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Original article

Outcome of breast-conserving treatment for axillary lymph node metastasis from occult breast cancer with negative breast MRI

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A B S T R A C T

Purpose: We conducted this study to investigate the prognosis and failure pattern after breast-conserving treatment (BCT) in patients with occult breast cancer (OBC) with negative breast magnetic resonance imaging (MRI) (MRI-OBC).

Materials and methods: Survival rates and failure patterns in 66 patients who received axillary lymph node dissection (ALND) and BCT for MRI-OBC between 2001 and 2013 at seven hospitals were analyzed. OBC was defined as adenocarcinoma in the axillary lymph node (ALN) +/− supraclavicular (SCN) or internal mammary lymph node (IMN) with a negative breast MRI.

Results: Fifty-four patients had only ALN metastasis (ALN only), and 12 patients had ALN metastasis along with SCN or IMN metastasis (ALN + SCN/IMN). Median follow-up was 82 months. The 5-year overall, disease-free, and breast cancer-free survival rates were 93.4%, 92.1%, and 96.8%, respectively. Nine patients experienced recurrence: breast (n = 4), regional lymph nodes (RLN, n = 1), distant metastases (DM, n = 2), breast/RLN (n = 1), and breast/RLN/DM (n = 1). Five-year disease-free survival was significantly higher in ALN only patients compared to ALN + SCN/IMN patients (96.1% vs. 75.0%; $p = 0.02$).

Conclusions: Patients with MRI-OBC were successfully treated with BCT. There was a small risk of ipsilateral breast cancer recurrence. Failure patterns depended on the extent of initial disease.

Introduction

Cancer of unknown primary (CUP) accounts for 5–10% of all cancer cases [1,2], and 10–40% of these patients have metastatic lesions limited to lymph nodes [3]. Axillary lymph node metastasis from unknown primary comprises less than 1% of all malignancies [4]. In females, this presentation is regarded as metastasis from occult breast cancer (OBC) [4–6]. Diagnosis of OBC can be made after imaging and pathologic examinations to exclude a primary breast tumor. With the development of advanced diagnostic modalities, the incidence of OBC has been decreasing [7]. Due to this rarity, there has been paucity of data to provide management guidelines for OBC. It has been recommended that females with OBC be managed like those with primary breast cancer [8], however, there are still unsolved issues regarding optimal treatment and prognosis.

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Recent studies have shown that there is no difference in survival outcome between mastectomy and breast-conserving treatment (BCT) for patients with OBC [9,10]. One was a meta-analysis of previous reports [9] and the other study was based on patient registry database [10]. Therefore, the methods for OBC diagnosis were heterogeneous or undefined in the previous studies. Given that advanced imaging modalities like breast magnetic resonance imaging (MRI) improve the ability to identify breast tumors [11,12], the prognosis of OBC could be affected if these modalities were utilized in the diagnosis. Prior studies have investigated outcome after BCT in patients with OBC diagnosed by contemporary imaging modalities [13,14], but these analyzed only a small number of patients and did not provide convincing evidence regarding prognosis and failure pattern. In this multicenter study, we aimed to investigate the prognosis and failure pattern after BCT in female patients with OBC with negative breast MRI (MRI-OBC). OBC was defined as adenocarcinoma or poorly differentiated carcinoma that presented as regional lymph node (RLN) metastasis in the absence of primary breast tumor.

Materials and methods

This study included female patients who received ALND and BCT for OBC between January 2001 and December 2013 at seven hospitals that are members of the Korean Radiation Oncology Group (KROG). Location of metastasis was identified and grouped as follows: axillary lymph nodes (ALN), supraclavicular lymph nodes (SCN), and internal mammary lymph nodes (IMN). The absence of breast tumor was confirmed by mammography and breast MRI in all patients. Other imaging modalities such as chest computed tomography (CT), positron emission tomography-computed tomography (PET-CT), or breast ultrasonography (US) were performed according to each institution's policy. Patients were excluded from this study if they had cancerous lesions in locations other than the ALN, SCN, or IMN, previous history of other cancer or contralateral breast cancer, or had previous radiotherapy. Patients who were thought to have cancer in the axillary tail of the breast rather than metastasis to ALN were also excluded. In addition to the location of metastasis, the following data were collected: level and number of lymph node metastases, results of tumor immunohistochemical (IHC) staining for estrogen receptor (ER), progesterone receptor (PR), and human epidermal growth factor receptor 2 (HER2), treatment details including surgery, radiotherapy, and systemic therapy. For evaluation of radiotherapy dose, an equivalent dose in 2 Gy fractions (EQD2) was calculated using the linear quadratic model with α/β ratio of 3.5 Gy.

Outcome data including death, locoregional recurrence (LR), distant organ metastasis (DM), and disease status were recorded. Overall survival (OS) was defined as the interval from the date of ALND or neoadjuvant chemotherapy (NAC) to death or the last follow-up date. Disease-free survival (DFS), and breast cancer-free survival (BCFS) were defined as the time from the date of ALND or NAC until cancer recurrence and breast cancer occurrence, respectively. For patients without recurrence, DFS and BCFS were calculated as the interval from the date of ALND or NAC until the date of death or last follow-up. Survival times were estimated using the Kaplan-Meier method. The log-rank test was used to compare survival between groups with different variables. A multivariate Cox stepwise regression model was used to evaluate the influence of variables on survival. Variables with significance at $p < 0.05$ on univariate analysis were retained for multivariate analysis. Statistical significance was defined as p-value <0.05. Statistical analyses were performed using SPSS software, version 22.0 for Windows (IBM Corp., Armonk, NY, USA). This study was approved by the institutional review board of each participating hospital and was exempt from obtaining informed consent from patients. The review committee of the KROG approved this retrospective multicenter study and named it KROG1803.

Results

Patient characteristics and treatment

A total of 66 patients were included for analysis. Details of patient and treatment characteristics are described in Table 1. Pathologic diagnoses of ALN were as follows: carcinoma (n = 27), adenocarcinoma (n = 24), ductal carcinoma (n = 7), poorly differentiated carcinoma (n = 6), lobular carcinoma (n = 1), and mucinous carcinoma (n = 1). ALND was performed in all patients; blind upper quadrantectomy was performed in 15 patients. No patients showed malignant lesion in the quadrantectomy specimen. Fifty-four patients had ALN metastases and 12 had ALN metastases along with SCN or IMN involvement (ALN + SCN/IMN). The median number of dissected lymph nodes was 18 (range, 2–77). Among 10 patients with SCN metastases, selective neck dissection was performed in one patient, while excision of metastatic SCN was performed in nine patients. Of 3 patients with IMN metastases, one received IMN excision and the other 2 had biopsy only.

All patients received radiotherapy. Except 3 patients, all patients received ipsilateral whole breast irradiation (WBI). Radiotherapy field was determined at the discretion of the attending radiation oncologist. Details of the fields by extent of nodal metastasis were presented in Table 2. In patients with ALN only metastases, total radiation doses to whole breast (WB) and/or RLN ranged from 40.05 Gy to 50.4 Gy. Radiotherapy was administered in 15–28 fractions, with a daily dose of 1.8–2.67 Gy EQD2 for WB and/or RLN ranged from 44.9 Gy to 50.0 Gy. Of the 10 patients with SCN metastasis, 9 patients received SCN radiotherapy with a total dose of 45–60 Gy in 20–30 fractions at 1.8–2 Gy per fraction, while 1 patient did not receive SCN irradiation. EQD2 for the SCN ranged from 43.4 Gy to 60.0 Gy. Of the 3 patients with IMN metastasis, 2 patients had IMN irradiation with a total dose of 50–60 Gy in 25–30 fractions with a daily dose of 2 Gy.

Chemotherapy was administered to all but 3 patients. NAC was administered before ALND in 11 patients. Of these 11 patients, 2 showed a complete response in ALN based on pathological examination of the surgical specimens. Hormonal therapy and anti-HER2 agents were used in 30 and 12 patients, respectively. Of the 28 patients with hormone receptor-positive (HR+, i.e. ER+/and or PR+) tumor, all received hormonal therapy. One patient with ER-/PR-/HER2-and another patient with unknown IHC status received hormonal therapy according to the attending physician's decision. Of the 19 patients with HER2+ cancer in ALN, 12 patients had undergone anti-HER2 therapies.

Failure patterns

The median follow-up period for all patients was 82 months (range, 10–178). Nine patients (13.6%) experienced recurrence. Sites of recurrence were as follows: four (6.1%) in the ipsilateral breast, one (1.5%) in the RLN, one (1.5%) in the breast and RLN, two (3.0%) in distant organs, and one (1.5%) in the breast, RLN, and distant organs simultaneously (Table 3). Cancer in the ipsilateral breast developed in six patients (9.1%) within 13–134 months after the completion of treatment. The incidence of breast cancer occurrence was significantly lower among patients who received WBI compared to those who did not (6.3% (4/63) vs. 66.7% (2/3); $p = 0.02$). Characteristics of the patients who developed breast cancer are provided in Supplementary Table 1.

Table 1
Patient's characteristics.

Characteristics		Number of patients (%)
Age	≤50	28 (42.4)
(median 54, range 32–78)	>50	38 (57.6)
Location of lymph node metastasis	ALN only	54 (81.8)
	ALN and SCN	9 (13.7)
	ALN and IMN	2 (3.0)
	ALN, SCN and IMN	1 (1.5)
Number of metastatic lymph nodes	≤4	39 (59.1)
(median 4, range 0[a]-75)	5–9	12 (18.2)
	>9	15 (22.7)
IHC subtype	ER+/and or PR+/HER2-	16 (24.2)
	ER+/and or PR+/HER2+	12 (18.2)
	ER-/PR-/HER2+	7 (10.6)
	ER-/PR-/HER2-	25 (37.9)
	Unknown	6 (9.1)
Mammography	Performed	66 (100)
	Not performed	0 (0.0)
Breast MRI	Performed	66 (100)
	Not performed	0 (0)
Breast US	Performed	62 (93.9)
	Not performed	4 (6.1)
Chest CT	Performed	66 (100)
	Not performed	0 (0.0)
PET-CT	Performed	63 (95.5)
	Not performed	3 (4.5)
Surgery for breast	Blind quadrantectomy	15 (22.7)
	Not performed	51 (77.3)
Radiotherapy field	WB	12 (18.2)
	WB + RNL	51 (77.3)
	RNL alone	3 (4.5)
Radiotherapy dose (EQD2)	≤48.6 Gy	39 (59.1)
(median 48.6 Gy)	>48.6 Gy	27 (40.9)
Chemotherapy regimen	CMF	2 (3.0)
	AC	9 (13.6)
	AC-T	48 (72.7)
	AT	4 (6.1)
Chemotherapy sequence	Neoadjuvant	11 (16.7)
	Adjuvant	52 (78.8)
	None	3 (4.5)
Hormone therapy	Administered	30 (45.5)
	Not administered	36 (54.5)
Anti HER2 therapy	Administered	12 (18.0)
	Not administered	54 (82.0)

Abbreviations: ALN, axillary lymph node; SCN, supraclavicular lymph node; IMN, internal mammary lymph node; IHC, immunohistochemical staining; ER, estrogen receptor; PR, progesterone receptor; HER2, human epidermal growth factor receptor 2; MRI, magnetic resonance imaging; US, ultrasonography; CT, computed tomography; PET-CT, positron emission tomography-computed tomography; EQD2, equivalent dose in 2 Gy fractions; CMF, cyclophosphamide, methotrexate, and fluorouracil; AC, doxorubicin and cyclophosphamide; AC-T, doxorubicin and cyclophosphamide followed by paclitaxel or docetaxel; AT, doxorubicin and paclitaxel or docetaxel; WB, whole breast; RLN, regional lymph node; WB + RLN, whole breast and regional lymph node.

[a] Neoadjuvant chemotherapy was administered before ALN dissection in 11 patients. Of the 11 patients, 2 showed pathological complete response of ALN in surgical specimens. The number of metastatic lymph nodes encompasses ALN, SCN, and IMN.

Table 2
Extent of radiotherapy according to location of metastatic lymph nodes.

	ALN only		ALN + SCN/IMN		
Extent of radiotherapy	≤3 (+) ALN	>3 (+) ALN	ALN + SCN	ALN + IMN	ALN + SCN + IMN
Breast alone	11 (35.5%)	–	1 (11.1%)	–	–
Breast/SCN	14 (45.2%)	20 (86.9%)	6 (66.7%)	1 (50.0%)	–
Breast/SCN/IMN	4 (12.9%)	3 (13.1%)	1 (11.1%)	1 (50.0%)	1 (100.0%)
ALN alone	1 (3.2%)	–	–	–	–
ALN/SCN	1 (3.2%)	–	1 (11.1%)	–	–
Total	31 (100.0%)	23 (100.0%)	9 (100.0%)	2 (100.0%)	1 (100.0%)

Abbreviation: ALN, axillary lymph node; SCN, supraclavicular lymph node; IMN, internal mammary lymph node; (+) ALN, number of positive axillary lymph nodes.

Survival rates

The 5-year OS, DFS, and BCFS of all patients were 93.4%, 92.1%, and 96.8%, respectively. When prognostic factors were evaluated in a univariate analysis, location of lymph node metastasis and receipt of WBI were significant for predicting DFS. Patients with more than 4 metastatic lymph nodes had lower 5-year DFS than did those with 4 or less nodal metastases without statistical significance (85.2% vs. 97.3%, $p = 0.19$). Furthermore, patient age, receipt of breast surgery, IHC subtype, and receipt of taxane chemotherapy were not related to DFS in the univariate analysis (Table 4). In multivariate analysis, the location of lymph node metastasis was the only prognostic

Table 3
Failure pattern according to location of lymph nodes metastases.

Sites of failure	ALN only (n = 54)	ALN + SCN/IMN (n = 12)	*p*-value
Breast	2 (3.7%)	2 (16.7%)	0.60
RLN	0 (0.0%)	1 (8.3%)	
Breast & RLN	1 (1.9%)	0 (0.0%)	
Distant	0 (0.0%)	2 (16.7%)	
Breast & RLN & distant	0 (0.0%)	1 (8.3%)	

Abbreviation: ALN, axillary lymph node; SCN, supraclavicular lymph node; IMN, internal mammary lymph node; RLN, regional lymph nodes.

factor for DFS; ALN + SCN/IMN were significantly related to inferior 5-year DFS (75.0% in ALN + SCN/IMN vs. 96.1% in ALN only, $p = 0.02$) (Fig. 1). Administration of WBI was associated with longer DFS in the univariate analysis but significance was lost in the multivariate analysis. The 8-year DFS for patients with WBI (n = 63) was 89.5%, and 50.0% for those without WBI (n = 3) ($p = 0.02$; Fig. 2).

Discussion

In this multicenter study we evaluated outcome and failure pattern after BCT in 66 female patients with MRI-OBC. To our knowledge, this is the largest study describing prognosis of BCT in the management of MRI-OBC. Multimodal BCT including ALND, radiotherapy, and systemic therapy resulted in a favorable outcome. Approximately 9% of our patients had a recurrence in the ipsilateral breast after completion of BCT. The anatomic extent of lymph node involvement was significantly associated with prognosis. Among the patients having metastases limited to the ALN, there was only a small number of LRs and none had metastasis to distant organs. Meanwhile, patients whose disease initially involved the SCN or IMN were at greater risk of both DM and LR after BCT.

In past years, mammography or breast US have been the main diagnostic tools for identifying breast lesions in patients with ALN metastasis with unknown primary [4,15,16]. However, these modalities exhibit low sensitivity for detecting the primary breast lesion [17]. The overall sensitivity of mammography for detecting breast cancer is approximately 77%, which is reduced to 47–64% in

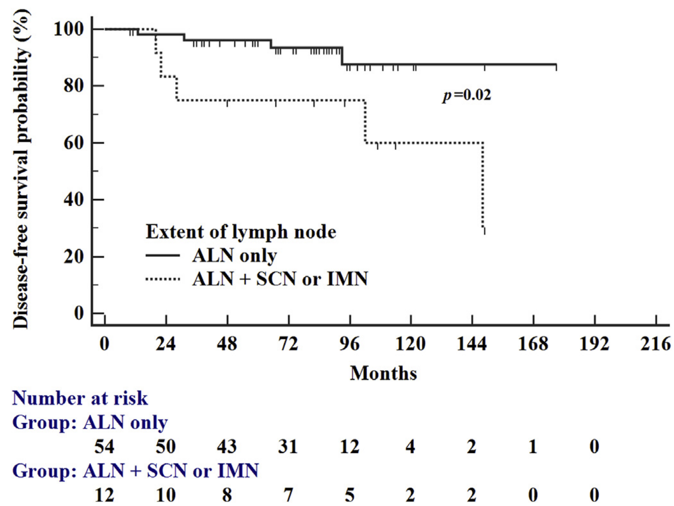


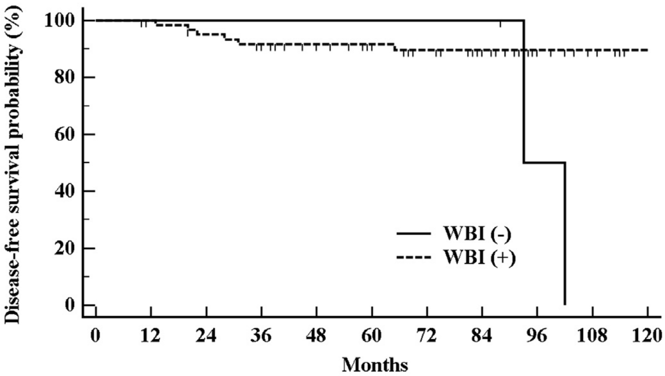
Fig. 1. Disease-free survival according to initial disease extent in patients with occult breast cancer.

females with dense breast tissue [17]. A study of mammographically diagnosed OBC showed that a primary breast tumor was identified in 20 of 64 patients (31.2%) after mastectomy [18]. Historically, up to 82% of patients with mammographically or ultrasonographically diagnosed OBC showed breast cancer in their mastectomy specimens [4,16,19,20]. Supplementing breast MRI to

Table 4
Prognostic factors for disease-free survival.

Characteristics		5-yr DFS (%)	10-yr DFS (%)	Univariate	Multivariate[a]	HR (95% CI)
Age	≤50 (n = 28)	89.1	77.8	0.58	–	–
	>50 (n = 38)	94.4	81.0			
Number of metastatic nodes	≤4 (n = 39)	97.3	84.1	0.19	–	–
	>4 (n = 27)	85.2	74.5			
Nodal location	ALN only (n = 54)	96.1	87.7	0.02	0.01	5.9 (1.4–25.5)
	ALN + SCN/IMN (n = 12)	75.0	60.0			
Surgery for breast	Not performed (n = 51)	91.7	82.1	0.92	–	–
	Performed (n = 15)	93.3	77.8			
Radiotherapy to breast	Not performed (n = 3)	100.0	0.0	0.02	–	–
	Performed (n = 63)	91.7	89.5			
HR + subtype	No or unknown (n = 38)	91.6	73.7	0.30	–	–
	Yes (n = 28)	90.6	92.9			
Taxane-based CTx	Not received (n = 14)	100.0	100.0	0.15	–	–
	Received (n = 52)	85.9	80.6			

Abbreviations: DFS, disease-free survival; HR, hazard ratio; CI, confidence interval; LNs, lymph nodes; ALN, axillary lymph nodes; SCN, supraclavicular lymph nodes; IMN, internal mammary lymph nodes; HR+, hormone-receptor positive; CTx, chemotherapy.
[a] Variables with significance at $p < 0.05$ on univariate analysis were retained for multivariate analysis.



Number at risk

	0	12	24	36	48	60	72	84	96	108	120
Group: WBI (-)	3	3	3	3	3	3	3	3	1	0	0
Group: WBI (+)	63	61	57	53	48	42	35	26	16	12	6

Fig. 2. Disease-free survival according to whole breast irradiation.

mammography or US elevates the detection sensitivity up to 100% in screening for breast cancer among high-risk patients [21,22]. Likewise, MRI could visualize a primary breast lesion in 36–86% of mammographically or ultrasonographically diagnosed OBC [23]. Therefore, breast MRI is a crucial modality for defining OBC in current clinical practice. In our study, all patients underwent breast MRI in conjunction with mammography to confirm the absence of a breast primary. Moreover, all participants were examined with chest CT, and over 95% received PET-CT to confirm the absence of other organ involvement. Accordingly, patients included in our study were diagnosed with truly OBC using modern imaging modalities. By analyzing the outcomes in these patients, we hoped to update knowledge regarding prognosis of OBC.

Mastectomy had been utilized for the management of OBC in previous years [24]. Non-academic centers or rural hospitals were more likely to perform mastectomy than BCT [10]. According to population-based studies, approximately 40% of OBC patients have been treated with mastectomy [6,10,25]. In a 2004 survey of 776 breast surgeons in the United States, 43% of responders preferred mastectomy while 37% opted for BCT [24]. Nonetheless, there is increasing evidences that BCT results in a comparable or better outcome than mastectomy in patients with OBC [9,10,26]. Even though several studies reported the outcome of OBC in past years, a large proportion of these studies included patients who had primary breast cancer revealed in their mastectomy specimen [4,18,27]. Moreover, diagnostic modalities used in previous studies were mainly mammography or US [15,16,18,28] (Table 5). Thus, it is possible that outcomes following BCT were undervalued in previous studies. Breast MRI has only recently become increasingly utilized as a routine tool in diagnosing OBC. A recent study showed favorable prognosis in MRI-OBC patients after BCT [14], with 4 recurrences among 25 patients (2 in the breast and 2 in distant organs), and a 5-year DFS of approximately 80%. We also found a favorable outcome after BCT in this study. Our 5-year DFS rate was 92.1% in all patients and 96.1% in patients with metastasis limited to the ALN. Taken together, BCT is an appropriate treatment for MRI-OBC, with low risk of local and regional recurrences.

Breast cancer occurred in 9% of our patients after completion of BCT. Other studies have reported ipsilateral breast occurrence rates ranging from 0 to 26% after various treatment modalities [13–16] (Table 5). The rates of breast cancer occurrence were different depending on type of breast surgery and whether MRI was used for diagnosis of OBC. Among patients who underwent BCT, the rate of breast cancer occurrence was lower when patients were examined with breast MRI. In studies where breast MRI was performed in less than 40% of the enrolled patients, 25–26% of patients had ipsilateral breast cancer occurrence after BCT [15,16]. However, in the study by McCartan et al. [14] and this one, where breast MRI was performed in all patients, the rates of breast cancer recurrence after BCT were 8% and 9.1%, respectively. In addition, in a study by Rueth et al. there was no breast cancer recurrence after BCT among 27 patients, 91% of whom underwent breast MRI [13]. The low rate of breast cancer recurrence in the studies by Rueth [13] and McCartan [14] might be partially attributable to the high proportion of TxN1 disease among their study populations. In addition, it is thought that confirmation of the absence of a breast primary tumor using MRI is the first step for successful breast cancer control in OBC patients treated with BCT.

Radiotherapy is an essential element when BCT is planned for OBC. Nonetheless, the target and dose are uncertain in patients with OBC. In our study, radiotherapy was applied to various regions depending on the number of involved lymph nodes, extent of disease involvement, and the treating physician's judgement (Table 2). Likewise, different irradiation fields were adopted in previous studies, with ipsilateral WBI having been performed in 73–100% of patients [13–16]. Two previous studies found that WBI was significantly associated with reduced breast cancer recurrence with a 5-year BCFS of 84% for the WBI group, and 34–64% for the non-WBI group [15,16]. However, these studies did not apply breast MRI to all patients, and are thus insufficient for fully evaluating the benefit of WBI. In studies where breast MRI was performed in all patients, the rate of breast cancer recurrence was 0–8% when WBI was performed [13,14]. Similarly, 6.3% of the patients who received WBI in our study developed breast cancer. We found that the rate of breast cancer recurrence was significantly lower in patients who received WBI than those who did not. However, there were only 3 patients in the non-WBI group, making it difficult to definitively conclude that WBI is essential for the treatment of OBC. Therefore, caution is necessary when interpreting the result. Interestingly, we also found that four of the six breast recurrence developed five years after the completion of BCT. The four recurrences were limited to the breast without a failure in other organs. Therefore, it is probable that the four breast cancer recurrences were secondary primary breast cancers rather than a true recurrence. Further studies are needed to ensure the benefit of WBI and to understand the pathogenesis of breast cancer recurrence in patients with OBC.

Prognosis of OBC differed depending on nodal stage in the present study. Advanced nodal stage has been previously reported to have negative impact on survival in OBC [6,25]. According to one study, OBC patients having less than four lymph node metastases (pT0/TxN1) had better survival than pT1N1 patients, and patients with more than four positive lymph nodes (pT0/TxN2 or pT0/TxN3) had similar survival to those with pT1N2/N3 breast cancer [6]. In our study, patients with more than four metastatic lymph nodes had lower DFS than did those with involvement of four or less nodes. However, DFS difference was not statistically significant. Our study's small sample size might have contributed to the absence of statistical significance of the number of positive lymph nodes. Instead of the number of metastatic nodes, the level of nodal metastasis was an important prognostic factor for DFS in our study. Because most studies on OBC included patients having metastasis limited to the ALN, the nodal stage presented in the previous studies took only the number of involved lymph nodes into account, not level of involvement. Unlike previous OBC studies, our study contained 12 patients with ALN + SCN/IMN metastasis. Based on the negative prognostic effect of ALN + SCN/IMN involvement in DFS, the level of nodal metastasis must be considered when determining the treatment strategy for OBC. Even if the patients

Table 5
Previous reports on outcome of multimodal treatment in patients with OBC.

Study	Types of study	No. cases	Years[a]	Breast MRI	Type of treatment	Extent of RT	Breast ca. occurrence	Survivals	Comment
Macedo et al[b)] [9]	Meta-analysis	241 (7 studies)	1973–2011	5–91.7%	ALND + TM (46.5%) ALND + RT (39.0%) ALND alone (14.5%)	NR	9.8%[c)] 12.7%[c)] 34.3%[c)]	17.9%[d)] (mortality rate) 9.5% 31.4%	Included studies that found primary tumor in mastectomy specimen (28.9%)
Hessler et al. [10]	Population based (NCDB)	1231	2004–2013	NR	TM (48.1%) ALND + RT (27.8%) ALND (8.6%) Observation (15.5%)	NR	NR	80.0% at 5-yrs (OS) 90.8% 76.2% 56.5%	–
Kim et al. [25]	Population based (SEER)	1045	1983–2013	NR	TM (39.3%), BCS (13.4%)	NR (RT in 49.6%)	NR	81.5% (RT), 5-yr OS 78.3% (non-RT)	–
Sohn et at al. [6]	Multicenter	142	1990–2009	NR	ALND + TM (38.0%) ALND + BCS (39.4%) ALND (22.5%)	NR (RT in 59.9%)	NR	92.5% at 10-yrs (OS) 98.0% 80.0%	About 67% had N1 disease
Masinghe et al. [15]	Single institution	53	1974–2003	28.3%	No breast surgery ALND (47%), Excision (45%), Sampling (8%)	Breast (23%), Breast + RNI (54%), RNI (11%) None (19%)	26.0%	69.4% at 5-yrs, DFS 54.8% at 10-yrs	N1 (43%), N2 (21%), NR (36%)
Barton et al. [16]	Single institution	48	1975–2009	36.4%	ALND (81.3%), lymph node excision (18.8%), lumpectomy (6.3%)	Breast (6.3%) Breast + SCN (56.3%) Breast + axilla (10.4%) No RT (27.0%)	25.0%	64.0% (breast RT),5-yr DFS 34.0% (non-breast RT)	–
Rueth et al. [13]	Single institution	36	2000–2011	91.7%	ALND (91.7%), TM (25.0%), no breast surgery (75.0%)	Breast (91.7%), RNI (77.8%)	0.0%	5-yr OS 100.0%	N1 (77.8%), N2 (16.7%), N3 (5.6%)
McCartan et al. [14]	Single institution	38	1996–2011	100.0%	ALND + WBRT (65.8%) ALND + TM (34.2%)	Breast (100%), RNI (55.3%), chest wall (46.2%)	8% (only in WBRT group)	77.0% for TM, 10-yr DFS 67.0% for WBRT	N1 (57.9%), N2 (31.6%), N3 (10.5%)
The present study	Multicenter	66	2001–2013	100.0%	ALND + BCT (100.0%)	Breast (18.2%), Breast + RNI (75.7%), RNI (6.1%)	9.1%	92.1% at 5-yrs, DFS 80.6% at 10-yrs	Included 12 patients with SCN or IMN metastasis

Abbreviation: MRI, magnetic resonance imaging; RT, radiotherapy; ALND, axillary lymph node dissection; TM, total mastectomy NR, not reported; LR, locoregional; NCDB, the National Cancer Database of the United States; OS, overall survival; SEER, the Surveillance, Epidemiology and End Results Program; BCS, breast-conserving surgery; RNI, regional lymph node irradiation; DFS, disease-free survival; SCN, supraclavicular lymph nodes.
[a] years of patient's accrual or periods of study inclusion.
[b] The meta-analysis included seven published studies.
[c] Locoregional recurrence rate.
[d] Crude mortality rate.

with ALN + SCN/IMN metastasis had a lower DFS than those without metastasis, the prognosis is still thought to be favorable, given that the 5-year DFS rate was 75%. Therefore, it is thought that BCT can be safely administered to patients with ALN + SCN/IMN metastases. In addition, since a quarter of the patients experienced distant metastasis, it is necessary to provide more effective systemic treatment for patients with positive ALN + SCN/IMN.

In breast cancer, treatment responsiveness and recurrence patterns differ according to molecular subtype [29]. Molecular subtype-specific treatments such as hormonal therapy and anti-HER2 treatment improve systemic and loco-regional disease control of breast cancer [30]. Therefore, tailored treatment according to the subtypes has been a standard in the management of breast cancer [30]. Such tailored treatment is considered to improve outcome of OBC as well. In our study, all patients with HR + cancer received hormonal treatments. Anti-HER2 treatments were administered to approximately 60% of our patients with HER2+ cancer. Because it has not been long since anti-HER2 therapies became available in treating node-positive breast cancer in our country [31], not all HER2+ OBC patients could have received anti-HER2 treatment. Given that HER2-targeted therapies result in favorable outcomes in node-positive HER2-positive breast cancer [32], such target agent should be incorporated in the management of OBC. Besides, current evidence supports that NAC can downstage the tumor and reduce extent of surgery in patients with breast cancer [33]. As such, patients with OBC are expected to benefit from the NAC. In previous studies, NAC was conducted in 23–69% of patients with OBC [13,14]. In our study, approximately 16% of patients received NAC before ALND. Even if there is not enough evidence to ensure the benefit of NAC in OBC management, we expect that administration of NAC can have a positive effect on reducing the extent of ALND or increasing DFS in patients with OBC.

Unlike other patients with CUP, where disease rapidly progresses and frequently disseminates to systemic organs [34], female patients with a small burden of metastases limited to the ALN have a favorable prognosis after multimodal BCT. Breast MRI in conjunction with other imaging modalities can identify a breast primary with good sensitivity. However, despite using sensitive diagnostic techniques, patients still are diagnosed with OBC. Further diagnostic approaches to discover the primary site of origin are needed. Diagnostic tools such as molecular breast imaging [35] or genomic analyses [34] are expected to assist this in the future.

The limitations of our study include small sample size, some missing data, and a retrospective study design with a relatively long inclusion period of 13 years. During the long inclusion period, there were changes in breast cancer management. Therefore, it could influence patient outcome. Further research involving more patients with an appropriate inclusion criteria is needed. Despite the drawbacks, this study is valuable for depicting the effect of BCT for patients with OBC.

Conclusions

Patients with MRI-OBC were successfully treated with multimodal BCT. There was only a small risk of post-treatment ipsilateral breast cancer recurrence with ipsilateral WBI. Hence, it is necessary to provide BCT as the first treatment option for MRI-OBC. The treatment failure patterns among the patients in our study depended on the initial extent of nodal involvement.

Declaration of competing interest

Conflict of interest relevant to this article was not reported.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.breast.2019.10.017.

WBI = whole breast irradiation.

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