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Prognosis of patients with axillary lymph node metastases from occult breast cancer: analysis of multicenter data

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Purpose: This study was conducted to evaluate prognosis of patients with level I/II axillary lymph node metastases from occult breast cancer (OBC).

Materials and Methods: Data of 53 patients with OBC who received axillary lymph node dissection (ALND) positive/negative (+/–) breast-conserving surgery between 2001 and 2013 were retrospectively collected at seven hospitals in Korea. The median number of positive lymph nodes (+LNs) was 2. Seventeen patients (32.1%) had >3 +LNs. A total of 48 patients (90.6%) received radiotherapy. Extents of radiotherapy were as follows: whole-breast (WB; n = 11), regional lymph node (RLN; n = 2), and WB plus RLN (n = 35).

Results: The median follow-up time was 85 months. Recurrence was found in four patients: two in the breast, one in RLN, and one in the breast and RLN. The 5-year and 7-year disease-free survival (DFS) rates were 96.1% and 93.5%, respectively. Molecular subtype and receipt of breast radiotherapy were significantly associated with DFS. Patients with estrogen receptor negative, progesterone receptor negative, and human epidermal growth factor receptor 2 negative (ER-/PR-/HER2-) subtype had significantly lower 7-year DFS than those with non-ER-/PR-/HER2- tumor (76.9% vs. 100.0%; p = 0.03). Whole breast irradiation (WBI) was significantly associated with a higher 7-year DFS rate (94.7% for WBI group vs. 83.3% for non-WBI group; p = 0.01). Other factors including patient's age, number of +LNs, taxane chemotherapy, and RLN irradiation were not associated with DFS.

Conclusion: Patients with OBC achieved favorable outcome after ALND and breast-targeting treatment. Molecular subtype and receipt of WBI was significant factors for DFS.

Keywords: Unknown primary neoplasms, Breast neoplasm, Lymph nodes, Radiotherapy

Introduction

Cancer of unknown primary site (CUP) is a rare disease entity in which metastatic cancerous lesions present without any evidence of primary tumor. In most patients with CUP, the disease tends to disseminate early and respond poorly to systemic agents [1]. However, there are favorable subsets of patients who have experienced prolonged survival after treatment for putative primary origin [1,2].

Cases of axillary lymph node adenocarcinoma with unknown primary site (AxCUP) which is detected in females are one of the favorable subsets of CUP [1]. AxCUP in females is generally regarded as a presentation of occult breast cancer (OBC). Hence, it has been recommended that AxCUP in females needs to be managed as per the treatment for primary breast cancer [3].

OBC accounts for only 0.1%–1.0% of all breast cancer cases [4,5]; therefore, there was little evidence regarding optimal treatment strategies for OBC. Recent studies reported that axillary lymph node dissection (ALND) along with breast-targeting treatment such as mastectomy or breast-conserving surgery (BCS) resulted in favorable survival among patients with OBC [5-7]. The addition of postoperative radiotherapy to surgical treatment was associated with improved survival when compared to surgery alone [5,8]. Nonetheless, there is little consensus regarding which area should be irradiated for patients with OBC. Given that patients with OBC have no cancerous lesion in the ipsilateral breast even after detailed imaging studies, it is questionable whether the breast needs to be irradiated or not. Moreover, it is unknown whether prophylactic radiotherapy to uninvolved regional lymph nodes (RLNs), such as supraclavicular lymph nodes (SCN) or internal mammary lymph nodes (IMN), has prognostic impact in patients with OBC with axillary lymph node involvement.

In this study, we evaluated prognosis and patterns of failure in patients with axillary lymph node metastasis from OBC.

Materials and Methods

1. Patients and treatments

Females who received breast-conserving treatment (BCT) including ALND and/or BCS for OBC between January 2001 and December 2013 were included in this study. OBC was defined as adenocarcinoma or poorly differentiated carcinoma in axillary lymph nodes without an evidence of primary breast tumor on physical examination and imaging studies including mammography, breast ultrasonography (US), magnetic resonance imaging (MRI) of the breast, chest computed tomography (CT), or positron emission tomography-computed tomography (PET-CT). Patients were ineligible for inclusion in this study if they had cancerous lesions in other organs other than the axillary lymph nodes, previous history of other cancer, or previous radiotherapy. Patients who had mastectomy with subsequent identification of primary breast tumor on pathologic evaluation were excluded from this study. Seven hospitals that are members of the Korean Radiation Oncology Group provided data of 53 patients who met the inclusion criteria of this study. The Institutional Review Board of each hospital approved this study. The informed consent was waived.

Mammography and either breast US or breast MRI were performed in all patients. All four patients who did not undergo breast MRI were evaluated with breast US and PET-CT. ALND and/or BCS was administered to all patients. Blind upper outer quadrantectomy was performed in 11 patients, while 42 patients underwent no breast surgery. The median number of dissected lymph nodes was 17 (range, 3 to 62). Immunohistochemical staining for estrogen receptor (ER), progesterone receptor (PR), and human epidermal growth factor receptor 2 (HER2) of tumor in lymph nodes was performed. ER/PR positivity was defined as an Allred score of 3–8 by immunohistochemistry (IHC). HER2 positivity was defined as either staining 3+ by IHC or 2+ by IHC with positive fluorescence in situ hybridization (FISH) or silver in situ hybridization (SISH). Taxane-based chemotherapy was provided to 71.7% of patients. Neoadjuvant systemic treatment was administered before ALND in five patients (9.4%). Among 15 patients with HER2-positive tumor, eight patients (53.3%) underwent anti-HER2 agents. Patient's characteristics are shown in Table 1. Radiotherapy was provided to all but five patients. Fields and doses of radiotherapy were decided according to each institutional policy. Whole breast or RLNs was treated with a total dose of 40.05–50.4 Gy at 1.8–2.67 Gy per fraction. Three patients received intensity-modulated radiotherapy, while others underwent three-dimensional conformal radiotherapy. Details of radiation fields are depicted in Table 2.

2. Statistical analysis

Overall survival (OS), disease-free survival (DFS), and breast cancer-free survival (BCFS) were defined as the interval from the date of ALND or the first day of neoadjuvant systemic treatment to death, cancer recurrence, and ipsilateral breast cancer occurrence, respectively. Survival probability was estimated using the Kaplan-Meier method and the log-rank test was used to compare survival between groups with different variables. Factors with a significance at $p < 0.05$ on univariate analysis were included in a multivariate Cox stepwise regression analysis. Statistical significance was calculated at 95% confidence level ($p < 0.05$). Statistical analyses were performed using SPSS version 22.0 for Windows (IBM Corp., Armonk, NY, USA).

Results

The median follow-up time was 85 months (range, 7 to 178 months). Recurrence was found in four patients (7.5%): two (3.7%) in the ipsilateral breast, one (1.9%) in RLN, and one (1.9%) in the ipsilateral breast and RLN (Table 3). No patient showed distant metastases. Cancer in the ipsilateral breast occurred in three patients (5.6%) within 7 to 93 months after the completion of treatment

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Table 1. Patient's characteristics

Characteristic	Value
Age (yr)	54 (32–79)
≤ 50	22 (41.5)
> 50	31 (58.5)
Breast MRI	
Done	49 (92.5)
Not done	4 (7.5)
Breast US	
Done	49 (92.5)
Not done	4 (7.5)
PET-CT	
Done	50 (94.3)
Not done	3 (5.7)
Chemotherapy	
CMF	2 (3.8)
AC	9 (17.0)
AC-T	36 (67.9)
AT	1 (1.9)
Taxol-carboplatin	1 (1.9)
None	4 (7.5)
Hormone therapy	
Done	26 (49.1)
Not done	27 (50.9)
Number of dissected LNs	17 (3–62)
≤ 18	28 (52.8)
> 18	25 (47.2)
Number of positive LNs	2 (0[a]–31)
≤ 3	36 (67.9)
4–9	13 (24.5)
> 9	4 (7.6)
Ratio of positive LNs	0.09 (0.00[a]–1.00)
≤ 0.2	36 (67.9)
> 0.2	17 (32.1)
Molecular subtype[a]	
ER+ or PR+ HER2-	15 (28.3)
ER+ or PR+ HER2+	11 (20.8)
ER- PR- HER2+	4 (7.5)
ER- PR- HER2-	17 (32.1)
Unknown	6 (11.3)

Values are presented as median (range) or number (%).
LNs, lymph nodes; MRI, magnetic resonance imaging; US, ultrasonography; PET-CT, positron emission tomography-computed tomography; 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; ER, estrogen receptor; PR, progesterone receptor; HER2, human epidermal growth factor receptor 2.
[a]Five patients received neoadjuvant systemic treatment before axillary lymph node dissection. Of the five patients, one showed pathological complete response of axillary lymph nodes in surgical specimens.

Table 2. Extent of radiotherapy according to lymph node status

Extent of radiotherapy	Number of positive lymph nodes	
	≤ 3	> 3
Breast alone	11 (30.7)	-
Breast & SCN	6 (16.7)	8 (47.1)
Breast & axilla & SCN	9 (25.0)	6 (35.3)
Breast & axilla & SCN & IMN	4 (11.1)	2 (11.7)
Axilla alone	1 (5.9)	-
Axilla & SCN	1 (2.7)	-
No radiation	4 (11.1)	1 (5.9)
Total	36 (100)	17 (100)

Values are presented as number (%).
SCN, supraclavicular lymph nodes; IMN, internal mammary lymph nodes.

Table 3. Sites of recurrence according to radiotherapy field

Radiotherapy field	Sites of recurrence		
	Breast	RLN	Breast & RLN
No radiotherapy (n = 5)	0	1	0
RLN alone (n = 2)	1	0	0
Breast alone (n = 11)	0	0	0
Breast + RLN (n = 35)	1	0	1

RLN, regional lymph node.

for OBC. Of the three patients who developed breast cancer, one did not have breast irradiation while two received radiotherapy to the ipsilateral breast for the treatment of OBC.

The 5-year DFS, BCFS, and OS of all patients were 96.1%, 98.0%, and 96.0%, respectively. The 7-year DFS, BCFS, and OS of all patients were 93.5%, 95.4%, and 96.0%, respectively. In the univariate analyses, molecular subtype and receipt of breast radiotherapy were significant factors for DFS. Patients with ER-/PR-/HER2- subtype had significantly lower 7-year DFS than those with non-ER-/PR-/HER2- tumor (76.9% vs. 100.0%; p = 0.03). In addition, whole breast irradiation (WBI) was significantly associated with a higher 7-year DFS rate (94.7% for WBI group vs. 83.3% for non-WBI group; p = 0.01) (Fig. 1). However, in multivariate analyses, there were no factors significantly associated with DFS. Other factors such as patient's age, number of metastatic lymph nodes, ratio of positive lymph nodes, types of breast surgery, RLN irradiation, and taxane chemotherapy were not related to patient's DFS (Table 4).

Discussion and Conclusion

In this study, we found that patients with OBC presenting as Ax-CUP achieved favorable outcome after ALND and BCT including WBI and systemic treatment. Tumor subtype of non-ER-/PR-/HER2- and administration of WBI was significantly associated with

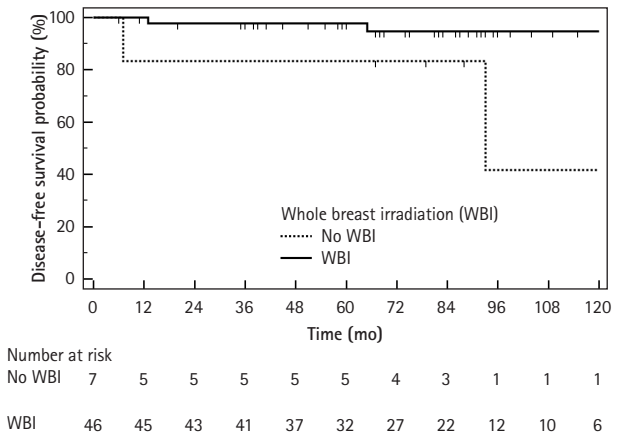

Fig. 1. Disease-free survival according to breast radiotherapy.

improved DFS. Patients in whom the ipsilateral breast was not irradiated had more frequent recurrence than those who received whole breast radiotherapy.

AxCUP in females is generally thought to be a metastases from primary breast cancer [2]. Therefore, thorough evaluation including breast imaging, pathologic diagnosis, and molecular-profiling is recommended to search for the primary breast lesion [3]. Defining OBC is likely to depend on what diagnostic tests are available at the time of diagnosis. About 70% of patients with OBC as defined by mammography present primary breast cancer on pathologic specimen after mastectomy [2]. With the introduction of more advanced imaging modalities like breast MRI, primary breast cancer could be identified in about two-thirds of mammographically defined OBC [9]. In our study, all but four patients were confirmed to have no lesions in the breasts by MRI. Four patients in whom breast MRI was not performed were examined using both breast

Table 4. Prognostic factors for disease-free survival

Characteristic	n	DFS (%)		p-value	
		5-yr	7-yr	Univariate	Multivariate
Age (yr)					
≤ 50	22	95.2	89.6	0.26	-
> 50	31	96.8	96.8		
Number of metastatic LNs (pathologic)					
≤ 3	36	97.1	93.2	0.70	-
> 3	17	94.1	94.1		
Ratio of positive LNs					
≤ 0.2	36	100	95.8	0.52	-
> 0.2	17	88.2	88.2		
Molecular subtype					
Other than ER- PR- HER2-	30	100	100	0.03	0.95
ER- PR- HER2-	17	100	76.9		
Unknown	6	100	100		
Partial mastectomy					
Not done	42	97.6	94.1	0.22	-
Done	11	90.9	90.9		
Radiotherapy					
Not done	5	75.0	75.0	0.15	-
Done	48	97.9	95.0		
Radiotherapy to breast					
Not done	7	83.3	83.3	0.01	0.52
Done	46	97.8	94.7		
SCN or IMN radiotherapy					
Not done	17	93.8	93.8	0.85	-
Done	36	97.2	93.2		
Taxane					
Not done	15	100	100	0.94	-
Done	38	94.7	91.4		

DFS, disease-free survival; LNs, lymph nodes; SCN, supraclavicular lymph nodes; ER, estrogen receptor; PR, progesterone receptor; HER2, human epidermal growth factor receptor 2; IMN, internal mammary lymph nodes.

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US and PET-CT and proven to have no primary breast lesion. Therefore, cases included in our study were truly OBC defined by contemporary imaging modalities. In such cases, it is challenging for oncologists to select the appropriate treatment to manage occult lesions in the ipsilateral breast.

Total mastectomy has been frequently used in patients with OBC. A study showed that 39% of OBC cases were treated with mastectomy based on the Surveillance, Epidemiology and End Results (SEER) database [8]. Similarly, 38% of Korean patients with OBC received mastectomy according to data of the Korean Breast Cancer Society cancer registry [4]. Besides, another study showed that mastectomy was more frequently performed than BCT if OBC patients were managed at non-academic centers (39.5% vs. 25.2%; $p < 0.001$) [5]. Complete removal of ipsilateral breast tissue could be an option for treatment of OBC. However, several recent studies noted that BCT is as effective as mastectomy for OBC in terms of achieving favorable survival outcome [4,5,7]. The 5-year OS rate ranges from 82% to 92% after mastectomy and was between 92% and 97% after BCT in patients with OBC presenting as AxCUP [4,5]. Likewise, we also found in the present study that survival outcome was good with BCT in patients with OBC. Given the favorable outcome with BCT which was observed in several other studies, it is reasonable and safe to provide BCT to patients with OBC.

In cases where breast conservation is planned, radiotherapy is an essential treatment for axillary presentation of OBC. In a study comparing survival outcomes of OBC according to treatment modalities, combination of ALND and radiotherapy was significantly associated with better survival than ALND alone or observation [5]. The benefit of radiotherapy was also confirmed in OBC patients with mastectomy or having a large number of metastatic lymph nodes [8]. Even if radiotherapy has been proven to be important in the management of OBC, there is little information regarding which area should be covered with radiotherapy. Most recent studies on OBC analyzed population-based data which had unavailable details of radiotherapy [4,5,8]. Even in studies presenting information about radiotherapy, almost all patients had WBI [7,10]. Thus, it has been difficult to evaluate the impact of ipsilateral breast irradiation in patients with OBC. In our study, we analyzed patients' data from multiple hospitals where diverse radiation fields were applied. Through this analysis, we expected to evaluate the prognostic significance of breast radiotherapy in patients with OBC.

Radiotherapy to the ipsilateral whole breast can be taken for granted in the management of axillary presentation of OBC. However, as seen in our study, various radiation fields have been in use (Table 2). It was not uncommon not to include the ipsilateral breast in the radiation field in patients with OBC. Previously, there were a couple of studies reporting unfavorable prognosis in OBC when breast radiotherapy was omitted. However, the studies are old and did not adopt breast MRI for the diagnosis of OBC in a large proportion of patients [11,12]. Thus, such reports cannot provide sufficient evidence for deciding the radiotherapy field for OBC defined using contemporary imaging modalities. Particularly, in OBC cases where the absence of breast lesion was confirmed using highly sensitive imaging modalities like breast MRI, there could be an attempt to exclude the breast from the irradiation field. In this study, we found that the 5-year DFS was significantly better in patients with whole breast irradiation than in those without breast radiotherapy among patients who underwent BCT. It is likely that females with OBC presenting as AxCUP have some subclinical cancer in the ipsilateral breast, which was undetectable even with contemporary imaging modalities. With the administration of radiotherapy to the breast, such subclinical primary breast cancer might be eliminated in patients with OBC. Therefore, ipsilateral WBI is thought to contribute in improving outcome of patients with OBC presenting as AxCUP. However, since the current analysis was conducted in a small cohort, further studies are necessary to determine the role of WBI in patients undergoing BCT for AxCUP.

We could not find an association between prophylactic irradiation of RLN and patient's outcome in the current study. However, considering that the range of number of positive lymph nodes (+LNs) was wide among patients included in our study, it is difficult to objectively evaluate the impact of RLN radiotherapy through this analysis. The 5-year DFS was comparable between the patients with less than four +LNs and those with four or more +LNs in our study. Given that most patients with four or more +LNs underwent SCN or IMN radiotherapy, it is probable that the poor prognosis in patients with large number of lymph node metastasis was offset by RLN irradiation. Further studies are necessary to know the impact of RLN radiotherapy in the axillary presentation of OBC.

We acknowledge the limitations of this study. Even though we collected data from multiple hospitals, the number of cases was still small. Since only four recurrences were noted among our patients, it was difficult to perform multivariate analyses of prognostic factors for survivals. In addition, the extent of radiotherapy varied across the participating hospitals. Only a small number of patients received radiotherapy to RLNs without breast irradiation. Therefore, it is probable that the significance of WBI could not be sufficiently evaluated. Given that the axillary presentation of OBC is a rare disease entity, it is necessary to collaborate with institutions in order to determine optimal strategies for the treatment of OBC.

Despite these drawbacks, our study has important implications for the determination of optimal radiation field for OBC with axillary lymph node involvement. As the sensitivity of imaging modalities increases, there might be attempts to exclude the ipsilateral

breast from the radiation field in the management of AxCUP in females. Our study demonstrated the importance of the extent of radiotherapy in these patients. Even in patients confirmed to have no lesion in the breast by contemporary imaging studies, it is necessary to include the ipsilateral breast in the radiation field in females with OBC presenting as AxCUP.

Conflict of Interest

No potential conflict of interest relevant to this article was reported.

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