EPIDEMIOLOGY

The effect of local therapy on breast cancer-specific mortality of women with occult breast cancer and advanced nodal disease (N2/N3): a population analysis

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Abstract

Purpose Current NCCN guidelines for occult breast cancer (OBC) recommend modified radical mastectomy, with the option for breast preservation with radiation instead of mastectomy for N1 patients. Our aim was to compare the effect of local therapy—mastectomy versus breast radiation—on breast cancer-specific mortality (BCSM) in a contemporary cohort of OBC patients of all nodal stages.

Methods Competing risk analyses were performed to evaluate the effect of local therapy, nodal stage, and other demographic and clinical prognostic variables on risk of BCSM for women registered in the SEER database with T0N+M0 breast cancer from 2004 to 2015.

Results Of the 353 women with OBC who underwent axillary nodal dissection, 152 received breast radiation and 201 underwent mastectomy. Overall, 57.5% had N1 disease, 54.4% had estrogen receptor (ER) positive tumors, 80.7% were white, and 88.1% received chemotherapy. Women treated with radiation were older ($p < 0.001$). The two groups were comparable with respect to all other variables analyzed. During a median follow-up of 66 months, 32 women died from breast cancer (radiation: 11, mastectomy: 21). Five-year cumulative incidence of BCSM was $8.0\% \pm 2.6\%$ with radiation versus $10.9\% \pm 2.6\%$ with mastectomy ($p = 0.309$). On multivariate analysis, independent predictors of BCSM included older age, higher N stage, and ER negativity, but the type of local therapy was not significantly associated with outcome.

Conclusions These results suggest that breast preservation is a reasonable alternative to mastectomy for OBC patients, regardless of nodal stage.

Keywords Breast cancer · Mastectomy · Radiation · Mortality · Occult primary neoplasm

Abbreviations

ALND	Axillary lymph node dissection
AJCC	American Joint Committee on Cancer
BCSM	Breast cancer-specific mortality
CI	Confidence interval
CSS	Cause-specific survival
ER	Estrogen receptor
HER2	Human epidermal growth factor receptor
HR	Hazard ratio
LRR	Locoregional recurrence
MRI	Magnetic resonance imaging
MRM	Modified radical mastectomy
NCCN	National Comprehensive Cancer Network
NCDB	National Cancer Database
PR	Progesterone receptor
SEER	Surveillance, Epidemiology, and End Results
OBC	Occult breast cancer
OS	Overall survival

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Introduction

Although it has been over a century since Halsted first described occult breast cancer (OBC) [1], the management of OBC remains controversial [2]. OBC is characterized by histologically-proven carcinoma in the regional lymph nodes without clinical or radiographic evidence of disease in the breast. Early reports estimated a prevalence of 0.35–0.5% [3, 4]. The current prevalence is likely lower, given the

widespread adoption of breast magnetic resonance imaging (MRI) which detects a breast lesion in about 70% of patients with otherwise occult primary disease [5]. Given the rarity of OBC, there are few data to guide optimal management. Historically, OBC has been treated similarly to primary breast cancer with nodal metastases with systemic chemotherapy, mastectomy, and axillary lymph node dissection (ALND). While ALND is important for locoregional control as well as staging and prognosis, the impact of surgical removal of the breast on survival is less clear, particularly for patients with negative breast MRI.

Current National Comprehensive Cancer Network (NCCN) local treatment guidelines [6] for OBC recommend modified radical mastectomy (MRM), with the option for breast preservation with radiation instead of mastectomy for patients with N1 disease. Previous studies have examined the impact of various locoregional treatments for OBC on survival and/or locoregional recurrence (LRR) with conflicting findings. However, a significant portion of these data come from patients who were treated prior to the widespread use of breast MRI and thus may not meet current definitions of OBC. Furthermore, the inclusion criteria used in many prior studies preclude extrapolation of results to patients with advanced nodal disease (N2/N3) staged by current guidelines. Our aim was to examine breast cancer-specific survival for the two locoregional treatments described in the NCCN guidelines—MRM and ALND with breast radiation—in a contemporary cohort of OBC patients with any nodal stage.

Methods

Data source and study population

We obtained de-identified patient-level data from the National Cancer Institute's Surveillance, Epidemiology, and End Results (SEER) Program database. SEER collects demographic, clinical, and survival data on all index cancer cases in 18 regions of the United States. The combined catchment areas comprise about 28% of the national population [7]. Data are coded by rigorously-trained chart abstractors using detailed algorithms to ensure consistency. We used SEER*Stat version 8.3.5 to identify females with only one primary tumor in the database [8] diagnosed with non-metastatic OBC (T0N+M0 by Derived AJCC 6th staging variables) between January 1, 2004 and December 31, 2015.

This study was certified by East Carolina University's Institutional Review Board as not meeting criteria for human subject research requiring full review.

Locoregional treatment definitions

Eligible patients were categorized into one of two mutually exclusive locoregional treatment groups according to surgical/treatment codes reported in the SEER database: (1) ALND and mastectomy or (2) ALND and whole breast radiation. ALND was defined as: (1) a breast surgical code that includes an axillary dissection (codes 50–74), and/or (2) SEER variable "Regional Nodes Examined" with code 97, and/or (3) documented removal of at least four regional lymph nodes per the precedent of prior studies [9, 10]. Mastectomy was defined as total mastectomy, nipple-sparing mastectomy, modified radical mastectomy, radical mastectomy, or extended radical mastectomy (breast surgical codes 30–75). Breast radiation was defined as breast surgical code 0 (no breast surgery) or 90 (surgery NOS), with SEER variable "Radiation Recode" values of external beam or radiation NOS; of note, this variable has high specificity, but its sensitivity is only moderate due to missing information [11]. Patients who underwent partial mastectomy (breast surgical codes 20–24) were excluded as they may not meet the definition of OBC.

Patient, tumor, and treatment-related characteristics at time of diagnosis of OBC

Patient characteristics included age, race, and ethnicity. Tumor characteristics included nodal stage, tumor grade, estrogen receptor (ER) status, progesterone receptor (PR) status, and human epidermal growth factor receptor (HER2) status. Since HER2 status was not recorded in the SEER database until 2010, this variable is unavailable for some patients. Per accepted standards [12, 13], borderline ER and PR values were recoded as positive and borderline HER2 values were recoded as unknown. Treatment-related characteristics included year of diagnosis and receipt of chemotherapy.

Study endpoints

The primary endpoint of the study was time to breast cancer-specific death following diagnosis of OBC. The secondary endpoint of the study was time to death from any cause following diagnosis of OBC. Patients alive at the time of last follow-up and/or at the end of the analysis period (December 31, 2015) were right censored.

Statistical analysis

Continuous variables were compared between groups using the two-sample t-test and categorical variables were compared by Fisher's exact test. Median follow-up was calculated using the reverse Kaplan–Meier method.

Overall survival (OS) curves were estimated using the product-limit (Kaplan–Meier) method and compared by the log-rank test. Kaplan–Meier 5-year survival rate is presented along with the standard error using Greenwood's formula. Cumulative incidence function for breast cancer-specific mortality (BCSM) was estimated and compared by Gray's test. 5-year unadjusted cumulative incidence is presented along with the standard error using the Aalen estimator.

Multivariable Cox's proportional hazards model was used to evaluate the association of local therapy (breast radiation versus mastectomy) with the risk of BCSM and overall mortality while controlling for risk factor effects. Prognostic factors included age, ER status, and receipt of chemotherapy. Year of diagnosis was included in the models to account for possible changes in treatment patterns over time. Hazard ratios (HRs) and 95% confidence intervals (CIs) are provided as measures of strength of association and precision, respectively. To evaluate whether local therapy was differentially affected by advanced nodal stage, age, ER status, or chemotherapy, two-way interaction terms were sequentially incorporated into the main effects Cox model.

Since OBC patients treated with neoadjuvant chemotherapy may not be offered the option for mastectomy or breast radiation until several months after diagnosis, a sensitivity analysis was performed to mitigate the potential for delayed entry bias by excluding patients with less than or equal to 6 months of follow-up.

Analyses were performed using JMP v13.0 and SAS v9.4 statistical software (Cary, NC). A p-value of less than 0.05 was considered statistically significant.

Results

Description of cohort

A total of 353 patients were included in the analysis. Of these, 152 women (43.1%) received breast radiation and 201 (56.9%) underwent mastectomy (Fig. 1). Patient characteristics, tumor characteristics, and treatment details are summarized in Table 1. Patients in the breast radiation group were significantly older compared to patients in the mastectomy
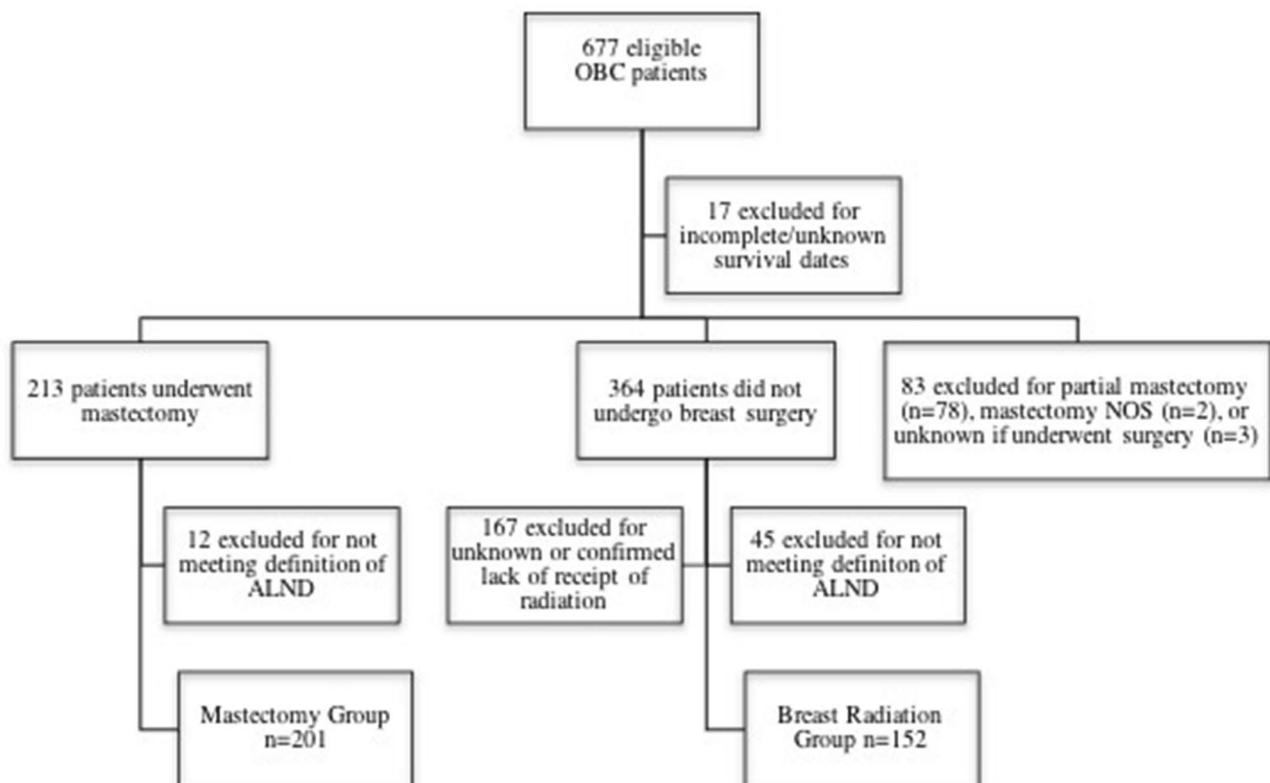

Fig. 1 Eligibility, inclusion and exclusion criteria of study population: Among 677 women diagnosed with T0N+M0 breast cancer during the study period, 353 met the inclusion criteria. *OBC* occult breast cancer, *ALND* axillary lymph node dissection

Table 1 Summary of patient, tumor, and treatment-related characteristics overall and by local therapy

Variable[a]	Statistic or category	Local therapy		Overall (N=353)	p-value
		Mastectomy (N=201)	Breast radiation (N=152)		
Age (years)	Mean (SD)	55.4 (12.5)	60.3 (11.6)	57.5 (12.3)	*<0.001*
	Median	54.0	60.0	57.0	
	Interquartile range	46.0 to 65.0	52.5 to 68.0	48.0 to 66.0	
Race	White	166 (82.6%)	119 (78.3%)	285 (80.7%)	0.377
	Black	25 (12.4%)	20 (13.2%)	45 (12.8%)	
	Other/unknown	10 (5.0%)	13 (8.6%)	23 (6.5%)	
Ethnicity	Non-Spanish–Hispanic–Latino	176 (87.6%)	139 (91.5%)	315 (89.2%)	0.299
	Spanish–Hispanic–Latino	25 (12.4%)	13 (8.6%)	38 (10.8%)	
Nodal stage	N1	116 (57.7%)	87 (57.2%)	203 (57.5%)	1.000
	N2	43 (21.4%)	33 (21.7%)	76 (21.5%)	
	N3	42 (20.9%)	32 (21.1%)	74 (21.0%)	
ER status	Negative	81 (40.3%)	56 (36.8%)	137 (38.8%)	0.634
	Positive	105 (52.2%)	87 (57.2%)	192 (54.4%)	
	Unknown	15 (7.5%)	9 (5.9%)	24 (6.8%)	
PR status	Negative	119 (59.2%)	80 (52.6%)	199 (56.4%)	0.381
	Positive	65 (32.3%)	60 (39.5%)	125 (35.4%)	
	Unknown	17 (8.5%)	12 (7.9%)	29 (8.2%)	
HER2 status	Negative	63 (31.3%)	48 (31.6%)	111 (31.4%)	0.933
	Positive	28 (13.9%)	23 (15.1%)	51 (14.5%)	
	Unknown/not 2010+[b]	110 (54.7%)	81 (53.3%)	191 (54.1%)	
Tumor grade	I/II	13 (6.5%)	7 (4.6%)	20 (5.7%)	0.605
	III/IV	51 (25.4%)	34 (22.4%)	85 (24.1%)	
	Unknown	137 (68.2%)	111 (73.0%)	248 (70.3%)	
Chemotherapy	Yes	183 (91.0%)	128 (84.2%)	311 (88.1%)	0.067
	No/unknown	18 (9.0%)	24 (15.8%)	42 (11.9%)	

Italicized values (*p*-value) indicate statistically significant results

SD standard deviation, *ER* estrogen receptor, *PR* progesterone receptor, *HER2* human epidermal growth factor receptor 2

[a]Categorical variables are presented as the number of patients and percentage for each column

[b]HER2 data were not recorded in SEER until 2010

group (mean 60.3 ± 11.6 vs. 55.4 ± 12.5 years; $p < 0.001$). The distribution of nodal stage was similar between the two groups. Most women had documentation confirming receipt of chemotherapy with a higher proportion in the mastectomy group versus breast radiation group (91.0% vs. 84.2%; $p = 0.0669$). 104 patients in the mastectomy group also received radiation (51.7%), of which 44 had N1 disease, 30 had N2 disease, and 30 had N3 disease.

Survival analyses

The median follow-up was 66 months (interquartile range 26–107) in the breast radiation group and 68 months (interquartile range 32–101) in the mastectomy group. Overall, 44 women died from all causes (15 in the breast radiation group, 29 in the mastectomy group), 32 from breast cancer (11 in the breast radiation group, 21 in the mastectomy

group). No significant difference in overall survival (Fig. 2a) was observed between the two groups (log-rank test: $p = 0.186$). Five-year OS is $87.8\% \pm 2.1$ ($90.3\% \pm 2.8\%$ in the breast radiation group vs. $85.9\% \pm 2.9\%$ in the mastectomy group). No significant difference in the cumulative incidence of BCSM (Fig. 2b) was observed between the two groups (Gray's test: $p = 0.309$). Overall cumulative incidence of BCSM at 5 years is $9.7\% \pm 1.8\%$ ($8.0\% \pm 2.6\%$ in the breast radiation group vs. $10.9\% \pm 2.6\%$ in the mastectomy group).

Results of the multivariable Cox's hazards regression analysis of the risk of BCSM are provided in Table 2. Local therapy (breast radiation versus mastectomy) was not significantly associated with risk of BCSM (HR = 0.621; 95% CI 0.296 to 1.304; $p = 0.2082$). Effect modification was evaluated by sequentially incorporating two-way interaction terms in the main effects model. None of the risk factors evaluated significantly impacted the effect of local therapy, including
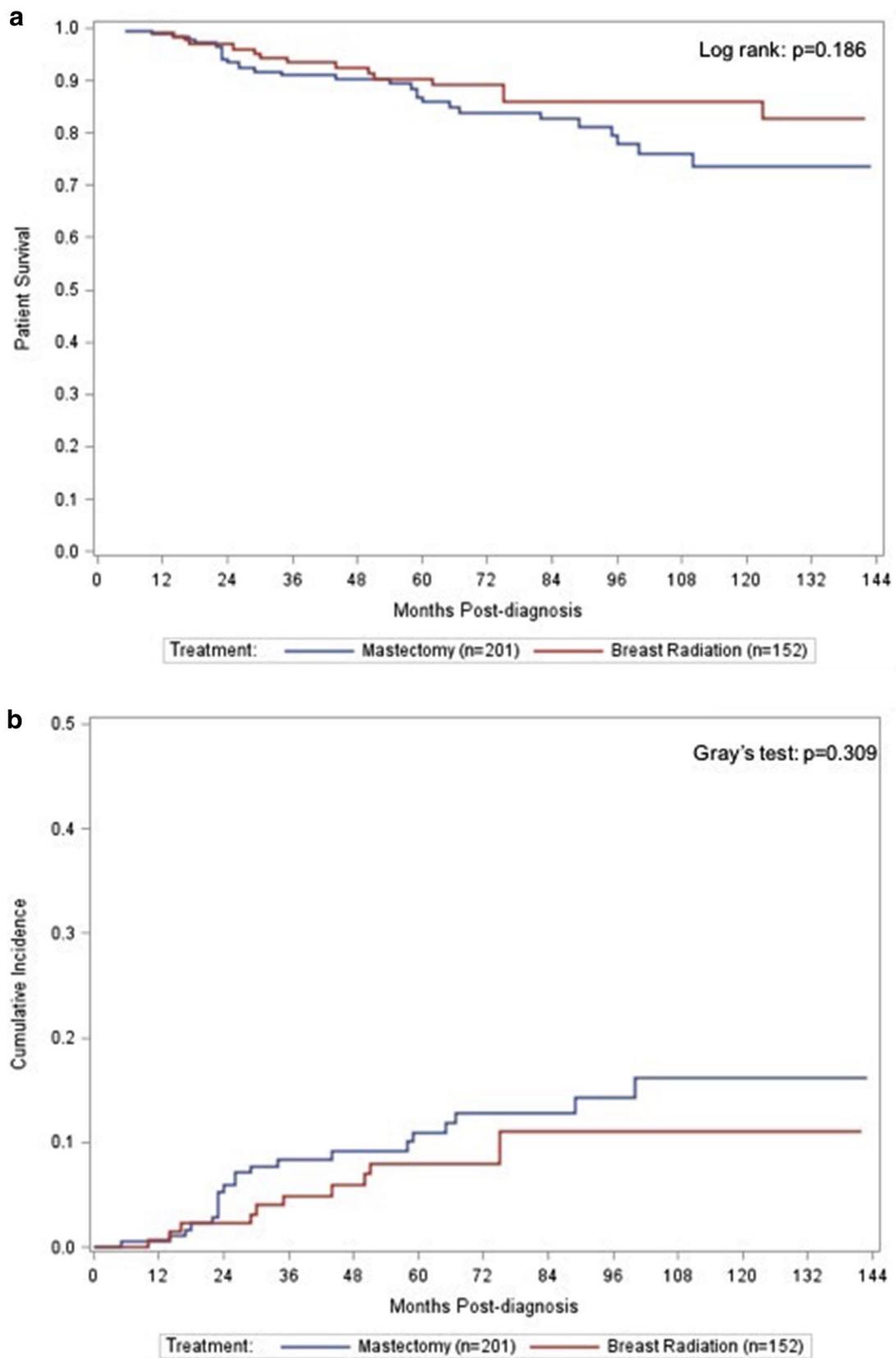
Fig. 2 Survival analyses for occult breast cancer patients treated with axillary lymph node dissection and either breast radiation or mastectomy. **a** Kaplan–Meier overall survival curves by local therapy. **b** Cumulative incidence function of breast cancer-specific mortality by local therapy

Table 2 Multivariable Cox's proportional hazards analysis for breast cancer-specific mortality (BCSM)

a. Main effects model for BCSM

Variable	Comparison	HR	95% CI	p-value
Local therapy	Breast radiation versus mastectomy	0.621	0.296–1.304	0.208
Nodal stage	N2/N3 versus N1	4.114	1.758–9.628	0.001
ER status	Negative versus positive/unknown	2.338	1.121–4.876	0.024
Chemotherapy	Yes versus no/unknown	1.404	0.388–5.079	0.605
Age	Per year increase	1.039	1.007–1.071	0.016
Year of diagnosis	Per year increase	1.071	0.935–1.229	0.323

b. Breast treatment effect modification

Model: main effects + two-way interaction	DF	Wald's χ^2	p-value
Main effects + local therapy × nodal stage	1	0.258	0.612
Main effects + local therapy × ER status	1	0.290	0.590
Main effects + local therapy × chemotherapy	1	0.146	0.703
Main effects + local therapy × age	1	0.631	0.427

Italicized values (p-value) indicate statistically significant results

ER estrogen receptor, HR hazard ratio, CI confidence interval, DF degrees of freedom

advanced nodal stage. In patients with advanced nodal disease (N2/N3) the HR (95% CI) for breast radiation versus mastectomy is 0.687 (0.301–1.570) vs. 0.426 (0.082–2.230) in patients with N1 disease.

Similar results were obtained when analyzing all-cause mortality (Table 3). Results suggest nodal stage, ER status, and age at diagnosis are important prognostic factors, irrespective of local therapy. Sensitivity analysis demonstrated similar results (data not shown).

Discussion

NCCN guidelines for locoregional treatment of OBC recommend MRM for advanced nodal disease, with the option for breast preservation with radiation and ALND restricted to patients with N1 disease. However, the evidence supporting these guidelines, particularly for N2/N3 disease, is limited [14, 15]. We sought to determine the impact of locoregional therapy on BCSM from OBC in the era of breast MRI. In this SEER analysis of contemporary OBC patients, we demonstrate that there is no significant survival benefit from mastectomy compared with breast radiation for not only patients with N1 disease, but also those with N2/N3 disease.

A recent meta-analysis [16] of the surgical management of OBC found similar LRR and OS among patients treated with ALND and either mastectomy (*n* = 112) or breast radiation (*n* = 94). A prior SEER analysis [9] reported that the type of definitive locoregional treatment was not associated with improved OS or cause-specific survival (CSS). However, these reports did not distinguish between N1 and N2/N3 disease. A recent National Cancer Database (NCDB) analysis [10] of a contemporary cohort of OBC patients excluded women with clinical N2b or N3 disease. A major strength of our study is the ability to evaluate the relationship between local therapy and survival outcomes while controlling for differences in nodal disease burden. We selected 2004 as the earliest year of diagnosis for our cohort as this was the 1st year SEER began reporting stage according to the American Joint Committee on Cancer (AJCC) staging schema.

Congruent with our results, the NCDB analysis [10] found lower N stage, age, and ER positivity to be independent predictors of OS. Hessler and colleagues demonstrated improved OS for patients treated with breast preservation (ALND and breast radiation) when compared to MRM. We observed a trend towards improved OS and CSS for patients treated with breast radiation as indicated by HR < 1; as our results have the same effect direction, it is possible that our analysis lacked sufficient statistical power to detect a significant survival difference. Other contributing factors may include differences in patient selection biases between the

two databases, as well as differences in study designs such as exclusion criteria.

Breast MRI is now recommended for patients who initially present following standard breast imaging with apparently OBC [17]. The significance of breast MRI in this setting may not be trivial. A systematic review [5] found that breast MRI detects a malignant breast lesion in 72% of patients with axillary breast cancer with clinically and mammographically occult primary disease. These pre-MRI occult primaries may be clinically significant. Indeed, in the pre-MRI era, observation of OBC without local therapy was associated with significantly poorer outcomes [16, 18, 19].

While the SEER database does not include information about breast imaging, we selected a contemporary cohort of patients to maximize the likelihood of MRI evaluation. It is difficult to determine precisely when MRI for OBC became routine practice. NCCN first listed OBC as a possible indication for breast MRI in the 2009 guidelines [17] and strengthened their recommendation in 2013 [20] by specifying that mammographically occult tumors warrant "special consideration" for MRI workup. Several specialized cancer centers reported on the utility of MRI in this patient population in the late 1990s [21–24]. National surveys of members of the Society of Breast Imaging demonstrate that 51% of breast imaging practices in the United States offered diagnostic breast MRI in 2003–2004 [25], and 75.5% in 2006 [26]. Breast MRI utilization rates in community practice increased more than 20-fold from 2000 to 2009 [27] and nearly tripled from 2005 to 2009 [28]. Taken together, these data suggest that a significant proportion of our cohort were likely evaluated with breast MRI. In contrast, based on the year of diagnosis, it is likely that a significant number of women in the prior SEER analyses [9, 29] may not have received MRI evaluation. In addition, most reports included in the aforementioned meta-analysis [16] defined OBC by negative clinical exam and mammography, so only 43% of patients had a preoperative MRI.

Our data are subject to the usual limitations inherent to retrospective database analyses. One limitation specific to SEER is the inability to differentiate between clinical and pathological stage. As SEER utilizes the best available staging data, it is possible that our analysis includes cT+ patients who had no carcinoma in the MRM specimen, although we did attempt to minimize this possibility by excluding patients who underwent partial mastectomy. Additionally, our study may have failed to capture OBC patients who were upstaged pathologically and thus categorized as T+ by SEER. Among OBC patients with negative MRI, the rate of positive pathology on mastectomy specimens has been reported to be 20–25% [14, 30].

Further studies are needed to evaluate LRR rates among OBC patients of all nodal stages. Two retrospective cohort studies [31, 32] of OBC patients treated with

Table 3 Multivariable Cox's proportional hazards analysis for all-cause mortality

a. Main effects model for all-cause mortality

Variable	Comparison	HR	95% CI	p-value
Local therapy	Breast radiation versus mastectomy	0.567	0.301–1.070	0.080
Nodal stage	N2/N3 versus N1	2.794	1.445–5.404	*0.002*
ER status	Negative versus positive/unknown	2.081	1.121–3.866	*0.020*
Chemotherapy	Yes versus no/unknown	1.028	0.394–2.680	0.955
Age	Per year increase	1.044	1.017–1.072	*0.002*
Year of diagnosis	Per year increase	1.095	0.968–1.238	0.149

b. Breast treatment effect modification

Model: main effects + two-way interaction	DF	Wald's χ^2	p-value
Main effects + local therapy × nodal stage	1	0.258	0.612
Main effects + local therapy × ER status	1	1.565	0.211
Main effects + local therapy × chemotherapy	1	0.548	0.459
Main effects + local therapy × age	1	0.631	0.427

Italicized values (*p*-value) indicate statistically significant results

ER estrogen receptor, *HR* hazard ratio, *CI* confidence interval, *DF* degrees of freedom

MRM or ALND with breast radiation observed similar LRR. Although the vast majority (100% [31] and 92% [32]) of the patients were evaluated with MRI, it is possible that some patients with false-negative MRIs were excluded as Rueth and colleagues [32] did not include OBC patients with carcinoma identified in mastectomy specimens. The infrequent LRR rate observed in these two studies may be partially attributable to a high frequency of N1 disease (84% [31] and 78% [32]). As suggested by Fayanju and colleagues [33], an international, multi-institutional patient registry would facilitate robust longitudinal outcome analyses for this rare presentation of breast cancer.

Conclusion

In patients with MRI-negative OBC, breast preservation appears to be a reasonable option for not only patients with N1 disease, but also for those with advanced nodal disease (N2/N3). Further studies are needed to determine whether the NCCN guidelines warrant reconsideration.

Data availability The data that support the findings of this study are available from SEER but restrictions apply to the availability of these data, which were used under a signed SEER Research Data agreement for the current study, and so are not publicly available. Data are however available from the authors upon reasonable request and with permission of SEER.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval This article does not contain any studies with human participants or animals performed by any of the authors.

Informed consent As this study is based on a publicly available database without identifying patient information, informed consent was not needed.

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