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Original Article

Locoregional Recurrence in Adenoid Cystic Carcinoma of the Breast: A Retrospective, Multicenter Study (KROG 22-14)

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Purpose This study aims to evaluate the treatment approaches and locoregional patterns for adenoid cystic carcinoma (ACC) in the breast, which is an uncommon malignant tumor with limited clinical data.

Materials and Methods A total of 93 patients diagnosed with primary ACC in the breast between 1992 and 2022 were collected from multi-institutions. All patients underwent surgical resection, including breast-conserving surgery (BCS) or total mastectomy (TM). Recurrence patterns and locoregional recurrence-free survival (LRFS) were assessed.

Results Seventy-five patients (80.7%) underwent BCS, and 71 of them (94.7%) received post-operative radiation therapy (PORT). Eighteen patients (19.3%) underwent TM, with five of them (27.8%) also receiving PORT. With a median follow-up of 50 months, the LRFS rate was 84.2% at 5 years. Local recurrence (LR) was observed in five patients (5.4%) and four cases (80%) of the LR occurred in the tumor bed. Three of LR (3/75, 4.0%) had a history of BCS and PORT, meanwhile, two of LR (2/18, 11.1%) had a history of mastectomy. Regional recurrence occurred in two patients (2.2%), and both cases had a history of PORT with (n=1) and without (n=1) irradiation of the regional lymph nodes. Partial breast irradiation (p=0.35), BCS (p=0.96) and PORT in BCS group (p=0.33) had no significant association with LRFS.

Conclusion BCS followed by PORT was the predominant treatment approach for ACC of the breast and LR mostly occurred in the tumor bed. The findings of this study suggest that partial breast irradiation might be considered for PORT in primary breast ACC.

Key words Adenoid cystic carcinoma, Breast neoplasms, Segmental mastectomy, Mastectomy, Radiotherapy, Recurrence pattern

Introduction

Adenoid cystic carcinoma (ACC) of the breast shows distinctive feature, apart from other forms of breast cancer, both in its histological characteristics and clinical behavior. Although ACC originates in the salivary glands, it can sporadically emerge in the breast, constituting 0.1% of all breast cancers [1]. It tends to manifest predominantly in older females, and the most common symptom is a palpable mass, usually near the areola or in the upper outer quadrant of the breast. Breast pain is also a characteristic symptom of ACC, although it is rare [2].

In terms of histopathology, distinguishing breast ACC from other breast cancers at the microscopic level reveals cribriform, tubular, and solid patterns. These are accompanied by dual-cell populations, including myoepithelial and ductal epithelial cells, which can at times mimic benign breast conditions or other malignancies [3]. Also, ACC typically manifests as a triple-negative breast cancer, lacking receptors for estrogen, progesterone, and human epidermal growth factor 2. Triple-negative breast cancers generally have a less favorable prognosis; however, ACC of the breast has shown favorable prognosis. In a review [4], the 5-year local recurrence rate and the 5-year distant metastasis rate of ACC was less than 10% and 15%, respectively. Similarly, a study based on the Surveillance, Epidemiology, and End Results (SEER) database presented that the 15-year survival rate for ACC of the breast was more than 90% [1].

Due to the rare incidence of breast ACC, there is a lack of a universally agreed-upon guideline for its treatment. Nevertheless, previous studies [4,5] suggest that when surgical removal is feasible, procedures like local excision, breast-conserving surgery (BCS), and mastectomy are preferred. Also, some studies suggest that post-operative radiation therapy (PORT) after surgery can help improve the survival for patients with ACC of the breast [6,7]. In another study [8], PORT showed significant benefit in the 5-year locoregional control rates by 12% among the BCS group. The 5-year locoregional control rate between the BCS followed by the PORT group and the mastectomy group was not significant-

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ly different. Despite these efforts, the best way to use radiation therapy for ACC of the breast remains unclear due to the lack of results from randomized controlled trials.

With the steady rise in breast cancer cases in South Korea, it is reasonable to assume a concomitant increase in diagnoses of ACC. However, current studies from South Korea are limited to a few case reports, without multi-institutional studies [9-11]. Therefore, this study aims to analyze treatment and recurrence patterns in patients with ACC of the breast, to better understand the treatment pattern and outcomes for ACC.

Materials and Methods

1. Study patients

Patient records were retrospectively collected from multi-institutions registered in the division of breast cancer in the Korean Radiation Oncology Group (KROG), including 13 centers. Eligible patients were women with pathologically confirmed primary ACC of the breast between January 1992 and December 2022. Exclusion criteria encompassed: bilateral cases, male patients, presence of distant metastasis at diagnosis, prior invasive ductal carcinoma, or ductal carcinoma *in situ* of the breast, other malignancies before or after ACC diagnosis, or history of chest irradiation. From collected patients (n=111), 18 were excluded due to data insufficiencies, constituting a final study cohort (n=93). The study achieved the waiver of written informed consent, aligning with the ethical standards of the Declaration of Helsinki. The KROG and the institutional review boards of participating centers also approved the medical records review.

2. Patient assessment

All patients underwent surgical resection: BCS or total mastectomy (TM). BCS included procedures such as wide local excision, lumpectomy, quadrantectomy, or partial mastectomy. TM involves the removal of the entire unilateral breast tissue, with variations such as simple, radical, modified radical, nipple-sparing, or skin-sparing mastectomy. Tumor size was recorded as the maximum diameter measured from the surgical specimen. In cases of multifocal or multicentric tumors, the largest diameter was noted. A positive resection margin indicated tumors on the inked edge, while a close margin had tumors within 1-mm of the ink. Absence of tumor on the inked edge denoted as a negative margin. For those requiring multiple surgeries due to initially positive margins, the final procedure determined the margin status. Histologic grading adhered to the Nottingham combined histologic grade and was conducted by specialized breast pathologists [12,13]. The histologic grade, according to the ACC of the breast grading system based on the proportion of solid growth, was not provided in this paper because the information was unavailable for about 80% of the patients [14]. Treatment decisions including surgical procedures, PORT, adjuvant chemotherapy, and endocrine therapy were determined by tumor histopathology and patient preference with informed consent. Local recurrence pertained to ACC recurrence within the treated breast or chest wall. 'Tumor bed recurrence' was defined when tumor was recurred within 2 cm from the primary site, and 'Elsewhere recurrence' was defined as otherwise. Regional recurrence involved metastasis to the ipsilateral axillary, internal mammary, or supraclavicular nodes. Any recurrence outside these parameters was classified as distant metastasis.

3. Statistics

The base of follow-up was the date of surgical resection. Chi-square or Fisher's exact tests were performed for categorical variables, and the Student's t test for continuous ones. Survival outcomes, including locoregional recurrence-free survival (LRFS), progression-free survival (PFS), and overall survival (OS) were calculated from the Kaplan-Meier method and assessed via the log-rank test. Both univariate and multivariate analyses were performed by Cox proportional hazard regression models. Factors with a significance level of $p < 0.10$ in univariate analysis progressed to multivariate consideration. A two-tailed $p < 0.05$ was set as the statistical significance threshold. All analyses utilized STATA ver. 17.0 (StataCorp LLC, College Station, TX).

Results

1. Patient characteristics

Patient characteristics are presented in Table 1. All patients underwent surgery, and 76 patients (81.7%) received PORT, whereas 17 patients (18.3%) did not. The median age of patients was 57 years (range, 21 to 84 years). Most patients were either cT1 (42.9%) or cT2 (53.1%) stage. The proportion of cT2-4 was higher (88.9% vs. 58.7%, $p < 0.001$) in the TM group, compared to BCS group. Most patients (93.9%) had cN0 stage. Higher proportion of histologic grade 2 in TM group was observed (85.8% vs. 50.0%, p=0.021). Regarding molecular subtype, there were 14 patients (15.1%) had tumors with estrogen receptor (ER) or progesterone receptor (PR) positive, one patient (1.1%) had those with human epidermal growth factor receptor 2 (HER-2) enriched, and rest of the patients showed those with triple-negative breast cancer (TNBC). The mean ki-67 value was 13.4% (interquartile range [IQR], 5 to 20). According to pathology report, mean tumor size was 2.4 cm (range, 0.4 to 9.0 cm) and TM group had more larger tumor size than BCS group (3.4 cm vs. 2.2

Table 1. Patient characteristics

Variable	Total (n=93)	TM (n=18)	BCS (n=75)	p-value
Age (yr), median (range)	57 (21-84)	58 (37-84)	57 (21-93)	0.687
Clinical T category				
1	39 (41.9)	2 (11.1)	37 (49.3)	< 0.001
2	51 (54.8)	13 (72.2)	38 (50.7)	
3	2 (2.2)	2 (11.1)	0	
4	1 (1.1)	1 (5.6)	0	
Clinical N category				
0	87 (93.6)	17 (94.4)	70 (93.3)	0.863
1	6 (6.4)	1 (5.6)	5 (6.7)	
Histologic grade				
1	32 (40.0)	1 (7.1)	31 (47.0)	0.021
2	45 (56.3)	12 (85.8)	33 (50.0)	
3	3 (3.7)	1 (7.1)	2 (3.0)	
Unknown	13	4	9	
Molecular markers				
ER+ or PR+	14 (15.1)	0	14 (18.7)	0.117
HER-2 enriched	1 (1.1)	0	1 (1.3)	
TNBC	78 (83.8)	18 (100)	60 (80.0)	
Ki-67 (%), mean (IQR)	13.4 (5-20)	13.9 (3-20)	13.2 (5-19)	0.847
Tumor size (cm), mean (range)	2.4 (0.4-9)	3.4 (0.9-9)	2.2 (0.4-5)	< 0.001
Tumor size (cm)				
> 2	38 (50.7)	3 (16.7)	35 (46.7)	0.020
≤ 2	55 (49.3)	15 (83.3)	40 (53.3)	
Metastatic lymph nodes				
pN0	88 (94.6)	16 (88.9)	72 (96.0)	0.230
pN+	5 (5.4)	2 (11.1)	3 (4.0)	
Resection margin				
Clear	68 (74.7)	11 (68.8)	57 (76.0)	0.818
≤ 1 mm	19 (20.9)	4 (25.0)	15 (20.0)	
Involved	4 (4.4)	1 (6.3)	3 (4.0)	
Unknown	2	2	0	
Lymphovascular invasion				
Absent	83 (94.3)	17 (94.4)	66 (94.3)	0.979
Present	5 (5.7)	1 (5.6)	4 (5.7)	
Unknown	5	0	5	
Perineural invasion				
Absent	53 (89.8)	11 (84.6)	42 (91.3)	0.481
Present	6 (10.2)	2 (15.4)	4 (8.7)	
Unknown	34	5	29	
Type of axillary surgery				
Sentinel lymph node biopsy	79 (85.0)	12 (66.7)	67 (89.3)	0.124
Axillary lymph node dissection	12 (12.9)	4 (22.2)	8 (10.7)	
Not done	2 (2.1)	2 (11.1)	0	
Chemotherapy				
Yes	39 (41.9)	7 (38.9)	32 (42.7)	0.771
No	54 (58.1)	11 (61.1)	43 (57.3)	
Hormone therapy				
Yes	16 (17.2)	0	16 (16.1)	0.031
No	77 (82.8)	18 (100)	59 (83.9)	

(Continued to the next page)

Table 1. Continued

Variable	Total (n=93)	TM (n=18)	BCS (n=75)	p-value
Post-operative radiation therapy				
Yes	76 (81.7)	5 (28.8)	71 (94.7)	< 0.001
No	17 (18.3)	13 (71.2)	4 (5.3)	

Values are presented as number (%) unless otherwise indicated. BCS, breast-conserving surgery; ER, estrogen receptor; HER-2, human epidermal growth factor receptor 2; IQR, interquartile range; pN, pathologic N stage; PR, progesterone receptor; TM, total mastectomy; TNBC, triple-negative breast cancer.

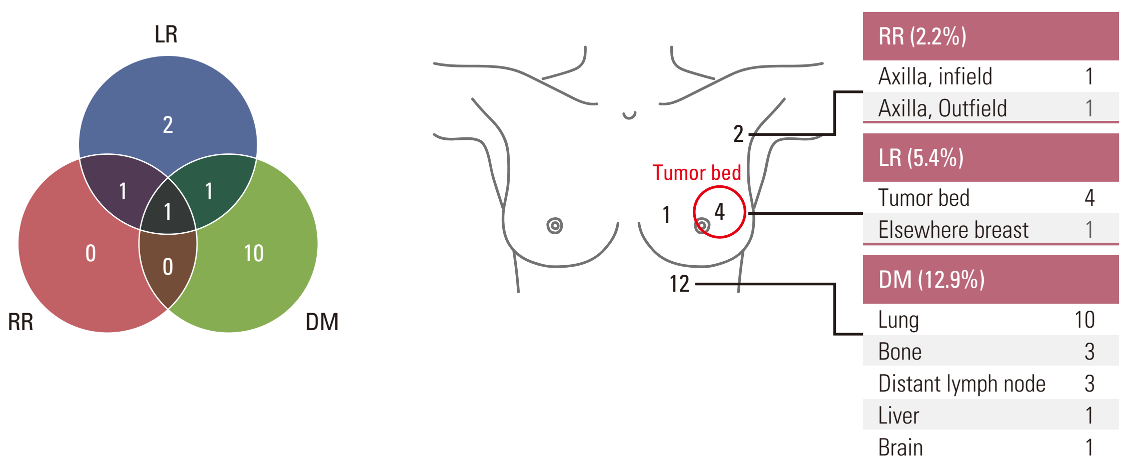

Fig. 1. Pattern of recurrence. DM, distant metastasis; LR, local recurrence; RR, regional recurrence.

cm, $p < 0.001$). Most of them did not have involved nodes (n=88, 94.6%), lymphovascular invasion (LVSI; n=83, 94.3%), or perineural invasion (PNI; n=53, 89.8%). Only four patients (4.4%) had involved resection margin. Types of axillary surgery between two groups were not significantly different, sentinel lymph node biopsy was performed to most patients (n=79, 85%).

Among BCS group, 94.7% (n=71) received PORT whereas 28.8% (n=5) received PORT among TM group ($p < 0.001$). Regarding radiation therapy (RT) field, all patients received PORT in BCS group, without axillar, supraclavicular, or internal mammary lymph nodal regions. On the contrary, in TM group, 60% (n=3) of patients who received PORT had regional nodal irradiation. The mean dose to tumor bed was 54.4 Gy (range, 36.0 to 65.0 Gy; 56.0 Gy in equivalent dose in 2 Gy fractions, with α/β=4 Gy [EQD2] [range, 33.3 to 75.8 Gy]) in BCS group, and 46.6 Gy (range, 40.1 to 52.8; 49.4 Gy in EQD2 [range, 44.5 to 58.2 Gy]) in TM group. The mean dose to breast or chest wall was 45.1 Gy (range, 26.0 to 50.4 Gy; 48.0 Gy in EQD2 [range 39.9 to 58.7 Gy]).

Only one of the 39 patients who received chemotherapy underwent neoadjuvant treatment, while the rest received adjuvant chemotherapy. The most common chemotherapy regimen was doxorubicin-cyclophosphamide, followed by docetaxel-cyclophosphamide.

2. Pattern of local, regional recurrence and distant metastasis

With a median follow-up period of 50 months (IQR, 22.1 to 95.3 months), five cases of local recurrence, two cases of regional recurrence, 12 cases of distant metastasis had occurred (Fig. 1). Among the five cases of local recurrence, four cases (80%) were found in the tumor bed, while the remaining one case was manifested elsewhere in the breast. When stratified by surgery type, BCS group (n=75) accounted for three cases, while TM group (n=18) had two cases (Table 2). Recurrence pattern according to treatment are summarized in Fig. 2. Patients without PORT (n=17) had a 5.9% (n=1) recurrence rate, compared to the 5.3% (n=4) in those with PORT (n=76). Within PORT group, patients receiving partial breast irradiation (PBI, n=7) experienced one case (14.3%) of local recurrence, while those receiving whole breast or chest wall irradiation (WBI, n=69) had three cases (4.4%). In terms of regional recurrence, we found a total of two cases, both of which were within the PORT group: one case was an infield recurrence while the other was not.

Table 2. Comparison of recurrence pattern according to treatments

Variable	LR (n=5)		RR (n=2)		DM (n=12)	
	No. (%)	p-value	No. (%)	p-value	No. (%)	p-value
Surgery						
BCS (n=75)	3 (4.0)	0.249	1 (1.3)	0.307	9 (12.0)	0.598
TM (n=18)	2 (11.1)		1 (5.6)		3 (16.7)	
PORT						
No (n=17)	1 (5.9)	0.919	0	> 0.99	3 (17.7)	0.522
Yes (n=76)	4 (5.3)		2 (2.6)		9 (11.8)	
PBI (n=7)	1 (14.3)	0.291	0	> 0.99	0	> 0.99
WBI (n=69)	3 (4.4)		2 (2.9)		9 (13.0)	
Adjuvant chemotherapy						
No (n=55)	2 (3.6)	0.382	1 (1.8)	0.792	6 (10.9)	0.492
Yes (n=38)	3 (7.9)		1 (2.6)		6 (15.8)	
Treatment modality						
BCS only (n=4)	0	0.337	0	0.218	1 (25.0)	0.514
BCS+RT (n=71)	3 (4.2)		1 (1.4)		8 (11.3)	
TM only (n=13)	1 (7.7)		0		2 (15.4)	
TM+RT (n=5)	1 (20.0)		1 (20.0)		1 (20.0)	

BCS, breast-conserving surgery; DM, distant metastasis; LR, local recurrence; PBI, partial breast irradiation; PORT, post-operative radiation therapy; RR, regional recurrence; RT, radiation therapy; TM, total mastectomy; WBI, whole breast or chest wall irradiation.

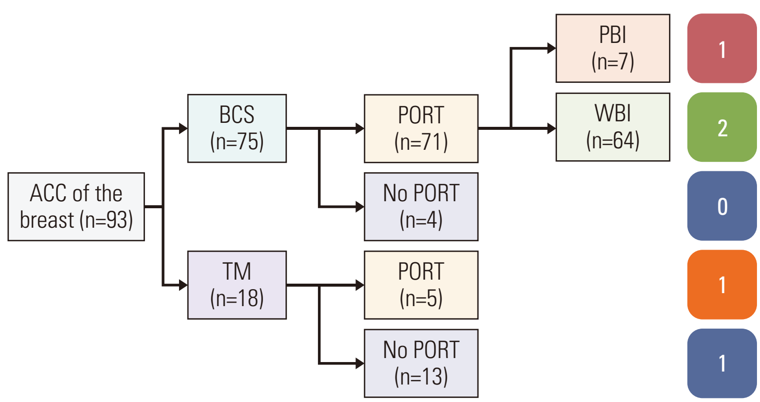

Fig. 2. Local recurrence pattern by treatment. ACC, adenoid cystic carcinoma; BCS, breast-conserving surgery; PBI, partial breast irradiation; PORT, post-operative radiation therapy; TM, total mastectomy; WBI, whole breast or chest wall irradiation.

BCS group (n=75) had a 1.3% regional recurrence rate (n=1) and the TM group (n=18) a 5.6% rate (n=1). Additionally, the group with PORT (n=76) exhibited a 2.6% rate of regional recurrence, regardless of type of surgery. Clinical and pathological characteristics of patients experiencing locoregional recurrence are listed in Table 3. Notably, among five patients who had local recurrence, 60% (n=3) had close or involved resection margin; two patients with involved resection margin and one patient with close resection margin. Among 88 patients who did not experience local recurrence, 22.7% (n=20) had close or involved resection margin. The time to local recurrence was roughly observed to be between 3 and 4 years after surgical resection.

Distant metastasis was detected in 12 patients. The primary distant metastasis site was lung (n=10). The bone and distant lymph nodes were reported to each three cases. Stratifying by surgery type, BCS group had nine cases (12%), and the TM group demonstrated three cases (16.7%). Patients without PORT (n=17) had a distant metastasis of 17.7% (n=3) and those with PORT (n=76) had an 11.8% (n=9). There was no significant difference (p=0.492) in distant metastasis rate between adjuvant chemotherapy group (n=6, 15.8%) and no adjuvant chemotherapy group (n=6, 10.9%).

Table 3. Clinical and pathologic characteristics of patients experiencing local recurrence

No.	Age (yr)	Laterality	Tumor size (cm)	pN	HG	RM	Surgery	E/P/H	Ki-67 (%)	Adjuvant treatment	Recurred site	Time to LR (mo)
1	74	Right	2.2	0	Int	-	BCS+SLNB	–/–/–	20	CTx+RT 50.4 Gy/ 28 fx (PBI)	Tumor bed	32.7
2	64	Left	4.0	0	Low	+	BCS+ALND	–/–/–	8	CTx+RT 61.6 (50.4) Gy/ 28 fx[a)]	Tumor bed → distant LN	35.8
3	64	Left	3.0	0	Low	Close	BCS+ALND	–/–/–	8	CTx+RT 50.4 Gy/ 28 fx	Tumor bed → axilla → distant LN, lung	36.4
4	74	Left	3.6	0	Int	+	TM+SLNB	–/–/–	44	RT (+RNI) 40.05 Gy/ 15 fx	Elsewhere breast, axilla	47.9
5	48	Right	4.5	0	High	-	TM+ALND	–/–/–	3	CTx	Tumor bed	44.5

ALND, axillary lymph node dissection; BCS, breast-conserving surgery; CTx, chemotherapy; E, estrogen receptor; fx, fraction; H, human epidermal growth factor receptor 2; HG, histologic grade; Int, intermediate; LN, lymph node; LR, local recurrence; P, progesterone receptor; PBI, partial breast irradiation; pN, pathologic N stage; RM, resection margin; RNI, regional nodal irradiation covering axillary and supraclavicular lymph nodes; RT, radiation therapy; SLNB, sentinel lymph node biopsy; TM, total mastectomy. [a)]This refers to the tumor bed dose and the breast dose, which were delivered using the simultaneous integrated boost technique.

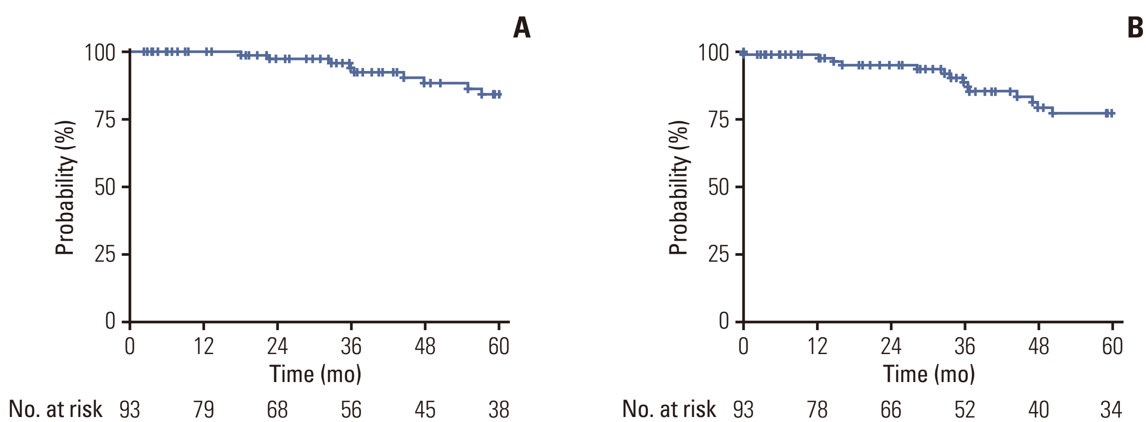

Fig. 3. Kaplan-Meier graphs for locoregional recurrence-free survival and progression-free survival in adenoid cystic carcinoma of the breast. (A) Locoregional recurrence-free survival. (B) Progression-free survival.

3. Survival outcomes

The 3-year and 5-year LRFS rates were 94.0% and 84.2%, respectively (Fig. 3A). PFS rates were 88.6% at 3 years and 77.2% at 5 years (Fig. 3B). OS rates were 98.5% at 3 years and 94.4% at 5 years. Univariate analysis for LRFS revealed that factors such as histologic grade 3 (hazard ratio [HR], 19.8; 95% confidence interval [95% CI], 3.59 to 108.93; p=0.001), positive metastatic lymph node (HR, 9.94; 95% CI, 1.97 to 50.00; p=0.005), LVSI (HR, 5.23; 95% CI, 3.10 to 24.83; p=0.037), and PNI (HR, 5.31; 95% CI, 1.01 to 27.95; p=0.049) were statistically significant (Table 4). PORT (HR, 1.04; 95% CI, 0.22 to 4.95; p=0.952), PBI (HR, 2.76; 95% CI, 0.33 to 23.02; p=0.348), and BCS (HR, 1.04; 95% CI, 0.22 to 4.89; p=0.964) were not statistically significant predictors for LRFS. In a subgroup analysis of patients who underwent BCS, PORT (HR, 0.35; 95% CI, 0.04 to 2.86; p=0.328) also did not appear as a significant predictor for LRFS. Multivariate analysis showed histologic grade 3 (HR, 29.91; 95% CI, 4.87 to 183.57; p=0.001) and the positive metastatic lymph node (HR, 12.71; 95% CI, 2.30 to 7.28; p=0.004) as significant predictors for LRFS. In terms

Table 4. Prognostic factors for LRFS and PFS

Variable	LRFS				PFS			
	Univariate		Multivariate		Univariate		Multivariate	
	HR (95% CI)	p-value	HR (95% CI)	p-value	HR (95% CI)	p-value	HR (95% CI)	p-value
Age < 50 yr	0.76 (0.16-3.59)	0.730	-	-	0.76 (0.21-2.70)	0.672	-	-
HG 3	19.8 (3.59-108.93)	0.001	21.0 (3.28-135.17)	0.001	9.43 (2.02-44.03)	0.004	16.4 (3.09-86.87)	0.001
Tumor size > 2 cm	3.07 (0.65-14.52)	0.157	-	-	1.41 (0.48-4.13)	0.533	-	-
pN+	9.94 (1.97-50.00)	0.005	12.71 (2.30-70.28)	0.004	14.59 (3.62-58.85)	0.001	8.49 (1.79-40.34)	0.007
Ki-67 ≥ 14%	2.50 (0.72-8.63)	0.148	-	-	3.31 (1.15-9.55)	0.027	2.75 (0.81-9.31)	0.705
Close or involved RM	3.10 (0.89-10.76)	0.075	-	-	1.58 (0.53-4.71)	0.415	-	-
LVSI[a)]	5.23 (3.10-24.83)	0.037	-	-	6.61 (1.83-23.88)	0.004	-	-
PNI[a)]	5.31 (1.01-27.95)	0.049	-	-	2.61 (0.55-12.32)	0.227	-	-
BCS (vs. TM)	1.04 (0.22-4.89)	0.964	-	-	1.41 (0.77-2.58)	0.261	-	-
PORT	1.04 (0.22-4.95)	0.952	-	-	0.69 (0.22-2.17)	0.525	-	-
PBI (vs. WBI)	2.76 (0.33-23.02)	0.348	-	-	1.52 (0.19-11.94)	0.689	-	-
Chemotherapy	2.12 (0.60-7.52)	0.246	-	-	1.80 (0.65-4.98)	0.260	-	-
ER/PR positive	N/A	1.000	-	-	N/A	1.000	-	-

BCS, breast-conserving surgery; CI, confidence interval; ER, estrogen receptor; HG, histologic grade; HR, hazard ratio; LRFS, locoregional recurrence-free survival; LVSI, lymphovascular invasion; N/A, not available; PBI, partial breast irradiation; PFS, progression-free survival; PNI, perineural invasion; PORT, post-operative radiation therapy; PR, progesterone receptor; RM, resection margin; TM, total mastectomy; WBI, whole breast or chest wall irradiation. [a)]These factors were excluded in the multivariate analysis for LRFS and PFS due to multicollinearity.

of PFS, univariate analysis demonstrated histologic grade 3 (HR, 9.43; 95% CI, 2.02 to 4.03; p=0.004), the positive metastatic lymph node (HR, 14.59; 95% CI, 3.62 to 58.85; p=0.001), Ki-67 ≥ 14% (HR, 3.31; 95% CI, 1.15 to 9.55; p=0.027), and LVSI (HR, 6.61; 95% CI, 1.83 to 23.88; p=0.004) as significant factors. However, histologic grade 3 (HR, 16.38; 95% CI, 3.09 to 86.87; p=0.001) and the positive metastatic lymph node (HR, 8.49; 95% CI, 1.79 to 40.34; p=0.007) were remained as significant factors in multivariate analysis.

Discussion

ACC of the breast is rare disease, representing about 0.1% of all breast cancers [1]. ACC has a unique composition of both epithelial and myoepithelial neoplastic cells. These cells can exhibit various growth patterns, such as cribriform, tubular, and solid [3]. Notably, ACC of the breast often lacks ER, PR, and HER2, classifying it as a TNBC. However, ACC of the breast typically has a low Ki-67 expression and low potential for malignancy [6]. It exhibits slow progression and generally shows a favorable prognosis. A population-based study demonstrated 5-year, 10-year, and 15-year survival rates of 98.1%, 94.9%, and 91.4%, respectively [1]. Recent studies have shown that the 5-year disease-free survival rate ranges from 82%-100%, and the 5-year OS rate was more than 80% [8,15-17].

In the past, the trend of treating ACC of the breast was local excision alone, resulting in recurrence rates between 6% and 37% [18]. However, a recent review by Goldbach et al. [19] reported a crude local recurrence rate of 9.9%. The use of PORT after BCS has increased, yet its definitive role remains uncertain, mainly due to the lack of results from randomized controlled trials. Some retrospective studies have shown the clinical effectiveness of PORT [6-8]. In the study conducted by Khanfir et al. [8], 66% (n=40) of the 61 patients with breast ACC received PORT. PORT improved the 5-year locoregional control rates by 12% in the BCS group (95% vs. 83%, p=0.03). Additionally, no significant difference was found in the 5-year locoregional control rate between the BCS followed by the PORT group and the mastectomy group (p=0.16). Meanwhile, a study of the SEER database (n=376) revealed that 60% (n=227) of patients underwent lumpectomy, while 40% (n=149) had a mastectomy. Regarding PORT, 93% (n=120) of the lumpectomy group and 7% (n=9) of the mastectomy group received it. PORT was identified as a strong prognostic factor for overall and cause-specific survival [7]. Another SEER database study (n=488) also showed absolute 10-year OS benefit of 10% (82.58% vs. 72.53%, p=0.029) in PORT group compared to no PORT group, but there was no significant difference in disease-specific survival between the two groups [6].

Our study, encompassing 93 patients, provides a comprehensive examination of breast ACC, with a relatively large sample size and detailed clinicopathological information. Most patients in our study cohort (76.3%) underwent BCS followed by PORT. Analysis of recurrence patterns showed that local recurrence preceded regional recurrence, which was confined to the axillary lymph nodes (n=2). Of the local recurrences, 80% were localized to the tumor bed. However, our data indicates that factors such as the type of surgery, PORT, RT field (PBI vs. WBI), and involved resection margin did not significantly influence LRFS or PFS. Instead, the presence of metastatic lymph nodes and a histologic grade of 3 were strongly correlated with worse LRFS and PFS, even in the multivariate analysis. We suppose that the survival concept inherent in LRFS may explain the observed results of pN+ as a significant prognostic factor for LRFS, even though there were no pN+ patients with local recurrence. Among the pN+ patients, three out of five developed distant metastases, and two of them died. The death rate in these patients was higher compared to other patients (2/5 vs. 3 /88). This likely influenced both PFS and LRFS. Regarding distant metastasis, our findings aligned to the recurrence patterns observed in ACC at other sites, with the lungs being the most common metastatic site [20]. Interestingly, use of adjuvant chemotherapy did not significantly influence distant metastasis rate, LRFS, or PFS. Therefore, given the observed predominant recurrence in the tumor bed and the lack of a significant correlation between either PBI or resection margin status and LRFS or PFS, we speculate that PBI might be as effective as WBI when administered as adjuvant RT following BCS.

This study has several limitations. Firstly, its retrospective design might lead to missed information and potential biases. Secondly, factors like lost follow-ups could skew our results. Given the relatively indolent course of ACC of the breast, the median follow-up period of 50 months for the participants in this study may be insufficient to reveal the detailed natural history of ACC of the breast. This issue should be further investigated through long-term follow-up in future studies, such as prospective cohorts. Third, the number of patients in this study remains limited, possibly resulting in the statistical insignificance of some factors. For instance, the count of those who solely received local excision or PORT after TM were 4 and 5, respectively. This brings into question the reported insignificance of PORT in both LRFS and PFS. Also, compared to the 69 patients who received WBI, only a limited number of patients, seven in total, received PBI. The lack of significance found between PBI and LRFS or PFS in this research should be interpreted with caution due to the imbalance in the number of study patients between the two groups.

In conclusion, surgical resection, especially BCS followed by PORT was the predominant treatment approach for ACC of the breast. Local recurrence mostly occurred in the tumor bed, which was a much less frequent event compared to distant metastasis. The findings of this study suggest that PBI might be considered for PORT in primary breast ACC. However, further research is needed to confirm these findings and to establish the optimal treatment approach; proper PORT indications after BCS or TM, and whether PBI could be a substitute for whole breast RT.

Ethical Statement

The institutional review board of each institution approved this study (approval number: H-2212-115-1389 at Seoul National University Hospital), and waived the requirement for obtaining informed consent.

Author Contributions

Conceived and designed the analysis: Lee SM, Jang BS, Shin KH.
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Contributed data or analysis tools: Lee SM, Shin KH.
Performed the analysis: Lee SM, Jang BS.
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Conflicts of Interest

Conflict of interest relevant to this article was not reported.

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