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Treatment of adenoid cystic carcinoma of the breast: Is postoperative radiation getting its due credit?

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ABSTRACT

Introduction: The role of postoperative radiation (PR) in treating mammary ACC is poorly defined. This study evaluated the impact of PR on survival outcomes for mammary ACC and the extent of utilization.
Methods: Patients who underwent surgery for mammary ACC from 2005 to 2015 in SEER database were analyzed. KM analyses of OS and DSS were done for PR versus no PR. Cox hazard regression models were used to determine predictors of OS and DSS.
Results: Of the 488 patients, 244 underwent PR. The PR group was younger, but other variables were similar between the 2 groups. OS was better for PR ($p = 0.029$). 10-year DSS was better for PR group by an absolute value of 6 % but did not reach statistical significance ($p = 0.537$). Age, radiation, nodal metastasis, and grade III/IV were independent predictors of OS while grade III/IV and AJCC stage III/IV independently predicted DSS.
Conclusion: PR improves OS for mammary ACC, but this study did not show increased utilization. Radiation should be considered after surgery for mammary ACC, particularly for patients with independent predictors of OS.

1. Introduction

Adenoid cystic carcinoma of the breast is a rare histologic subtype of breast cancer which constitutes less than 1 % of all breast malignancies [1–4]. Because the disease is rare and has favorable prognosis, there is limited data to generate treatment algorithms [5]. Evidence-based treatment, so far, is derived from individual case reports and case series. Surgical resection is generally accepted as the standard treatment [6]. However, detailed recommendations about postoperative radiation or role of axillary staging are currently lacking [7].

Coates et al., through their large population-based retrospective study, demonstrated survival benefit associated with postoperative radiation treatment [5]. This SEER database study reviewed mammary ACC patients from 1988 to 2005 and showed OS and DSS benefits with postoperative radiation. Another group of researchers examined mammary ACC patients within the SEER database over a different period, from 1998 to 2011, and reported similar overall survival and disease specific survival benefits with postoperative radiation treatment [9]. Both studies recommended incorporating postoperative radiation to treatment guidelines for mammary ACC.

Mammary ACC tends to have an infiltrative growth pattern which may account for higher rates of positive margins following breast conserving surgery [10]. This often results in higher local recurrence rates. A multi-institutional study examined the role of postoperative radiation in the setting of breast-conserving surgery for ACC and reported higher rates of locoregional control for the radiation group [10]. These researchers also made a case for inclusion of postoperative radiation, particularly after breast conserving surgery.

Granted that the prognosis is favorable, and the incidence of axillary nodal metastasis and distant metastasis are documented as ranging between 0.8 % and 2 % [11,12] and 0 %–9 % [4,11,13–15], respectively. Survival benefits, as indicated above, cannot be overlooked. It is noteworthy that earlier experience with higher rates of positive resection margins and local recurrences has promoted mastectomy as the standard surgical treatment until recently. With

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recent studies documenting equivalent locoregional control between breast conserving surgery combined with postoperative radiation and mastectomy, the more reason to examine the role of postoperative radiation and the stronger the case for inclusion in treatment algorithms for mammary ACC.

This study sought to assess the impact of postoperative radiation on survival outcomes for patients with mammary ACC over a more recent decade. It also evaluated the extent to which this treatment modality has been incorporated to the management of mammary ACC in recent years, considering the evidence in the existing literature review.

2. Methods

2.1. Data source

The Surveillance, Epidemiology, and End Results (SEER) Program of the National Cancer Institute (NCI) is an authoritative source of information on cancer incidence and survival in the United States. SEER currently collects and publishes cancer incidence and survival data from population-based cancer registries covering approximately 34.6% of the U.S. population. The SEER Program registries routinely collect data on patient demographics, primary tumor site, tumor morphology and stage at diagnosis, first course of treatment, and follow-up for vital status.

2.2. Patient selection

All patients entered into the database who underwent an operation for primary breast ACC between 2005 and 2015 were selected. Exclusions were made for those patients lacking histologic confirmation of diagnosis, information on type of surgical procedure and receipt of radiation therapy. Since no personally identifying information is contained within the SEER database, this study was exempt from review by the Institutional Review Board.

2.3. Analysis

Patients were divided into two groups: the group that received postoperative radiation and the group that did not. Descriptive statistics was used to present the demographic characteristics of the study population. The proportions of the patients who underwent postoperative radiation, for each year included in the study, were presented as percentages. Clinicopathologic characteristics were compared between the 2 groups using the Chi-Square test for the categorical variables and Fisher's exact test for the continuous variables. Analyses for OS and DSS for the two groups were done using the Kaplan-Meier method. The survival curves were compared using log-rank testing. Cox proportional hazards model was used for univariate analysis to determine predictors of overall survival and disease specific survival for the entire study population. Multivariate analysis was also conducted using Cox proportional hazards model to determine independent predictors of overall survival and disease specific survival. Significance levels were set at $p < 0.05$ and all tests were two sided.

3. Results

3.1. Patient characteristics

Four hundred and eighty-eight patients satisfied the inclusion criteria for the study. Two hundred and forty-four patients (50 %) received postoperative radiation. The patient characteristics, tumor factors and treatment information were presented in Table 1. Demographics were similar for both groups except for age at diagnosis. The patients who were treated with postoperative radiation were significantly younger ($p = 0.008$). The white race was represented in the study population at a significantly higher proportion compared to blacks and other races ($p = 0.03$).

3.2. Tumor characteristics

The tumor grade was documented for 362 patients (74.2 %); 182 patients in the postoperative radiation group and 180 patients in the no postoperative radiation group. The two groups were similar in the distribution of the tumor grades ($p = 0.560$). For AJCC staging, both groups were also similar ($p = 0.403$). The vast majority were stages I (284 out of 488, 58.2 %) and II (199 out of 488, 40.1 %). While both groups were similar in terms of T stage and M stage ($p = 0.946$ and 0.082, respectively), nodal metastasis was significantly higher in the postoperative radiation group ($p = 0.035$). Both groups had similar estrogen receptor (ER) and progesterone receptor (PR) status; $p = 0.779$ and 0.645, respectively. HER2/NEU status became available in SEER databases from 2010. Two hundred and fifty-four (254) patients had HER2/NEU status documented and only 4 were positive (1.6 %) (Table 1).

3.3. Treatment characteristics

There was an even distribution of patients who had postoperative radiation and those who did not, 244 patients for each group. Regarding type of surgery, the number of patients who underwent partial mastectomy in the postoperative radiation group was almost twice that for patients who did not receive postoperative radiation. The group that did not receive postoperative radiation had ten times the number of simple mastectomies compared to the postoperative radiation group ($p = 0.001$). No significant difference was recorded for the use of postoperative chemotherapy between the two groups ($p = 0.205$) (Table 1). Of note, the overall trend did not show an increase in the utilization of postoperative radiation over the study period (Fig. 5).

3.4. Survival outcomes

For the entire cohort, prior to the categorization by receipt of postoperative radiation, five-year OS and DSS were 88.45 %, 95 % CI (84.82%–91.26 %) and 95.68 %, 95 % CI (93.11%–97.31 %) accordingly. While the ten-year OSS and DSS were 77.60 %, 95 % CI (71.24%–82.72 %) and 92.98 %, 95 % CI (88.11%–95.90 %) respectively (Figs. 1 and 2). Overall survival was significantly better for the radiation group (log rank p value = 0.029). Five-year and ten-year OS for the postoperative radiation group were 91.2%, 95 % CI (86.15%–94.47 %) and 82.58 %, 95 % CI (73.86%–88.61 %), respectively (Fig. 3). Five-year and ten-year OS for the no postoperative radiation group were 85.66 %, 95 % CI (79.90%–89.87 %) and 72.53 %, 95 % CI (62.63%–80.22 %%), respectively (Fig. 3). Five-year DSS were comparable for both groups 95.43 % vs 95.99 %. Ten-year DSS was better for the radiation group by an absolute value of 6 % but the difference was not statistically significant, ($p = 0.537$) (Fig. 4). Median OS and DSS could not be calculated for both groups as survival was greater than 50 % at all time points (Figs. 3 and 4).

On univariate analysis, age, radiation, grades III and IV, AJCC stages II and III/IV, nodal metastasis, and estrogen receptor status were predictors of OS while age, grades III and IV, AJCC stages II and III/IV, nodal metastasis, M1 status, modified radical mastectomy, and chemotherapy were predictors of DSS (Table 2). On multivariate analysis, age, radiation, nodal metastasis, and grade III/IV were independent predictors of OS while grade III/IV and AJCC stage III/IV independently predicted DSS (Table 3).

A subgroup analysis of node-negative patients who underwent

Table 1
Clinicodemographic characteristics.

Characteristics	Postoperative radiation (%)	No postoperative radiation (%)	P value
Age at diagnosis (mean ± SD)	59.8 ± 11.3	62.9 ± 13.9	0.008
Race			0.031
White	201	200	
Black	34	23	
Other	9	21	
Sex			0.082
Female	244	241	
Male	0	3	
Grade			0.560
Well differentiated	82	87	
Moderately differentiated	70	61	
Poorly differentiated	28	27	
Undifferentiated	2	5	
AJCC7 stage			0.403
I	143	141	
II	100	99	
III/IV	1	4	
Tumor stage			0.946
T1	145	142	
T2	91	93	
T3	8	9	
Nodal status			0.035
N0	230	239	
N1	14	5	
M status			0.082
M0	244	241	
M1	0	3	
Surgery			<0.001
Partial mastectomy	224	114	
Simple mastectomy	8	101	
Modified radical mastectomy	12	29	
Chemotherapy	33	24	0.205
Estrogen receptor status			0.779
Positive	45	47	
Negative	185	177	
Borderline	1	2	
Progesterone receptor status			0.645
Positive	24	25	
Negative	206	198	
Borderline	1	1	

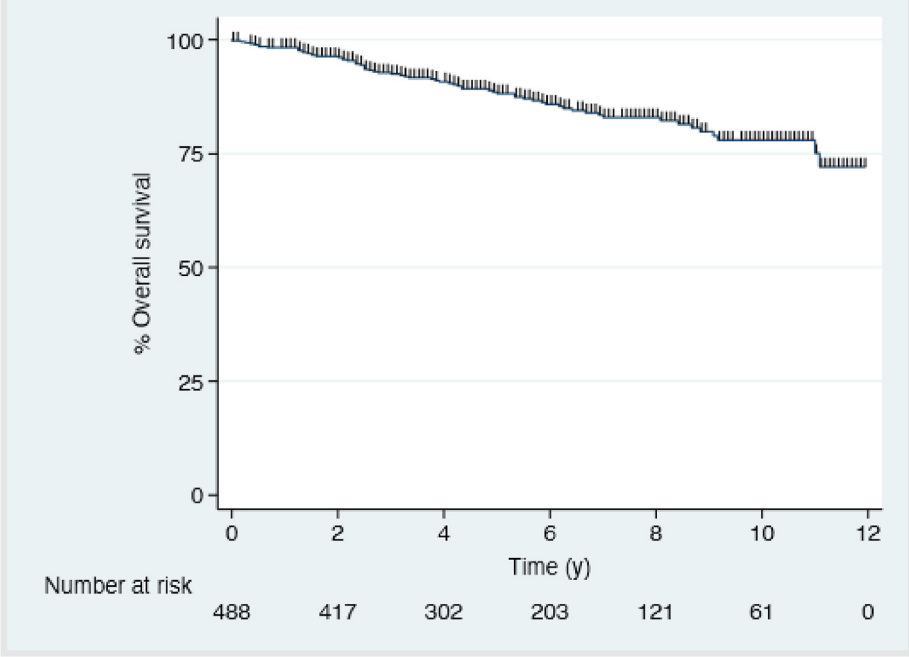

Fig. 1. Kaplan-Meier survival plot for overall survival of the entire cohort.

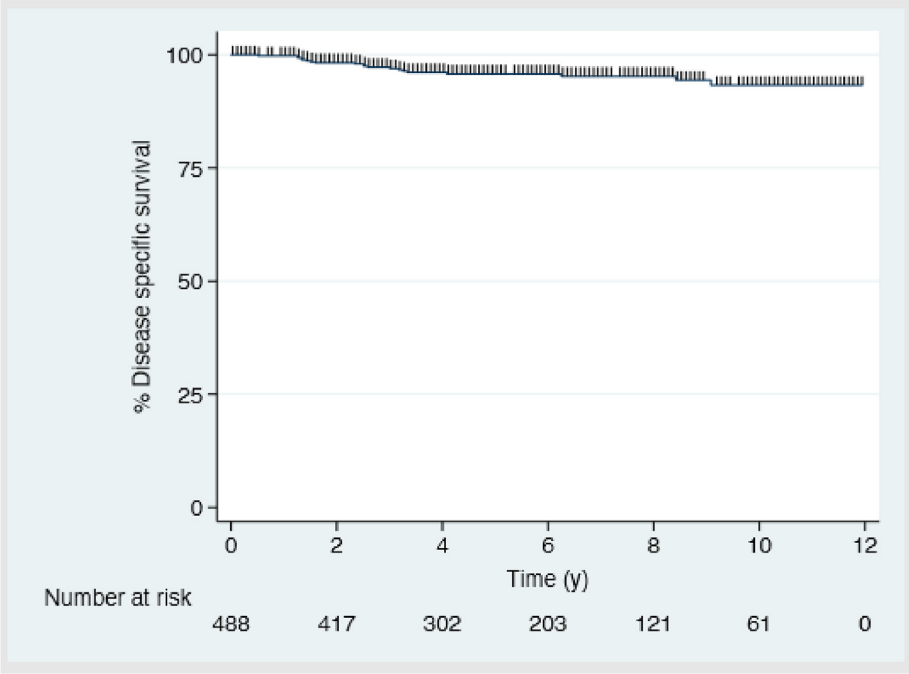

Fig. 2. Kaplan-Meier survival plot for disease specific survival of the entire cohort.

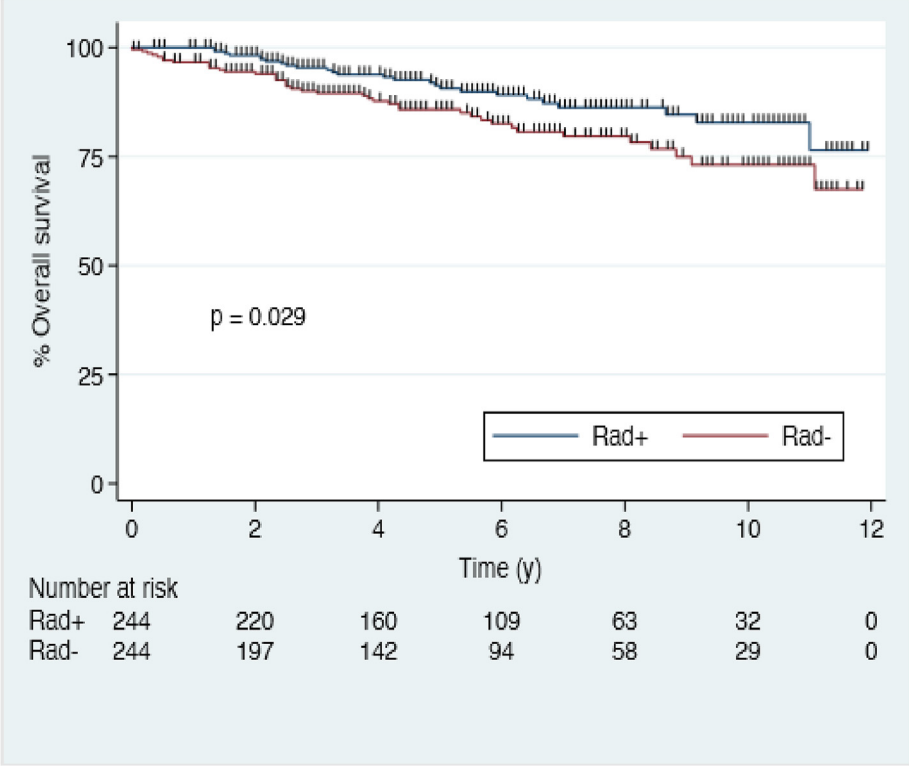

Fig. 3. Kaplan-Meier survival plots for overall survival of patients who underwent postoperative radiation versus those who did not.

partial mastectomy showed persistent trend of better OS for patients who underwent postoperative radiation. Five-year and ten-year OS for the postoperative radiation group were 92.8%, 95 % CI (87.5%–95.9 %) and 82.3 %, 95 % CI (71.8%–89.1 %), respectively. Five-year and ten-year OS for the no postoperative radiation group were 79.5 %, 95 % CI (69.1%–86.7 %) and 67.1 %, 95 % CI (52.6%–78.1 %), respectively. Log rank test for the OS survival curves showed statistically significant difference with p value = 0.002 (Fig. 5). Five-year and ten-year DSS were comparable for both groups 97.1 % vs 97.8 % (log rank p value = 0.856) (Fig. 6). The clinicodemographic

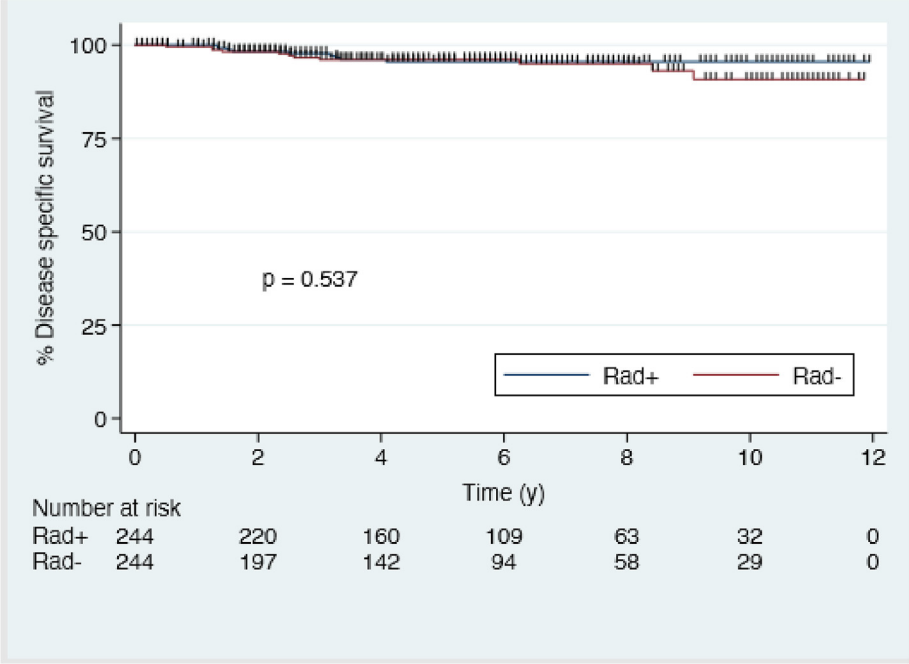

Fig. 4. Kaplan-Meier survival plots for disease specific survival of patients who underwent postoperative radiation versus those who did not.

Table 2
Univariate analysis for predictors of overall survival and disease specific survival.

Characteristics	OS			DSS		
	HR	95%CI	P value	HR	95 % CI	P value
Age at diagnosis	1.064	1.043–1.085	<0.0001	0.956	0.920–0.994	0.022
Radiation	1			1		
No radiation	1.714	1.048–2.803	0.032	1.318	0.546–3.182	0.538
Race recorded						
White	1			1		
Other (Native Am, Asian)	1.059	0.384–2.926	0.911	1.868	0.427–8.173	0.407
Black	1.211	0.598–2.453	0.595	1.452	0.420–5.017	0.555
Grade						
Well differentiated	1			1		
Moderately Differentiated	1.227	0.606–2.487	0.570	7.361	0.885–61.230	0.065
Poorly differentiated	4.712	2.426–9.156	<0.0001	33.511	4.288–261.865	0.001
Undifferentiated	4.681	1.346–16.277	0.015	53.641	4.843–594.1862	0.001
Stage (AJCC7)						
I	1			1		
II	1.673	1.029–2.723	0.038	4.061	1.447–11.397	0.008
III/IV	3.642	0.871–15.238	0.077	24.205	4.661–125.696	<0.0001
Tumor stage						
T1	1			1		
T2	1.598	0.977–2.613	0.062	2.732	1.055–7.029	0.038
T3	1.271	0.390–4.148	0.690	4.297	0.889–20.769	0.070
Nodal status						
N0	1			1		
N1	5.340	2.721–10.478	<0.0001	19.282	7.864–47.281	<0.0001
M status						
M0	1			1		
M1	3.213	0.445–23.224	0.247	11.095	1.469–83.808	0.020
Surgical treatment						
Partial mastectomy	1			1		
Simple mastectomy	0.672	0.339–1.332	0.255	0.912	0.251–3.316	0.889
Modified Radical mastectomy	1.607	0.831–3.106	0.159	5.017	1.905–13.214	0.001
Chemotherapy						
Yes	1			1		
No	0.750	0.393–1.433	0.384	0.216	0.088–0.529	0.001
Estrogen receptor status						
Negative	1			1		
Positive	0.410	0.176–0.951	0.038	0.819	0.190–3.531	0.789
Progesterone receptor status						
Negative	1			1		
Positive	0.638	0.256–1.591	0.335	0.819	0.190–3.531	0.789

Table 3
Multivariate analysis for predictors of overall survival and disease specific survival.

Characteristics	OS			DSS		
	HR	95%CI	P value	HR	95 % CI	P value
Age at diagnosis	1.050	1.026–1.073	<0.0001	0.975	0.940–1.011	0.168
Radiation	1			1		
No radiation	2.749	1.026–5.694	0.006	1.442	0.448–4.640	0.539
Stage (AJCC7)						
I	1			1		
II	6.304	0.840–47.305	0.073	2.496	0.751–8.292	0.135
III/IV	5.609	0.138–227.847	0.362	6.479	1.025–40.948	0.047
Grade						
Well differentiated	1			1		
Moderately differentiated	1.379	0.619–3.073	0.432	5.605	0.642–48.894	0.119
Poorly/undifferentiated	4.928	2.412–10.068	<0.0001	25.546	3.160–206.544	0.002
Tumor stage						
T1	1					
T2	0.244	0.035–1.696	0.154			
T3	0.233	0.015–3.519	0.293			
Nodal status						
N0	1					
N1	5.450	1.718–17.290	0.004			
M status						
M0	1					
M1	0.529	0.017–16.837	0.718			
Estrogen receptor status						
Negative	1					
Positive	0.428	0.159–1.150	0.092			
Surgical treatment						
Partial mastectomy	1			1		
Simple mastectomy	0.479	0.201–1.144	0.098	0.456	0.092–2.243	0.334
Modified Radical mastectomy	0.736	0.249–2.176	0.579	2.275	0.618–8.384	0.217
Chemotherapy						
Yes	1			1		
No	1.111	0.431–2.864	0.828	0.884	0.292–2.674	0.827

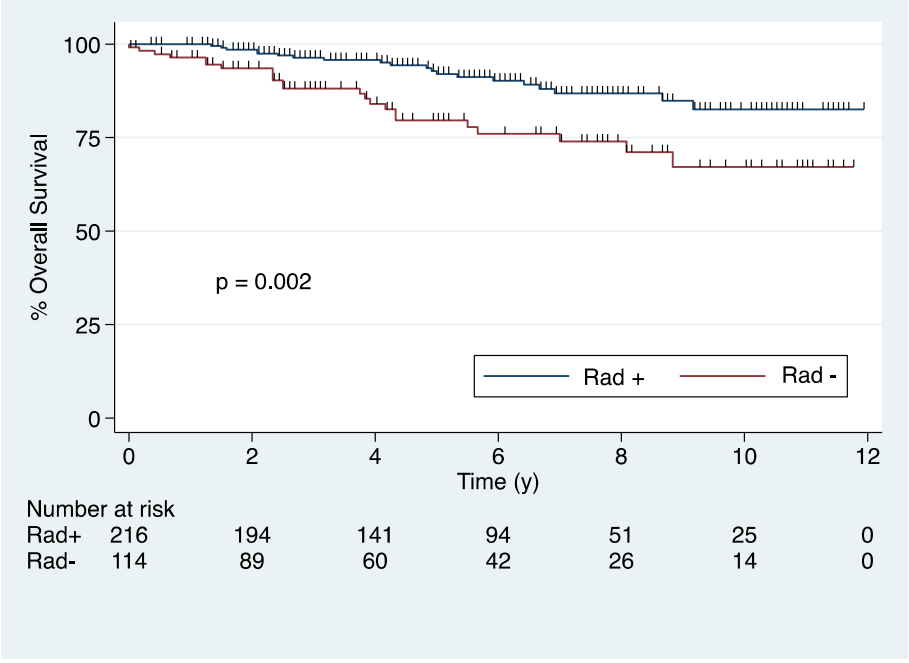

Fig. 5. Kaplan-Meier survival plots for overall survival of node negative patients who underwent partial mastectomy (postoperative radiation versus none).

characteristics and independent predictors of OS and DSS for this subgroup are displayed in Tables 4 and 5, respectively. Based on SEER classification of cause of death, the vast majority of deaths in the node negative patients were due to diseases of heart (24 %), mammary ACC (17 %), miscellaneous malignant cancer (11 %), other cause of death (11 %), and cerebrovascular disease (6 %).

4. Discussion

Mammary ACC is rare [1–4]. It also has a good survival profile

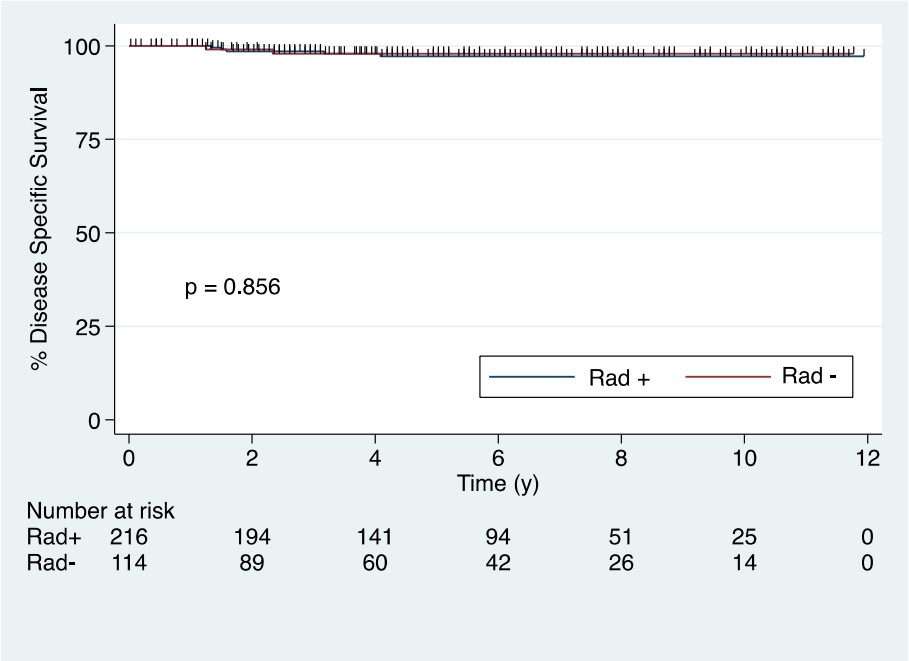

Fig. 6. Kaplan-Meier survival plots for disease specific survival of node negative patients who underwent partial mastectomy (postoperative radiation versus none).

Table 4
Clinicodemographic characteristics of node-negative patients who underwent partial mastectomy.

Characteristics	Postoperative radiation (%)	No postoperative radiation (%)	P – Value
Age at diagnosis (mean ± SD)	60.1 + 11.4	65.9 ± 14.8	<0.001
Race			0.047
White	178	92	
Black	29	10	
Other	9	12	
Sex			0.345
Female	216	114	
Grade			0.084
Well differentiated	77	49	
Moderately differentiated	59	19	
Poorly differentiated	24	11	
Undifferentiated	2	3	
AJCC7 stage			0.460
I	140	72	
II	76	41	
III/IV	0	1	
Tumor stage			0.597
T1	140	72	
T2	73	42	
T3	3	0	
M status			>0.999
M0	216	114	
M1	0	0	
Chemotherapy	20	6	0.200
Estrogen receptor status			0.639
Positive	38	24	
Negative	165	81	
Borderline	1	0	
Progesterone receptor status			0.794
Positive	19	11	
Negative	184	92	
Borderline	1	0	

[5,8]. These factors may subtly undermine the additional survival benefit conferred by postoperative radiation [6]. While there are no prospective and randomized data to drive treatment algorithms for mammary ACC, there are 2 retrospective, large SEER database studies that addressed the role of postoperative radiation. Both studies concluded that postoperative radiation translates to better survival profile [5,8]. The first study included patients diagnosed and treated between 1988 and 2005. Findings from the first study were published in 2010 [5]. The latter study was published in 2016 and covered patients in the database up until 2011 [6]. The finding

Table 5
Multivariate analysis for predictors of overall survival and disease specific survival for node-negative patients who underwent partial mastectomy.

Characteristics	OS			DSS		
	HR	95%CI	P- Value	HR	95 % CI	P-Value
Age at diagnosis	1.074	1.045–1.103	<0.0001	1.012	.952–1.076	0.686
Radiation with surgery	1					
No radiation	1.642	0.828–3.256	0.155	1.008	0.187–5.412	0.992
Estrogen receptor status	1					
Positive	0.165	0.034–0.803	0.026	0.452	0.023–8.680	0.599
Chemotherapy						
Yes	1			1		
No	0.669	0.196–2.277	0.520	0.221	0.041–1.202	0.081
Stage (AJCC 7th edition)						
I vs II/III/IV	1.640	0.849–3.167	0.140	2.601	0.564–12.00	0.220

is not category one level of evidence [16], however, for a rare condition that has a good survival profile, this may be the best that we have to address the role of postoperative radiation in the treatment. It is noteworthy that none of the national and international standards of care for oncology like ASCO, ASTRO and ASBrS has addressed this topic. The NCCN standard of care guidelines briefly mentioned the use of local therapy in the treatment of mammary ACC. This may represent a gap in treatment. A statistically significant better OS credited to postoperative radiation carries respectable merit to warrant its recommendation in the treatment pathway for mammary ACC.

This study explored the data on mammary ACC patients who underwent surgery to see the proportion that received postoperative radiation over the study period. Each year of diagnosis was evaluated, and it showed a range between 36.8 % and 67.3 % (Fig. 7). No trend was demonstrable to suggest increased adoption of postoperative radiation over successive years. Essentially, despite the evidence attesting to the benefit of postoperative radiation, there does not appear to be translation to increased utilization among oncology practitioners. Translation of new research evidence into practice is a multistep process and can sometimes take time [17,18]. However, the published evidence has been around for 10 years and was reinforced by the second study 5 years ago.

Diseases that are infrequently encountered are more likely to be mismanaged because providers are less familiar with the latest evidence regarding their treatment. With recent efforts to promote multidisciplinary approach to cancer treatment, oncology practitioners are referencing national and international guidelines of treatment more frequently. As such, appropriate efforts and resources should be dedicated to examining and incorporating this evidence regarding survival benefit of postoperative radiation to guidelines drawn by frontline oncology associations, such as NCCN, ASCO, ASTRO and ASBrS, for treatment of mammary ACC.

This study showed that 30.7 % (150 out of 488) of the patients underwent simple mastectomy or modified radical mastectomy (Table 1). Coates et al. and Sun et al. reported 39.6 % and 36.4 %, respectively, for total mastectomy or modified radical mastectomy in their series [5,8]. For a disease with a documented excellent survival profile, this finding raises the question why more breast conservation was not applied. Though, it is mostly triple negative (ER, PR, and HER2/NEU) but the biology is rather indolent [19–22], unlike the aggressive triple negative invasive ductal or lobular breast cancer. Could this finding reflect a knowledge gap among oncology care providers? This presents another valid reason to highlight a well-defined treatment algorithm for this disease in the notable oncology guidelines which are easily and frequently

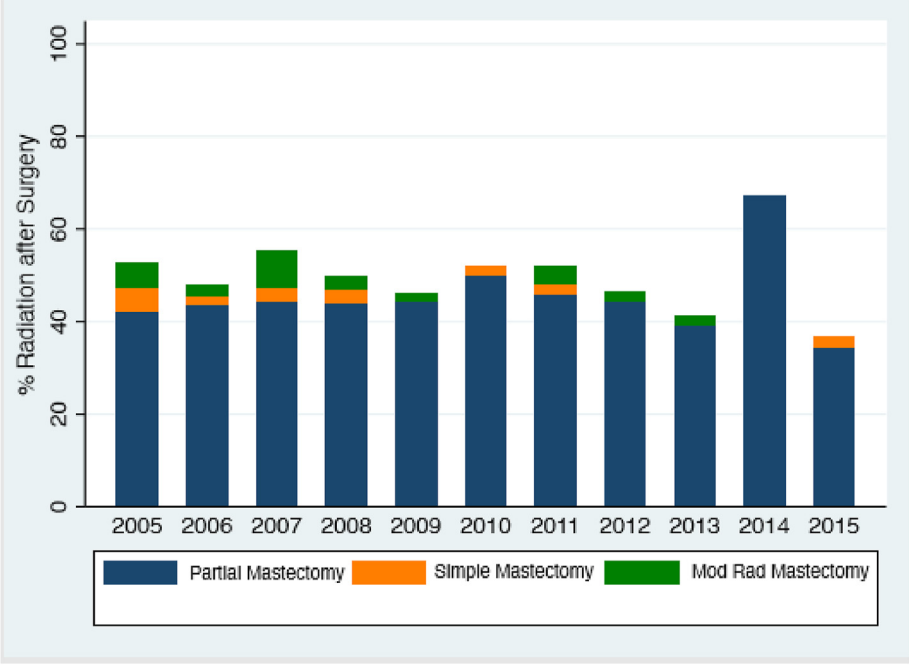

Fig. 7. Histogram showing proportion of patients who underwent postoperative radiation by year of diagnosis.

accessed by care providers. Emphasis on the beneficial role of postoperative radiation may potentially translate to greater utilization of breast conserving procedures [9,13]. With the SEER database, the reason for total mastectomy or modified radical mastectomy could not be ascertained. We hypothesize that this may not be unconnected with presumed aggressive biology (due to triple negative status), previous evidence regarding infiltrative growth pattern of mammary ACC and associated greater risk of recurrence with breast conservation, particularly for patients who did not receive postoperative radiation.

To eliminate biases which may arise due to nodal status (positive nodal status may negatively impact survival from the disease) and type of surgery (total mastectomy patients are likely those who had more extensive local disease and may experience poor OS), we conducted a subgroup analysis for node-negative patients who were treated with partial mastectomy. Postoperative radiation still conferred statistically significant better OS.

This study also showed postoperative radiation to be a positive independent predictor of overall survival. Advanced age is a negative independent predictor of overall survival and disease specific survival. Other independent predictors of OS and/or DSS were AJCC stage III, nodal metastasis and poorly differentiated or undifferentiated disease (Grades 3/4). It is reasonable to propose that patients with these independent predictors should be strongly considered for postoperative radiation treatment in the treatment pathway for mammary ACC.

This is a retrospective study with associated recall or documentation bias. The lack of central pathology review adds to its limitations. To reduce potential errors of misdiagnosis, only patients with histologically confirmed diagnosis were included in the study. Other limitations include lack of granular details or data like surgical margin status, details of radiation therapy and chemotherapy, and data for local recurrence. Regarding patients who received postoperative radiation, 96 % of patients were treated with beam radiation, 3 % were treated with brachytherapy while 1 % had the radiation modality not recorded or specified. Additional details like dose of radiation, inclusion or not of nodal areas in the treatment fields as well as the boost addition in the lumpectomy bed were not available in the SEER data.

Despite these limitations, this is a large sample size study. The SEER database is a national database drawn from 35 % of the population of the United States. Therefore, the findings are generalizable. The data shows overall survival benefit of postoperative radiation. Thus, it should be recommended as part of treatment for mammary ACC, particularly in patients with negative independent predictors of overall survival identified in this study.

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Author contribution

Andrew Gomez-Seoane BA: 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.

Alan Davis PhD: Statistical analysis; review of the manuscript for important intellectual content and final approval of the version to be submitted.

Tolutope Oyasiji MD, MRCSI, MHSA, FACS: Study concept; literature review; acquisition, 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.

Declaration of competing interest

No actual or potential conflict of interest exists.

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