts D, Karpowicz M, Hanna EY, Weber RS, El-Naggar AK. Clinical significance of Myb protein and downstream target genes in salivary adenoid cystic carcinoma. Cancer Biol Ther 2011;12(7):569–73.
[20] Vranic S, Frkovic-Grazio S, Lamovec J, Serdarevic F, Gurjeva O, Palazzo J, Bilalovic N, Lee LM, Gatalica Z. Adenoid cystic carcinomas of the breast have low Topo IIα expression but frequently overexpress EGFR protein without EGFR gene amplification. Hum Pathol 2010;41(11):1617–23.
[21] Weigelt B, Horlings HM, Kreike B, Hayes MM, Hauptmann M, Wessels LF, de Jong D, Van de Vijver MJ, Van't Veer LJ, Peterse JL. Refinement of breast cancer classification by molecular characterization of histological special types. J Pathol 2008;216(2):141–50.
[22] Zaloudek C, Oertel YC, Orenstein JM. Adenoid cystic carcinoma of the breast. Am J Clin Pathol 1984;81(3):297–307.
[23] Azoulay S, Laé M, Fréneaux P, Merle S, Al Ghuzlan A, Chnecker C, Rosty C, Klijanienko J, Sigal-Zafrani B, Salmon R, et al. KIT is highly expressed in adenoid cystic carcinoma of the breast, a basal-like carcinoma associated with a favorable outcome. Mod Pathol 2005;18(12):1623–31.
[24] McClenathan JH, de la Roza G. Adenoid cystic breast cancer. Am J Surg 2002;183(6):646–9.
[25] Kulkarni N, Pezzi CM, Greif JM, Suzanne Klimberg V, Bailey L, Korourian S, Zuraek M. Rare breast cancer: 933 adenoid cystic carcinomas from the National Cancer Data Base. Ann Surg Oncol 2013;20(7):2236–41.
[26] Millar BA, Kerba M, Youngson B, Lockwood GA, Liu FF. The potential role of breast conservation surgery and adjuvant breast radiation for adenoid cystic carcinoma of the breast. Breast Cancer Res Treat 2004;87(3):225–32.
[27] Leeming R, Jenkins M, Mendelsohn G. Adenoid cystic carcinoma of the breast. Arch Surg 1992;127(2):233–5.
[28] Sumpio BE, Jennings TA, Merino MJ, Sullivan PD. Adenoid cystic carcinoma of the breast. Data from the Connecticut Tumor Registry and a review of the literature. Ann Surg 1987;205(3):295–301.