Original article

# Outcome of radiotherapy for clinically overt metastasis to the internal mammary lymph node in patients receiving neoadjuvant chemotherapy and breast cancer surgery

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## ARTICLE INFO

## ABSTRACT

*Purpose:* This study was aimed to assess the outcome of radiotherapy and determine prognostic factors for survival in breast cancer patients with clinically overt metastasis to the internal mammary lymph node (IMN+).
*Methods:* We retrospectively reviewed the medical records of 193 patients with IMN + breast cancer who received neoadjuvant chemotherapy (NAC), breast surgery without internal mammary lymph node (IMN) dissection, and postoperative radiotherapy at 9 hospitals between 2009 and 2013. Breast-conserving surgery or mastectomy was performed after taxane-based NAC. Radiotherapy was administered to the whole breast/chest wall and regional nodes. IMN-covering radiotherapy was performed in 92.2% of patients with median dose of 58.4 Gy (range, 44.9–69.1 Gy). The overall survival (OS), disease-free survival (DFS), and IMN failure-free survival (IMNFFS) were analyzed.
*Results:* After median follow-up of 71 months, 9 patients (4.7%) developed IMN failure and simultaneous distant metastasis. The 5-year DFS, OS, and IMNFFS was 68.6%, 81.8%, and 95.3%, respectively. Non-triple-negative breast cancer, Ki-67 $\leq$ 10%, pathological complete response (CR) in tumor and axillary node, and radiologic CR of IMN after NAC were significant factors for predicting higher DFS; however, IMN radiation dose was not significant determinants for DFS. The 5-year DFS of patients with IMN-dose $\leq$ 50.0 Gy and those with >50.0 Gy was 86.7% and 76.7%, respectively ($p = 0.41$).
*Conclusions:* A multimodality strategy including NAC, breast surgery, and IMN-covering radiotherapy was effective for patients with overt IMN + breast cancer. Even without an IMN dissection, most patients were IMN failure-free with an IMN-focusing radiotherapy.

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## 1. Introduction

Lymphatic metastasis of breast cancer mainly occurs via the axillary, transpectoral, and IMN chains [1]. More than 20% of the lymphatics flow into the IMN while approximately 90% of the breast lymphatics drain into the axillary lymph nodes (ALN) [2,3]. Clinically apparent IMN+ in the absence of ALN metastasis is

classified as N2b, while IMN+ in the presence of ALN involvement is staged as N3b [4]. Although the IMN is defined as a regional node similar to the ALN, previous studies have suggested that breast cancer involving IMN has a worse prognosis than that involving ALN metastasis [5,6]. Nonetheless, in studies in which breast surgery and effective adjuvant treatments were administered, patients with IMN + breast cancer could achieve favorable outcomes [7,8]. Although there are controversies regarding the negative prognostic influence of IMN+, there is increasing need to optimize management for IMN + breast cancer.

A study conducted in the 1960s showed that extended mastectomy, including IMN dissection, did not improve breast cancer survival compared to mastectomy alone [9]. Less than 40% of IMN + patients survived 5 years after the extended mastectomy in the absence of adjuvant treatment [9]. Given the unsuccessful outcome after IMN dissection, a multimodal treatment combining breast surgery, IMN-encompassing radiotherapy, and systemic therapies has been advocated for IMN + breast cancer [8,10—14]. Considering that surgical removal of the IMN is not performed in the multimodal strategy, radiotherapy is primarily responsible for local control in the IMN region. In addition, given that neoadjuvant chemotherapy (NAC) is increasingly used to treat locoregionally advanced breast cancer [15], radiotherapy is needed to be adjusted according to the response to NAC. However, no consensus has so far been reached on the optimal radiotherapeutic approach for IMN + breast cancer. This study is aimed to assess the outcomes of radiotherapy and define an optimal regimen for postoperative radiotherapy in IMN + breast cancer patients undergoing NAC followed by breast surgery without IMN dissection.

## 2. Materials and methods

We retrospectively reviewed the medical records of patients with IMN + breast cancer who received NAC, followed by breast surgery and postoperative radiotherapy, at 9 hospitals in South Korea between January 2009 and December 2013. The inclusion criteria were IMN + breast cancer without distant organ metastasis, curative breast surgery, and completion of planned NAC and radiotherapy schedules. Patients underwent IMN dissection or those in whom the radiologic response of the IMN after NAC could not be assessed were excluded. IMN+ was defined as IMN measuring $\geq 0.5$ cm on breast magnetic resonance imaging (MRI) before the initiation of NAC or confirmation of tumor deposit in the IMN by fine needle aspiration (FNA) or core-needle biopsy.

The IMN size was determined by measuring the longest diameter of the IMN on breast MRI. The IMN response to NAC was evaluated by comparing the IMN size measured before NAC and before breast surgery. The radiation dose to the IMN was converted to an equivalent dose in 2 Gy fractions (EQD2) using the linear quadratic model with $\alpha/\beta$ of 3.5 Gy.

After the treatment was completed, patients were followed up according to the surveillance protocol of each institution. Outcome data were collected for the following: disease status at last follow-up visit, locoregional recurrence (LRR), distant metastasis (DM), and death. Overall survival (OS) was defined as the interval between the date of NAC and the date of last follow-up or death. Disease-free survival (DFS), IMN failure-free survival (IMNFFS), LRR-free survival (LRRFS), and DM-free survival (DMFS) were defined as the interval from the date of NAC to the date of cancer recurrence, IMN recurrence, LRR, and DM, respectively. In patients without disease recurrence, the DFS, IMNFFS, LRRFS, and DMFS were calculated as the interval from the date of NAC until the date of last follow-up or death.

The survival duration was estimated using the Kaplan—Meier method and the log-rank test was used to compare survival between groups with different variables. A receiver operating characteristics (ROC) analysis was used to define the cut-off point in continuous variables. The continuous variables were dichotomized according to the cut-off point indicated by the ROC analysis. A multivariate Cox stepwise regression model was used to access the impact of variables on the survival outcomes. Variables with a significance at p < 0.05 on univariate analysis were included in the multivariable analysis. The p-values of <0.05 were considered statistically significant. Statistical analyses were performed using the MedCalc Statistical Software version 19.3.1 (MedCalc Software Ltd, Ostend, Belgium; https://www.medcalc.org; 2020). The Institutional Review Board at the principal investigator's hospital approved this study and waived off the requirement of patient informed consent.

## 3. Results

### 3.1. Patient and treatment

In total, 193 patients with a median age of patients was 44 years (range, 20—73 years) were include in this study. Patient characteristics are shown in Table 1. All patients had undergone breast MRI prior to initiation of NAC and breast surgery. Positron emission tomography-computed tomography was performed in 166 patients (96.4%) at time of breast cancer diagnosis. The median size of the IMN was 0.8 cm (range, 0.2—2.0 cm) at initial breast cancer diagnosis. The distribution of the IMN size and cytologic results are described in Table 2. After completion of NAC, 124 (64.2%) patients showed radiologic complete response on breast MRI before breast cancer surgery.

The clinical target volume (CTV) was contoured to include whole breast (WB)/chest wall (CW) and/or regional lymph nodes. Following areas were encompassed as the CTV: WB/CW alone in 2 patients (1.0%), WB/CW in conjunction with supraclavicular lymph node (SCN) in 13 (6.7%), WB/CW with IMN in 7 (3.6%), and a combination of WB/CW, SCN, and IMN in 171 (88.6%) patients. The CTV for IMN was delineated in a region encompassing the first three or fourth intercostal spaces longitudinally and margins around IMN vessels mediolaterally. Radiation fields were modified to adequately cover the CTV using three-dimensional conformal radiotherapy (n = 174) or intensity-modulated radiotherapy (IMRT, n = 18). For IMRT, tomotherapy (n = 3) or volumetric modulated arc therapy (n = 15) was used. Radiation dose to the CTV was 50—68.4 Gy with a daily dose of 1.8—2.0 Gy (n = 182) or 40.05—48 Gy with a daily dose of 2.67—3.2 Gy (n = 11). Accordingly, the median EQD2 for each radiation field were as follows: 54 Gy (range, 44—70 Gy) for the WB/CW field, 48 Gy (range, 0—58 Gy) for the SCN field, and 50 Gy (range, 0—69 Gy) for the IMN field. The IMN chains were included in the radiation field in 178 (92.2%) patients with a median EQD2 of 58.4 Gy (range, 44.9—69.1 Gy). The remaining 15 (7.7%) patients did not undergo IMN-focusing radiotherapy. There was a significant trend for applying a higher IMN radiation dose (EQD2 > 50.0 Gy) in patients with TNBC, multiple IMN adenopathy involving multiple intercostal spaces (ICS), IMN size measuring $\leq 0.8$ cm, or cytology-positive IMN (Table 3).

Further, 183 (94.8%) patients received taxane-containing agents and all patients, except 1 patient, with ER+ and/or PR + tumors (n = 93) underwent endocrine therapy. Among the patients with ER+ and/or PR + tumors, 66 (70.9%) received tamoxifen, 22 (26.6%) received aromatase inhibitors, and 4 (4.3%) received other endocrine agents. Except 5 patients, all patients with HER2+ tumor

**Table 1**
Patient characteristics.

| Characteristics | | Number of patients (%) |
|---|---|---|
| Age (years) | <40 | 68 (35.2) |
| | ≥40 | 125 (64.8) |
| Histologic grade | 1−2 | 96 (49.7) |
| | 3 | 80 (41.5) |
| | Unknown | 17 (8.8) |
| Tumor subtype | ER+/or PR+/HER2- | 60 (31.1) |
| | ER+/or PR+/HER2+ | 33 (17.1) |
| | ER-/PR-/HER2+ | 35 (18.1) |
| | ER-/PR-/HER2- | 65 (33.7) |
| Ki-67 (%) of breast tumor | ≤10% | 45 (23.3) |
| | >10% | 148 (76.7) |
| cT stage | 1−2 | 113 (58.5) |
| | 3−4 | 80 (41.5) |
| cN stage | N2b | 14 (7.3) |
| | N3b | 179 (92.7) |
| ypT stage | ypT0 or ypTis | 44 (22.8) |
| | ypT1 or ypT2 | 118 (61.1) |
| | ypT3 or ypT4 | 31 (16.1) |
| ypN stage | ypN2b | 87 (45.1) |
| | ypN3b | 106 (54.9) |
| ypStage | ypTisN2b or ypT1N2b | 41 (21.2) |
| | Non- ypTis/T1N2b | 152 (78.8) |
| Extent of IMN | Single ICS | 123 (63.7) |
| | Multiple ICS | 70 (36.3) |
| Size of IMN | <0.8 cm | 69 (35.8) |
| | ≥0.8 cm | 124 (64.2) |
| No. Of involved IMN | Single | 123 (63.7) |
| | Multiple | 70 (36.3) |
| Cytologic examination of IMN | Negative | 16 (8.3) |
| | Positive | 59 (30.6) |
| | Not done | 118 (61.1) |
| IMN response to NAC | Complete response | 124 (64.2) |
| | Residual IMN (+) | 69 (35.8) |
| Type of breast surgery | Breast-conserving surgery | 88 (45.6) |
| | Mastectomy | 105 (54.4) |
| Type of axillary surgery | Sentinel lymph node biopsy | 30 (15.5) |
| | Axillary lymph node dissection | 163 (84.5) |
| EQD2 of the IMN[1] | ≤50.0 Gy | 100 (51.8) |
| | >50.0 Gy | 93 (48.2) |
| Interval between surgery and RT | ≤37 days | 100 (51.8) |
| | >37 days | 93 (48.2) |

Abbreviations: ER: Estrogen receptor, PR: Progesterone receptor, HER2: Human epidermal growth factor receptor type 2, IMN: Internal mammary node, NAC: Neoadjuvant chemotherapy, ICS: Intercostal space, EQD2: Biologically equivalent dose in 2 Gy fractions, RT: Radiotherapy.
1) The radiotherapy dose was calculated using the EQD2, assuming the $\alpha/\beta$ ratio of 3.5 Gy.

(n = 68) received an anti-HER2 agent.

### 3.2. Outcomes and prognostic factors

Over the median follow-up of 71 months (range, 6−166 months), 64 (33.1%) patients developed disease recurrence. The sites of recurrence were local site alone in 1 (0.5%) patient; regional lymph nodes in 2 (1.0%) patients; regional and distant site in 18 (9.3%) patients; simultaneous local, regional, and distant sites in 6 (3.1%) patients; local and distant site in 6 (3.1%) patients; and distant site alone in 31 (16.1%) patients. Nine (4.7%) had IMN recurrence; 7 patients had IMN recurrences simultaneously with DM, while 2 patients had IMN recurrences coincidently with local and distant site failures. The 5-year DFS, OS, IMNFFS, LRRFS, and DMFS were 68.6%, 81.8%, 95.3%, 82.5%, and 70.2%, respectively, and the 10-year DFS, OS, IMNFFS, LRRFS, and DMFS were 62.6%, 70.2%, 93.6%, 81.0%, and 64.1%, respectively.

In univariate analyses for DFS, non-TNBC, Ki-67 ≤ 10%, pathologic CR (ypCR) in the tumor and ALN (ypTisN2b or ypT0N2b), radiologic CR of the IMN after NAC, BCS, and an interval between breast surgery and radiotherapy of ≤37 days were significantly associated with favorable DFS. In multivariate analysis, non-TNBC, Ki-67 ≤ 10%, ypCR in the tumor and ALN, radiologic CR in the IMN, and BCS were significantly related to a higher DFS. To evaluate the association between the IMN radiation dose and DFS, the survival of patients was compared according to the IMN EQD2 (Table 4). The DFS was not significantly different by IMN EQD2 in most subgroups, except for those with TNBC. In patients with TNBC, the 5-year DFS was lower in the high IMN EQD2 (>50.0 Gy) than the low IMN EQD2 (≤50.0 Gy) group (46.2% vs. 67.8%, *p* = 0.03) (Table 5). There were no significant factors associated with IMNFFS (Supplementary Table 1).

## 4. Discussions

In this retrospective analysis of 193 patients from 9 hospitals, we found that patients with overt IMN + breast cancer could achieve a favorable outcome with a multimodality approach including NAC, breast surgery and IMN-covering postoperative radiotherapy. Even without IMN dissection, 93% patients were IMN failure free at the 10-year follow-up after the multimodal treatment. There was a tendency to administer high IMN radiation doses in patients with TNBC, multiple ICS-involving IMN adenopathy, and cytology-positive IMN+. However, the high IMN radiation dose was not associated with improved outcome. Additionally, we found that TNBC, high Ki-67, not achieving ypCR in the tumor and ALN, and persistent IMN adenopathy after NAC were significant factors for predicting unfavorable DFS. Therefore, our study suggests that patients with these risk factors require further intensified locoregional and systemic therapies to improve breast cancer outcomes.

The risk of microscopic IMN+ is increased in patients with a young age at diagnosis, ALN metastasis, and inner quadrant-located tumors [16−18]. According to studies in which IMN dissection was conducted, the incidence of microscopic IMN+ was 4%−9% and 27%−29% in pN0 and pN + patients, respectively [9,18]. Based on studies showing improved breast cancer outcomes after prophylactic IMN irradiation in patients with ALN metastasis [19−21], a treatment strategy has been established to include elective IMN

**Table 2**
Size of internal mammary lymph node and cytologic results.

| Cytologic evaluation of the IMN | Size of the IMN | | | |
|---|---|---|---|---|
| | <0.5 cm | 0.5−1.0 cm | 1.1−1.5 cm | 1.6−2.0 cm |
| Negative for metastasis | 0 (0.0%) | 14 (10.8%) | 2 (4.2%) | 0 (0.0%) |
| Positive for metastasis | 6 (100.0%) | 40 (30.8%) | 10 (20.8%) | 3 (33.3%) |
| Not done | 0 (0.0%) | 76 (58.4%) | 36 (75.0%) | 6 (66.7%) |
| All | 6 (100.0%) | 130 (100.0%) | 48 (100.0%) | 9 (100.0%) |

Abbreviations: IMN: Internal mammary lymph node.
The long diameter of the internal mammary lymph node was measured on breast MRI prior to the initiation of neoadjuvant chemotherapy. The largest IMN was measured in each patient.

**Table 3**
Patient characteristics according to radiation dose to the internal mammary lymph node.

| Characteristics | | No. Of patients (%) | | p-value |
|---|---|---|---|---|
| | | IMN EQD2 ≤ 50.0 Gy (n = 100) | IMN EQD2 > 50.0 Gy (n = 93) | |
| Age | <40 years | 31 (45.6) | 37 (54.4) | 0.20 |
| | ≥40 years | 69 (55.2) | 56 (44.8) | |
| Tumor subtype | Non-TNBC | 74 (57.8) | 54 (42.2) | 0.01 |
| | TNBC[1] | 26 (40.0) | 39 (60.0) | |
| Ki-67 (%) | ≤10% | 23 (51.1) | 22 (48.9) | 0.91 |
| | >10% | 77 (52.0) | 71 (48.0) | |
| cT stage | 1–2 | 61 (54.0) | 52 (46.0) | 0.47 |
| | 3–4 | 39 (48.7) | 41 (51.3) | |
| cN stage | N2b | 6 (42.9) | 8 (57.1) | 0.48 |
| | N3b | 94 (52.5) | 85 (47.5) | |
| ypStage | ypTisN2b or ypT1N2b | 24 (58.5) | 17 (41.5) | 0.33 |
| | Non- ypTis/T1N2b | 76 (50.0) | 76 (50.0) | |
| Extent of IMN | Single ICS | 71 (57.7) | 52 (42.3) | 0.02 |
| | Multiple ICS | 29 (41.4) | 41 (58.6) | |
| IMN diameter | <0.8 cm | 24 (34.8) | 45 (65.2) | <0.01 |
| | ≥0.8 cm | 76 (61.3) | 48 (38.7) | |
| No. Of involved IMN | Single | 70 (59.3) | 48 (40.7) | <0.01 |
| | Multiple | 30 (40.0) | 45 (60.0) | |
| Path + IMN[2] | Negative or unknown | 89 (66.4) | 45 (33.6) | <0.01 |
| | Positive | 11 (18.6) | 48 (81.4) | |
| Residual IMN after NAC | No residual | 64 (51.6) | 60 (48.4) | 0.94 |
| | Residual (+) | 36 (52.2) | 33 (47.8) | |
| Type of surgery | BCS | 44 (50.0) | 44 (50.0) | 0.64 |
| | Mastectomy | 56 (53.3) | 49 (46.7) | |

Abbreviations: IMN: Internal mammary lymph node, EQD2: Biologically equivalent dose in 2 Gy fractions, TNBC: Triple-negative breast cancer, ICS: Intercostal space, NAC: Neoadjuvant chemotherapy, BCS: Breast-conserving surgery.
1)TNBC was defined as ER-/PR-/HER2-on breast tumor immunohistochemistry.
2) Tumor deposit in the IMN assessed by fine-needle aspiration biopsy or core-needle biopsy was defined as Path + IMN positivity.

radiotherapy in patients with ALN metastatic breast cancer [22]. To control occult microscopic IMN+, a radiation dose of 45–50.4 Gy in 24–28 fractionations has been administered to the IMN chains [19,21,23,24]. However, the optimal treatment is controversial for patients with overt IMN+. Considering that a greater radiation dose is necessary to control macroscopic disease than in treating microscopic tumor foci [25], it can be postulated that a high IMN radiation dose is necessary to control overt IMN+. Moreover, in cases without IMN dissection, the radiation dose should be adjusted to eliminate gross metastatic lesions, since radiotherapy is a sole local treatment in patients with overt IMN + breast cancer.

Several studies have reported the outcome of multimodal treatment, excluding IMN dissection, in patients with clinically apparent IMN + breast cancer (Table 6) [8,11–14,26]. All previous studies included <100 patients and the data were retrospectively collected at a single institution. Of the tumors included in the studies, 47%–73% were negative for hormone receptor expression. Further, IMN+ was mostly determined by radiologic examinations; only 2%–57% of the participants were diagnosed with IMN + by both radiologic findings and histopathologic evaluation of the IMN. In addition, a radiation dose of 45.0–66.5 Gy was administered to the IMN chains, and the amount of IMN radiation dose was determined at the discretion of the physician [8,11,12,14] or the IMN response to NAC [26]. In a study by Zhang et al. a dose of 66 Gy was prescribed to the IMN region in patients with residual radiographic IMN adenopathy after NAC, while and IMN dose of 60 Gy was given to patients showing complete radiologic response after NAC [26]. Except the study by Zhang et al. the dose prescription of IMN radiotherapy was not guided by specific tumor characteristics. In our study, patients with TNBC, small size IMN lymphadenopathy, multiple ICS-involving IMN adenopathy, and cytology-positive IMN + tended to receive higher IMN dose than those without these features. Given that small-size IMN adenopathy was more likely to be evaluated by histopathological examination than large-size IMN, the tendency of administering a higher IMN dose to

small-size IMN might attributed to the distribution pattern of cytology-positive IMN+ in our study. This trend in radiotherapy prescription suggests that the IMN characteristics at breast cancer diagnosis influenced the IMN dose prescription in the participating hospitals. However, the administered prescription scheme did not offset the unfavorable outcome in patients with adverse risk factors. Moreover, an IMN dose >50 Gy (EQD2) was not associated with improved DFS in our analysis.

Previously, there have been conflicting results regarding an association between IMN radiation dose and disease control in patients with overt IMN + breast cancer. In a study by Park et al. administering of higher radiation doses to PET-positive IMN was not associated with better outcomes [11]. The study included 12 patients with cN3b breast cancer and prescribed doses of 50.4–55.8 Gy to the PET-positive IMN region; of the 12 patients, 3 patients did not undergo IMN-covering radiotherapy. During a median follow-up of 38 months, 1 out of the 9 patients who received IMN-covering irradiation had IMN recurrence, while none had IMN failure among the 3 patients without IMN-covering radiotherapy (5-year IMNFFS, 88% vs. 100%, p = 0.54). Based on this result, the authors concluded that administering a higher radiation dose to the PET-avid IMN was not associated with additional gains in the breast cancer outcome. However, the study had a small sample size of only 12 patients. Moreover, no statistical comparison of the tumor characteristics between the patients receiving a high IMN dose and those without IMN-focusing radiotherapy was conducted in the study. Contrary to the study of Park et al. another study showed a significant association between IMN radiation dose and breast cancer survival. In a study by Yang et al. the DFS was significantly influenced by the IMN dose in patients with large IMN adenopathy (≥1 cm) [8]. The 5-year DFS in patients receiving a high IMN EQD2 (≥63.6 Gy) and low IMN EQD2 (<63.6 Gy) was 69.3% and 33.3%, respectively (p < 0.01). Although such a dose-response relationship was only found in patients with large IMN, the study suggested that there might be a subset of

**Table 4**
Prognostic factors for disease-free survival.

| Characteristics | | No. Of pts | 5-yr DFS (%) | Univariate | Multivariate | HR (95% CI) |
|---|---|---|---|---|---|---|
| Age (years) | <40 | 68 | 61.9 | 0.12 | – | – |
| | ≥40 | 125 | 72.2 | | | |
| Histologic type | IDC | 185 | 67.8 | 0.25 | – | – |
| | Others | 8 | 87.5 | | | |
| Tumor subtype | Non-TNBC | 128 | 75.8 | <0.01 | <0.01 | 2.6 (1.5–4.4) |
| | TNBC[1] | 65 | 54.8 | | | |
| Ki-67 (%) | ≤10% | 45 | 93.2 | <0.01 | 0.01 | 2.8 (1.3–6.2) |
| | >10% | 148 | 60.9 | | | |
| cT stage | 1–2 | 113 | 72.9 | 0.19 | – | – |
| | 3–4 | 80 | 62.6 | | | |
| cN stage | N2b | 14 | 63.5 | 0.73 | – | – |
| | N3b | 179 | 69.1 | | | |
| ypStage | ypTis or T0N2b | 41 | 86.9 | <0.01 | 0.01 | 3.2 (1.3–8.3) |
| | Non-ypTis/T0N2b | 152 | 63.8 | | | |
| IMN extent | Single ICS | 123 | 80.5 | 0.46 | – | – |
| | Multiple ICS | 70 | 82.2 | | | |
| No. Of involved IMN | Single | 118 | 80.6 | 0.47 | – | – |
| | Multiple | 75 | 82.0 | | | |
| Size of IMN | <0.8 cm | 69 | 77.8 | 0.03 | – | – |
| | ≥0.8 cm | 124 | 63.6 | | | |
| Path + IMN[2] | Negative or unknown | 134 | 69.5 | 0.46 | – | – |
| | Positive | 59 | 66.6 | | | |
| Residual IMN after NAC | No residual | 124 | 76.1 | <0.01 | <0.01 | 2.3 (1.4–3.8) |
| | Residual (+) | 69 | 55.5 | | | |
| Type of surgery | BCS | 88 | 80.3 | <0.01 | <0.01 | 2.3 (1.4–4.5) |
| | Mastectomy | 105 | 58.7 | | | |
| Axillary OP | SLNBx | 30 | 66.2 | 0.08 | – | – |
| | ALND | 163 | 82.5 | | | |
| EQD2 of IMN[1] | ≤50.0 Gy | 100 | 86.7 | 0.41 | – | – |
| | >50.0 Gy | 93 | 76.7 | | | |
| OP to RT interval | ≤37 days | 100 | 76.6% | 0.03 | – | – |
| | >37 days | 93 | 60.4% | | | |

Abbreviations: DFS: Disease-free survival, HR: Hazard ratio, CI: Confidence interval, IDC: Invasive ductal carcinoma, TNBC: Triple-negative breast cancer, IMN: Internal mammary lymph node, ICS: Intercostal space, NAC: Neoadjuvant chemotherapy, BCS: Breast-conserving surgery, OP: Operation, SLNBx: Sentinel lymph node biopsy, ALND: Axillary lymph node biopsy, EQD2: Biologically equivalent dose in 2 Gy fractions, RT: Radiotherapy.
1)TNBC was defined as ER-/PR-/HER2-on breast tumor immunohistochemistry.
2)Tumor deposit in the IMN assessed by fine-needle aspiration biopsy or core-needle biopsy was defined as Path + IMN positivity.

**Table 5**
Impact of the radiotherapy dose to the internal mammary lymph node on disease-free survival.

| Characteristics | | No | 5-year DFS (%) | | p-value |
|---|---|---|---|---|---|
| | | | IMN EQD2 ≤ 50.0 Gy (n = 100) | IMN EQD2 50.0 Gy (n = 93) | |
| Tumor subtype | Non-TNBC | 128 | 73.6 | 79.0 | 0.19 |
| | TNBC[1] | 65 | 67.8 | 46.2 | 0.03 |
| Ki-67 (%) | ≤10% | 45 | 91.3 | 95.0 | 0.31 |
| | >10% | 148 | 65.7 | 57.4 | 0.13 |
| ypStage | ypTis or T0 N2b | 41 | 85.8 | 87.8 | 0.93 |
| | Non-ypTis/T0N2b | 152 | 67.6 | 60.0 | 0.48 |
| Size of IMN | <0.8 cm | 69 | 82.5 | 75.3 | 0.99 |
| | ≥0.8 cm | 124 | 68.9 | 58.0 | 0.08 |
| Path + IMN[2] | Negative or unknown | 134 | 70.6 | 67.6 | 0.99 |
| | Positive | 59 | 81.8 | 62.4 | 0.34 |
| Residual IMN after NAC | No residual | 124 | 75.9 | 76.3 | 0.91 |
| | Residual (+) | 69 | 65.5 | 44.8 | 0.15 |
| Type of surgery | BCS | 88 | 81.1 | 79.5 | 0.95 |
| | Mastectomy | 105 | 64.8 | 52.2 | 0.22 |

Abbreviations: DFS: Disease-free survival, IMN: Internal mammary lymph node, EQD2: Biologically equivalent dose in 2 Gy fractions, TNBC: Triple-negative breast cancer, NAC: Neoadjuvant chemotherapy, BCS: Breast-conserving surgery.
1)TNBC was defined as ER-/PR-/HER2-on breast tumor immunohistochemistry.
2)Tumor deposit in the IMN assessed by fine-needle aspiration biopsy or core-needle biopsy was defined as Path + IMN positivity.

patients who can benefit from elevated IMN radiation dose.

In our analysis, an IMN EQD2 > 50 Gy was not associated with improved DFS. The 5-year DFS rate tended to be lower in patients receiving an IMN dose of >50 Gy than those receiving an IMN dose ≤50 Gy, although there was no statistical significance. Moreover, among patients with TNBC, the DFS was significantly inferior in patients with an IMN dose of >50 Gy compared to those with ≤50.0 Gy. Among patients with TNBC, a high IMN dose was more frequently given to cases with an IMN measuring <0.8 cm and cytology-positive IMN+ (Supplementary Table 2). Such imbalances in tumor characteristics between the IMN dose groups might contribute to the inverse relationship between the IMN dose and

**Table 6**
Previous studies on the outcome of multimodal treatment in breast cancer patients with apparent metastasis at the internal mammary lymph node.

| Studies | Sample size | Median FU (months) | Cytology + for IMN metastasis | HR (−) tumor | Treatment scheme[a] | Median IMN radiation dose (range) | CR[b] of IMN after NAC | IMN recurrence | 5-year survival rates |
|---|---|---|---|---|---|---|---|---|---|
| Zhang et al. [26] | 96 | 41 | 9% | 58.9% | NAC-OP-RT | 60.0 Gy (50.0—66.0 Gy) | 72.3% | 11% | DFS 56%, OS 76% |
| Park et al. [11] | 12 | 38 | 0% | 58.0% | NAC-OP-RT | 50.4 Gy (45.0—66.4 Gy) | NR | 5.5% | DFS 67%, OS 79% |
| Joo et al. [12] | 70 | 51 | 57% | 54.0% | NAC-OP-RT | 60.0 Gy (56.0—66.0 Gy) | NR | 2.9% | DFS 72%, OS 77% |
| Sachdev et al. [13] | 19 | 38 | 0% | 73.7% | NAC-OP-RT (78.9%) or OP-RT-CTx (21.1%) | 50.4 Gy (45.0—64.4 Gy) | NR | 0% | NR |
| Kim et al. [14] | 95 | 43 | 2% | 53.7% | NAC-OP-RT (81.1%) or OP-RT-CTx (18.9%) | 50.0 Gy±boost (9 −12 Gy) | 67.5% | 3.2% | DFS 70%, OS 84% |
| Yang et al. [8] | 84 | 58 | 48% | 47.6% | NAC-OP-RT (78.6%) or OP-RT-CTx (21.4%) | 62.5 Gy (50.0—66.5 Gy) | NR | 2.4% | DFS 72%, OS 81% |

Abbreviations: FU: Follow-up, IMN: Internal mammary lymph node, HR: Hormone receptor, CR: Complete response, OP: Operation, RT: Radiotherapy, CTx: Chemotherapy, fx: Fractionations, NR: Not reported, DFS: Disease-free survival, OS: Overall survival, NAC: Neoadjuvant chemotherapy.
[a] Dissection of the internal mammary lymph node was not performed in any study.
[b] Response of the IMN was assessed based on imaging studies.

DFS. However, given that size and cytologic positivity of the IMN were not significant adverse factors for DFS in this study, other factors could have contributed to the inferior outcome in patients with TNBC administered a high IMN dose. In addition, an insignificant inverse association between the IMN dose and DFS was found in patients with other factors, such as Ki-67 > 10%, non-ypCR in the tumor and ALN, the IMN measuring ≥0.8 cm, cytology-positive IMN+, and radiological residual IMN after NAC. As most of these factors were analyzed as risk determinants for inferior DFS in our study, it is assumed that a high IMN dose could not negate the adverse effect of the prognostic factors. However, since multiple factors were differently distributed between the IMN dose groups, it is difficult to conclude that escalating the IMN dose is unnecessary for patients with overt IMN + breast cancer. Further studies are needed to provide solid evidence for optimizing the IMN radiation dose in the management of IMN + breast cancer.

The tumor subtype and response to NAC were found to be significant prognostic factors of DFS in our study. In addition, non-TNBC subtype, Ki-67 < 10%, disappearance of IMN adenopathy after NAC, and achieving ypCR in the tumor and ALN were predictive of favorable DFS. In particular, given that patients with ypCR in the tumor and ALN had a 5-year DFS rate of 85.8% with an IMN dose of ≤50.0 Gy, it is possible to minimize the IMN radiation dose for patients with the favorable features. Moreover, patients with a poor response to NAC and an aggressive tumor type, such as TNBC or high Ki-67, are thought to need more intensive treatment. Considering that most patients included in our study received taxane-based chemotherapy, more potent agents than the conventional drug might be necessary for patients with the above-mentioned adverse features. In addition, although no IMN radiation dose-outcome relationship was found in this analysis, the efficacy of high-dose IMN irradiation should be tested in patients with the adverse factors in future studies.

The current study has limitations. First, as the data were retrospectively collected from 9 hospitals, some of the variables were missing; for example, not all patients had information regarding nuclear grade of the tumor. Therefore, the prognostic effect of the nuclear grade was not analyzed in this study. Furthermore, treatment-related toxicities could not be evaluated since the details were not available. Lastly, since the IMN dose was decided based on the physician's preference, there were considerable differences in the tumor characteristics between the IMN dose groups; therefore, the impact of the IMN dose could not be objectively assessed. Even with these limitations, this study provides important information regarding the outcomes and prognostic factors in patients with IMN + breast cancer after multimodality treatment.

## 5. Conclusions

In conclusion, a multimodality strategy including NAC and breast surgery, followed by IMN-covering radiotherapy was an effective treatment for patients with IMN + breast cancer. Even without IMN dissection, most patients were IMN failure free with an IMN-focusing radiotherapy. Patients with a non-TNBC subtype, low Ki-67, ypCR in the tumor and ALN, and complete radiologic response of IMN adenopathy after NAC were significant prognostic factors for favorable DFS. Therefore, these factors might help stratify the IMN radiation dose for patients with overt IMN + breast cancer.

## Ethics approval and informed consent

This retrospective chart review study involving human participants was in accordance with the ethical standards of the institutional and national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. The Institutional Review Board of Yonsei University College of Medicine approved this study and waived off the requirement of patient informed consent.

## Declaration of competing interest

The authors declare that they have no conflict of interest.

## Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.breast.2020.12.011.

## References

[1] Bland KI, Copeland EM, Klimberg VS. 2 - anatomy of the breast, axilla, chest wall, and related metastatic sites. In: Bland KI, Copeland EM, Klimberg VS, Gradishar WJ, editors. The breast. fifth ed. Elsevier; 2018. 20–36.e2.

[2] Estourgie SH, Nieweg OE, Olmos RA, Rutgers EJ, Kroon BB. Lymphatic drainage patterns from the breast. Ann Surg 2004;239:232–7.

[3] Blumgart EI, Uren RF, Nielsen PM, Nash MP, Reynolds HM. Lymphatic drainage and tumour prevalence in the breast: a statistical analysis of symmetry, gender and node field independence. J Anat 2011;218:652–9.

[4] Brierley JDGM, Wittekind C. TNM classification of malignant tumours. eighth ed. Oxford, UK: Wiley Blackwell; 2017.

[5] Madsen EV, Aalders KC, van der Heiden-van der Loo M, Gobardhan PD, van Oort PM, van der Ent FW, et al. Prognostic significance of tumor-positive internal mammary sentinel lymph nodes in breast cancer: a multicenter cohort study. Ann Surg Oncol 2015;22:4254–62.

[6] Noguchi M, Ohta N, Koyasaki N, Taniya T, Miyazaki I, Mizukami Y. Reappraisal of internal mammary node metastases as a prognostic factor in patients with breast cancer. Cancer 1991;68:1918–25.

[7] Veronesi U, Arnone P, Veronesi P, Galimberti V, Luini A, Rotmensz N, et al. The value of radiotherapy on metastatic internal mammary nodes in breast cancer. Results on a large series. Ann Oncol 2008;19:1553–60.

[8] Yang K, Kim H, Choi DH, Park W, Noh JM, Cho WK. Optimal radiotherapy for patients with internal mammary lymph node metastasis from breast cancer. Radiat Oncol 2020;15:16.

[9] Veronesi U, Marubini E, Mariani L, Valagussa P, Zucali R. The dissection of internal mammary nodes does not improve the survival of breast cancer patients. 30-year results of a randomised trial. Eur J Canc 1999;35:1320–5.

[10] Common terminology criteria for adverse events (CTCAE) U. S. Department of Health & human services. National Institutes of Health, National Cancer Institute; 2010.

[11] Park HJ, Shin KH, Cho KH, Park IH, Lee KS, Ro J, et al. Outcomes of positron emission tomography-staged clinical N3 breast cancer treated with neo-adjuvant chemotherapy, surgery, and radiotherapy. Int J Radiat Oncol Biol Phys 2011;81:e689–95.

[12] Joo JH, Kim SS, Ahn SD, Choi EK, Jung JH, Jeong Y, et al. Impact of pathologic diagnosis of internal mammary lymph node metastasis in clinical N2b and N3b breast cancer patients. Breast Canc Res Treat 2017;166:511–8.

[13] Sachdev S, Goodman CR, Neuschler E, Kalakota K, Cutright D, Donnelly ED, et al. Radiotherapy of MRI-detected involved internal mammary lymph nodes in breast cancer. Radiat Oncol 2017;12:199.

[14] Kim J, Chang JS, Choi SH, Kim YB, Keum KC, Suh CO, et al. Radiotherapy for initial clinically positive internal mammary nodes in breast cancer. Radiat Oncol J 2019;37:91–100.

[15] Burstein HJ, Curigliano G, Loibl S, Dubsky P, Gnant M, Poortmans P, et al. Estimating the benefits of therapy for early-stage breast cancer: the St. Gallen International Consensus Guidelines for the primary therapy of early breast cancer 2019. Ann Oncol 2019;30:1541–57.

[16] Lukesova L, Vrana D, Svach I, Zlamalova N, Gatek J, Vlachova Z, et al. Prognostic influence of internal mammary node drainage in patients with early-stage breast cancer. Anticancer Res 2016;36:6641–6.

[17] Gong J, Yu Y, Wu G, Lin C, Tu X. Should internal mammary lymph node sentinel biopsy be performed in breast cancer: a systematic review and meta-analysis. World J Surg Oncol 2019;17:135.

[18] Huang O, Wang L, Shen K, Lin H, Hu Z, Liu G, et al. Breast cancer subpopulation with high risk of internal mammary lymph nodes metastasis: analysis of 2,269 Chinese breast cancer patients treated with extended radical mastectomy. Breast Canc Res Treat 2008;107:379–87.

[19] Thorsen LB, Offersen BV, Dano H, Berg M, Jensen I, Pedersen AN, et al. DBCG-IMN: a population-based cohort study on the effect of internal mammary node irradiation in early node-positive breast cancer. J Clin Oncol 2016;34: 314–20.

[20] Poortmans PM, Collette S, Kirkove C, Van Limbergen E, Budach V, Struikmans H, et al. Internal mammary and medial supraclavicular irradiation in breast cancer. N Engl J Med 2015;373:317–27.

[21] Whelan TJ, Olivotto IA, Parulekar WR, Ackerman I, Chua BH, Nabid A, et al. Regional nodal irradiation in early-stage breast cancer. N Engl J Med 2015;373:307–16.

[22] Network NCC. Breast cancer. 2020., version 4.

[23] Postma EL, van Wieringen S, Hobbelink MG, Verkooijen HM, van den Bongard HJ, Borel Rinkes IH, et al. Sentinel lymph node biopsy of the internal mammary chain in breast cancer. Breast Canc Res Treat 2012;134:735–41.

[24] Hennequin C, Bossard N, Servagi-Vernat S, Maingon P, Dubois JB, Datchary J, et al. Ten-year survival results of a randomized trial of irradiation of internal mammary nodes after mastectomy. Int J Radiat Oncol Biol Phys 2013;86: 860–6.

[25] Halperin EC. Perez & brady's principles and practice of radiation oncology. seventh ed. Philadelphia: Wolters Kluwer; 2018.

[26] Zhang YJ, Oh JL, Whitman GJ, Iyengar P, Yu TK, Tereffe W, et al. Clinically apparent internal mammary nodal metastasis in patients with advanced breast cancer: incidence and local control. Int J Radiat Oncol Biol Phys 2010;77:1113–9.