Internal mammary node abnormality in imaging studies and treatment outcomes in patients with breast cancer

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Received November 17, 2023; Accepted February 22, 2024

DOI: 10.3892/ol.2024.14352

Abstract. The clinical significance of mild internal mammary node (IMN) enlargement (Mild-IMN) is uncertain. This study aimed to evaluate the relationship between treatment outcomes and IMN status in patients with breast cancer who underwent postmastectomy radiation therapy between January 2010 and December 2018. Overall, 250 patients were categorized based on IMN status: Clinically normal IMN (Normal-IMN; n=172), Mild-IMN (n=39) and clinically metastatic IMN (cMet-IMN; n=39). None of the patients in the Normal- or Mild-IMN groups received IMN irradiation. In the cMet-IMN group, 25 patients underwent IMN irradiation with an IMN boost (10 Gy in 5 fractions), while 14 patients did not. The median follow-up time was 80.0 months (range, 7.2-147.6 months). The 7-year overall survival (OS), disease-free survival (DFS) and IMN recurrence-free survival (IRF) rates were 80.2, 73.0 and 93.4%, respectively. Multivariate analyses indicated that only cMet-IMN had a significant impact on OS [hazard ratio (HR), 1.66; 95% CI, 1.01-3.68; P=0.05] and DFS (HR, 1.91; 95% CI, 1.08-3.39; P=0.03), while cMet-IMN did not have a significant impact on IRF (HR, 1.66; 95% CI, 0.41-6.78; P=0.48). Additionally, receiving an IMN boost had no influence on OS (HR, 1.11; 95% CI, 0.37-2.34; P=0.84), DFS (HR, 1.28; 95% CI, 0.51-3.22; P=0.60) or IRF (HR, 1.94; 95% CI, 0.22-17.47; P=0.55). In conclusion, the impact of Mild-IMN on clinical outcomes was small. Although irradiation for cMet-IMN is important, the impact of the cMet-IMN boost with 10 Gy in 5 fractions on clinical outcomes may also be limited.

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Key words: breast cancer, postmastectomy radiation therapy, internal mammary node, treatment outcome

Introduction

Breast cancer is the most frequently diagnosed cancer worldwide (1). Although various systemic therapies have been used in combination with local treatments in recent years, surgery and postoperative radiation therapy remain important treatment modalities for localized breast cancer (2). However, the role of internal mammary node (IMN) irradiation as a component is a controversial subject (3).

The IMN is known as an important lymphatic drainage pathway in breast cancer (4). The frequency of IMN metastases increases with the number of axillary lymph node metastases (n=0, 3-6%; n=1-3, 14-26%; n=4-, 20-43%) (5). However, in clinical practice, IMN metastatic recurrence is rare (10-year IMN recurrence rate, 1.5%) (6). The National Comprehensive Cancer Network (NCCN) guidelines recommend IMN irradiation for patients with breast cancer, whereas the Japanese Breast Cancer Society Practice Guidelines weakly recommend IMN irradiation for patients requiring regional lymph node irradiation (7,8).

Several studies have indicated that in certain cases, such as those with the presence of IMN metastasis, the number of axillary node metastases ≥4, or the number of axillary node metastasis=1-3 with central/medial primary location, may benefit from IMN irradiation (9-11). However, it remains uncertain whether mild IMN enlargement (Mild-IMN), defined as IMN enlargement (<0.5 cm) without fluorine-18 fluorodeoxyglucose (FDG) uptake and larger than the contralateral IMN, is a high-risk factor. Although FDG-positron emission tomography/computed tomography (FDG-PET/CT) has a high detection power for lymph node metastasis evaluation, some Mild-IMNs without FDG uptake actually demonstrate IMN metastases (12-14). Therefore, this study aimed to investigate the relationship between treatment outcomes and IMN status in patients with breast cancer treated with postmastectomy radiation therapy (PMRT).

Materials and methods

Study population. Between January 2011 and December 2018, a total of 296 initial patients with breast cancer (cancer center, 243; community hospital, 53) were treated with PMRT, which is performed for the patients with large tumor

size (≥T3, Union for International Cancer Control 8th (15)) and large number of axillary lymph node metastases (≥4). Patients with the following characteristics were excluded from the study: (1) bilateral breast cancer (n=9), (2) no available follow-up CT images (n=13), and (3) no neoadjuvant chemotherapy (NAC) or adjuvant chemotherapy (AC) (n=24). Subsequently, we retrospectively evaluated the remaining 250 breast cancer patients who underwent PMRT. The present study was approved (approval. no. 2023-526 and gai 2023-13) by the Ethics Committee of our institutions (National Hospital Organization Shikoku Cancer Center, Matsuyama, Japan; Ehime Prefectural Central Hospital, Matsuyama, Japan), and the opt-out consent was applied because of the retrospective nature of this study.

Imaging evaluation. Imaging follow-ups with FDG-PET/CT or CT were performed between 6-month and 1-year after PMRT and subsequently at approximately 1-year intervals, as determined by the attending physicians.

Clinically metastatic IMN (cMet-IMN) was defined as that with a size of ≥0.5 cm or that with FDG uptake (16-18). Mild-IMN was defined as that with a size of <0.5 cm, lacking FDG uptake and that larger than the contralateral IMN, a condition not identified during PMRT planning. Clinically normal IMN (Normal-IMN) constituted the remaining category. Based on this detailed IMN status evaluation, patients with breast cancer were divided into three groups (cMet-IMN, Mild-IMN, and Normal-IMN).

Treatment. All 250 patients underwent mastectomy with axillary lymph node dissection or sentinel lymph node biopsy. All patients received neoadjuvant chemotherapy (NAC) or AC before PMRT. A PMRT dose of 50 Gy in 25 fractions was administered to the chest wall encompassing the supraclavicular or infraclavicular region and excluding the axillary region from the treatment region. The IMN region received additional irradiation in all the 39 patients with cMet-IMNs. Among these, 25 patients with cMet-IMN received an additional IMN boost of 10 Gy in 5 fractions, specifically directed at highly suspected ipsilateral IMN metastasis detected on imaging examination. The remaining 14 patients with cMet-IMNs did not receive an additional IMN boost. The cMet-IMN boost was selected based on the preference of the radiation oncologists (one radiation oncologist, planning without an IMN boost; the other radiation oncologists, planning with an IMN boost) and not based on the IMN size after systemic therapy. Eight patients received an additional tumor bed boost of 10 Gy in 5 fractions due to a positive surgical margin. Five patients received a supraclavicular boost of 10 Gy in five fractions because imaging examinations strongly indicated ipsilateral supraclavicular node metastasis, and lymph node resections were not performed.

All the patients were treated with three-dimensional conformal radiation therapy. Two photon-tangential fields of 4-6 MV using the field-in-field technique were applied on the chest wall, with or without the IMN region. Two photon-opposing fields of 4-6 and 10 MV were used in the supraclavicular and infraclavicular regions, respectively. A single-electron filed of 4-12 MeV was used for the IMN boost and positive surgical margin boost. Two 10 MV photon-opposing fields were used in the supraclavicular boost plan.

NAC or AC was administered to all the patients. The anthracycline with or without taxane regimen, such as EC (epirubicin and cyclophosphamide) ± DTX/PTX/nab-PTX (docetaxel, paclitaxel, or nab-paclitaxel) ± HER (trastuzumab) (n=48), FEC (5-fluorouracil, epirubicin, and cyclophosphamide) ± DTX/PTX ± HER (n=55), AC (doxorubicin and cyclophosphamide) ± DTX/PTX ± HER (n=18), were used in NAC. Similarly, the anthracycline with or without taxane regimen, such as EC ± DTX/PTX/nab-PTX ± HER (n=47), FEC ± DTX/PTX ± HER (n=38), AC ± DTX ± HER (n=28), were used in AC. Taxane-based regimens such as TC (taxane and cyclophosphamide) + HER (n=1) were used for NAC. Similarly, taxane-based regimens such as TC ± HER (n=13) were used in AC. Additionally, tegafur/gimeracil/oteracil (n=2) was used in AC. After PMRT, 36 patients were treated with HER ± hormonal therapy, four patients were treated with chemotherapy, such as tegafur/gimeracil/oteracil (n=3) or capecitabine (n=1), and 154 patients were treated with hormonal therapy. Of these, the most commonly used regimens were EC (epirubicin 90 mg/m^2 i.v./cyclophosphamide 600 mg/m^2 i.v. q21 for 4 cycles) or FEC (5-fluorouracil 500 mg/m^2 i.v./epirubicin 60-100 mg/m^2 i.v./cyclophosphamide 500 mg/m^2 i.v. q21 for 4 cycles).

Breast cancer was classified into four groups according to estrogen receptor (ER), progesterone receptor (PR) and human epidermal growth factor receptor 2 (HER2) status. Based on the immunohistochemistry (IHC), ER-positive (≥1%) and PR-positive (≥1%) were determined. HER2-positive was determined by IHC or fluorescence in situ hybridization (FISH). In detail, based on IHC, HER2 protein expression rates were classified into four groups (0 to 3+). The cases of 2+ HER2 protein expression rates were reviewed by FISH. Finally, the cases that were positive by FISH and 3+ by IHC were determined to be HER2-positive. Luminal A-like breast cancer is ER-positive and PR-positive, HER2-negative. Luminal B-like HER2-positive breast cancer is ER-positive and HER2-positive. Luminal B-like HER2-negative breast cancer is ER-positive and HER2-negative. Non-luminal HER2-positive breast cancer is ER-negative, PR-negative, and HER2-positive. Triple-negative breast cancer is ER-negative, PR-negative, and HER2-negative. The number of patients with luminal A-like, luminal B-like HER2-positive, luminal B-like HER2-negative, non-luminal HER2-positive, and triple-negative tumors was 98 (39.2%), 27 (10.8%), 40 (16.0%), 34 (13.6%), and 51 (20.4%), respectively. In this study, treatment outcomes were analyzed by these ER, PR, and HER2 status. In addition, nuclear grade was evaluated according to the criteria of the National Surgical Adjuvant Study of Breast Cancer (NSAS-B) protocol (19).

Statistical analysis. Survival and recurrence-free times were calculated from the initiation of PMRT for breast cancer. The Kaplan-Meier method was used to generate curves for overall survival (OS), disease-free survival (DFS), and IMN recurrence-free survival (IRF) rates. Univariate and multivariate Cox proportional hazards models were used to determine hazard ratios (HRs), 95% confidence intervals (CIs), and p values. Statistical significance was

Table I. Characteristics.

Characteristics	Value
Age, years	
Median (range)	55 (30-86)
<55, n (%)	129 (48.4)
≥55, n (%)	121 (51.6)
ECOG-PS, n (%)	
0	236 (94.4)
1	14 (5.6)
cT stage (UICC 8th), n (%)	
1	31 (12.4)
2	140 (56.0)
3	47 (18.8)
4	32 (12.8)
cN stage (UICC 8th), n (%)	
0	40 (16.0)
1	117 (46.8)
2	34 (13.6)
3	59 (23.6)
cTNM stage (UICC 8th), n (%)	
1	14 (5.6)
2	114 (45.6)
3	122 (48.8)
Histologic type, n (%)	
Invasive ductal carcinoma	217 (86.8)
Invasive lobular carcinoma	16 (6.4)
Others	17 (6.8)
Nuclear grade, n (%)	
1	38 (15.2)
2	81 (32.4)
3	92 (36.8)
Unknown	39 (15.6)
Laterality, n (%)	
Left	141 (56.4)
Right	109 (43.6)
Tumor location, n (%)	
Medial/central	119 (47.6)
Lateral	131 (52.4)
ER status, n (%)	
Positive	182 (72.8)
Negative	68 (27.2)
PR status, n (%)	
Positive	146 (58.4)
Negative	104 (41.6)
HER2, n (%)	
Positive	61 (24.4)
Negative	189 (75.6)
IMN status, n (%)	
cMet-IMN	39 (15.6)
Mild-IMN	39 (15.6)
Normal-IMN	172 (68.8)
RT schedule, n (%)	
PMRT alone	212 (84.8)
PMRT + boost	38 (15.2)
IMN boost	25 (10.0)
Positive surgical margin boost	8 (3.2)
Supraclavicular lymph node boost	5 (2.0)
NAC or AC, n (%)	
NAC	122 (48.8)
Anthracycline with or without taxane regimen	121 (48.4)
Taxane-based regimen	1 (0.4)
AC	128 (51.2)
Anthracycline with or without taxane regimen	113 (45.2)
Taxane-based regimen	13 (5.2)
Tegafur/gimeracil/oteracil	2 (0.8)
Systemic therapy after PMRT, n (%)	
Trastuzumab and/or hormonal therapy	36 (14.4)
Hormonal therapy	154 (61.6)
Others	4 (1.6)
No	56 (22.4)

ECOG-PS, Eastern Cooperative Oncology Group Performance Status; UICC, Union for International Cancer Control; ER, estrogen receptor; PR, progesterone receptor; HER2, human epidermal growth factor receptor 2; IMN, internal mammary node; cMet-IMN, clinically metastatic IMN (size of ≥0.5 cm with FDG uptake); Mild-IMN, mild IMN enlargement (size of <0.5 cm and larger size compared with the contralateral IMN without FDG uptake); Normal-IMN, clinically normal IMN (size of <0.5 cm and equal or smaller size compared with the contralateral IMN without FDG uptake); RT, radiotherapy; PMRT, postmastectomy radiation therapy; NAC, neoadjuvant chemotherapy; AC, adjuvant chemotherapy; FDG, fluorodeoxyglucose.

defined as $p \leq 0.05$. Statistical analyses were performed using the JMP software (JMP version 14.3.0; SAS Institute, Cary, NC, USA).

Results

Clinical characteristics. A total of 217 (86%) patients had ductal carcinoma, with 188 classified as scirrhous, 20 as solid tubular, and 9 in other categories. All 39 patients with cMet-IMN showed FDG uptake, with a median cMet-IMN size of 1.1 cm (range, 0.6-2.1 cm). These patients received radiation to the IMN region in addition to radiation to the chest wall, supraclavicular, or infraclavicular regions. Among them, 25 (64.1%) patients received boost irradiation in the IMN region (10 Gy in 5 fractions). Thirty-nine patients with Mild-IMN did not exhibit FDG uptake, whereas the remaining 172 patients had Normal-IMN. General condition was assessed using the Eastern Cooperative Oncology Group Performance Status (ECOG-PS), with PS=0 in 94.4% (n=236) of the patients (20). Further details regarding the patient characteristics are presented in Table I.

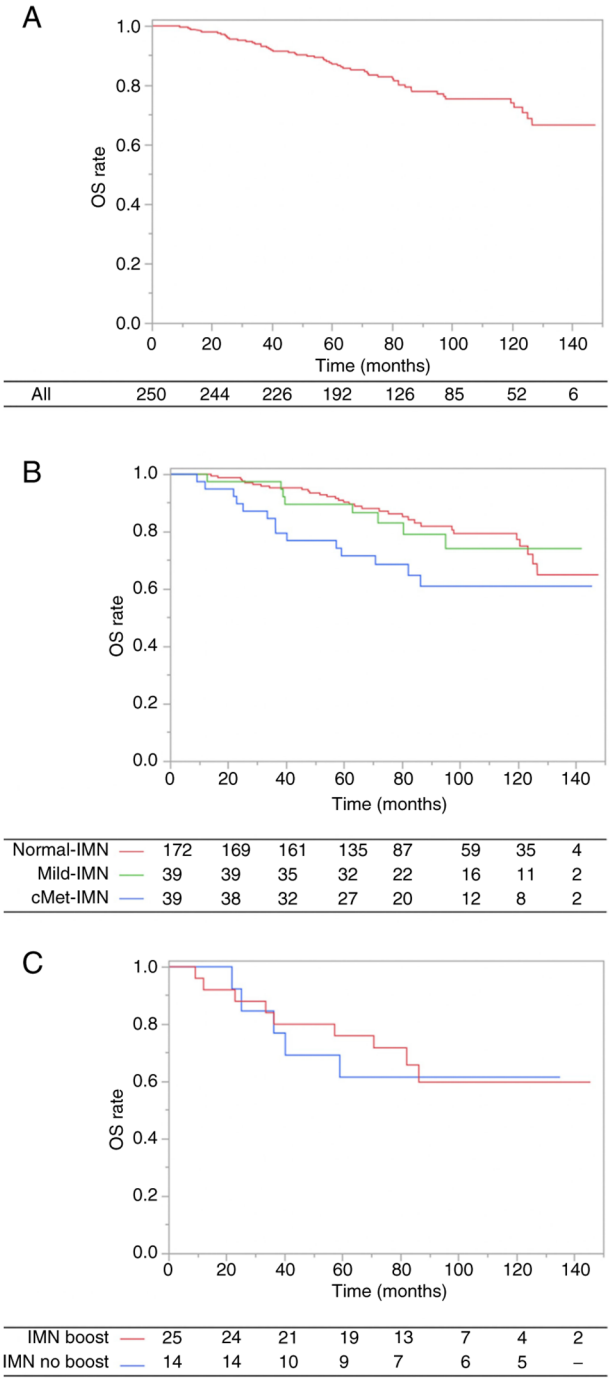

Figure 1. OS rate of patients with breast cancer. (A) Kaplan-Meier curve of OS. (B) Kaplan-Meier curves of OS according to IMN status. (C) Kaplan-Meier curves of OS in patients with cMet-IMN according to whether or not IMN boost was applied. In patients with cMet-IMN, the 2 Gy x5 fraction IMN boost did not improve OS (IMN boost vs. IMN no boost; HR, 1.12; 95% CI, 0.37-3.34; P=0.84). cMet-IMN, clinically metastatic IMN; HR, hazard ratio; IMN, internal mammary node; Mild-IMN, mild IMN enlargement; Normal-IMN, clinically normal IMN; OS, overall survival.

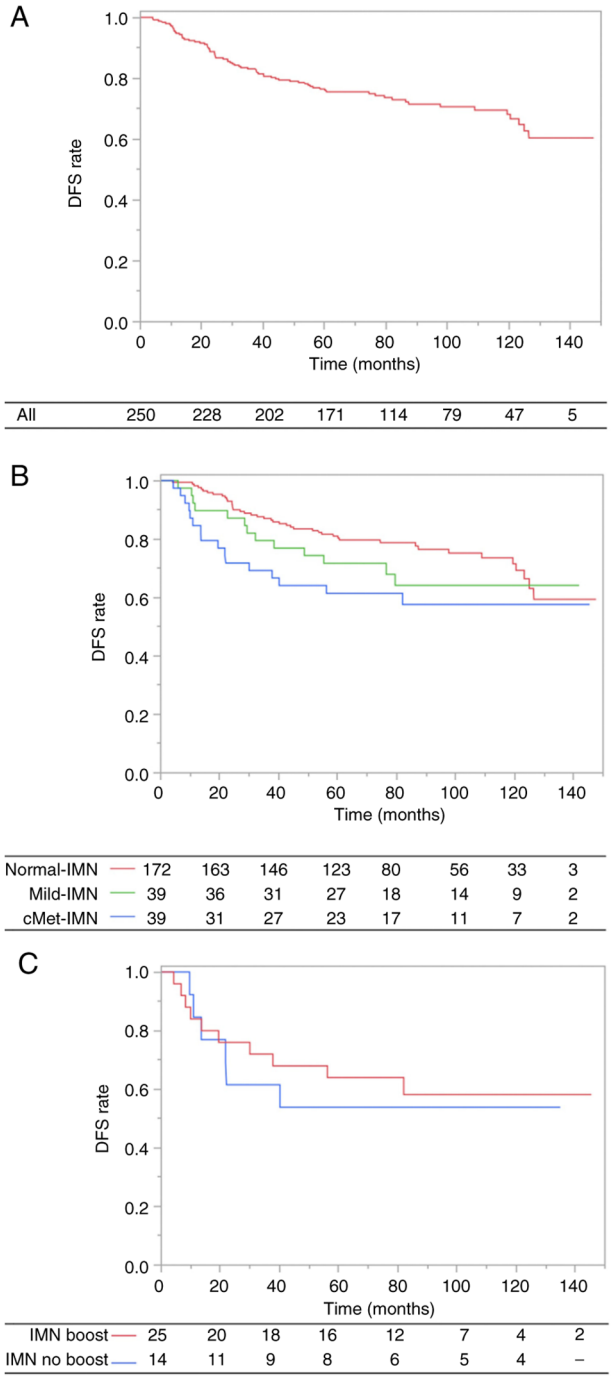

Figure 2. DFS rate of patients with breast cancer. (A) Kaplan-Meier curve of DFS. (B) Kaplan-Meier curves of DFS according to IMN status. (C) Kaplan-Meier curves of DFS in patients with cMet-IMN according to whether or not IMN boost was applied. In patients with cMet-IMN, 2 Gy x5 fraction IMN boost did not improve DFS (IMN boost vs. IMN no boost; HR, 1.20; 95% CI, 0.44-3.30; P=0.73). cMet-IMN, clinically metastatic IMN; DFS, disease-free survival; IMN, internal mammary node; Mild-IMN, mild IMN enlargement; Normal-IMN, clinically normal IMN.

Overall survival. The median follow-up time for OS was 80.0 months (range, 7.2-147.6 months). At the time of analysis, 54 patients (Normal-IMN, 32; Mild-IMN, 8; cMet-IMN, 14) had died. Thirty-three patients experienced cause-specific death was 33 (84.6%) patients (Table SI). The 7-year OS rate was 80.2% (Normal-IMN, 84.2%; Mild-IMN, 79.1%; cMet-IMN, 64.8%; Fig. 1A and B).

In univariate analysis, age (<55 years vs. ≥55 years; HR, 1.79; 95% CI, 1.03-3.10; P=0.04), progesterone receptor (PR) status (positive vs. negative; HR, 1.70; 95% CI, 1.00-2.90; P=0.05), and IMN status (Normal-IMN vs. cMet-IMN; HR, 2.08; 95% CI, 1.11-3.90; P=0.02) were identified as significant factors for OS. However, in IMN status, Mild-IMN did not have an impact on OS (Normal-IMN vs. Mild-IMN; HR, 1.04, 95% CI, 0.48-2.27;

Table II. UVA and MVA for overall survival.

	UVA		MVA	
Variables	HR (95% CI)	P-value	HR (95% CI)	P-value
Age (<55 years vs. ≥55 years)	1.79 (1.03-3.10)	0.04	1.90 (1.03-3.50)	0.04
cT stage (UICC 8th) (1-2 vs. 3-4)	1.29 (0.74-2.26)	0.37	-	-
cN stage (UICC 8th) (0-1 vs. 2-3)	1.67 (0.98-2.84)	0.06	-	-
Nuclear grade (1-2 vs. 3)	1.39 (0.80-2.41)	0.24	-	-
Laterality (left vs. right)	1.11 (0.65-1.92)	0.70	-	-
Tumor location (medial/central vs. lateral)	0.91 (0.53-1.55)	0.72	-	-
ER status (positive vs. negative)	1.50 (0.85-2.64)	0.16	-	-
PR status (positive vs. negative)	1.70 (1.00-2.90)	0.05	1.44 (0.79-2.62)	0.23
HER2 status (positive vs. negative)	1.98 (0.96-4.07)	0.06	-	-
IMN size (Normal-IMN vs. Mild-IMN)	1.04 (0.48-2.27)	0.92	-	-
IMN size (Normal-IMN vs. cMet-IMN)	2.08 (1.11-3.90)	0.02	1.93 (1.01-3.68)	0.05

UICC, Union for International Cancer Control; ER, estrogen receptor; PR, progesterone receptor; HER2, human epidermal growth factor receptor 2; IMN, internal mammary node; cMet-IMN, clinically metastatic IMN; Mild-IMN, mild IMN enlargement; Normal-IMN, clinically normal IMN; UVA, univariate analysis; MVA, multivariate analysis; HR, hazard ratio; FDG, fluorodeoxyglucose.

Table III. UVA and MVA for disease-free survival.

	UVA		MVA	
Variables	HR (95% CI)	P-value	HR (95% CI)	P-value
Age (<55 years vs. ≥55 years)	1.21 (0.77-1.93)	0.41	-	-
cT stage (UICC 8th) (1-2 vs. 3-4)	1.25 (0.77-2.03)	0.37	-	-
cN stage (UICC 8th) (0-1 vs. 2-3)	1.55 (0.97-2.45)	0.06	-	-
Nuclear grade (1-2 vs. 3)	1.35 (0.84-2.15)	0.21	-	-
Laterality (left vs. right)	1.16 (0.73-1.84)	0.54	-	-
Tumor location (medial/central vs. lateral)	0.88 (0.55-1.39)	0.58	-	-
ER status (positive vs. negative)	1.13 (0.67-1.88)	0.65	-	-
PR status (positive vs. negative)	1.29 (0.81-2.05)	0.28	-	-
HER2 status (positive vs. negative)	1.92 (1.03-3.58)	0.04	1.71 (0.87-3.38)	0.12
IMN size (Normal-IMN vs. Mild-IMN)	1.34 (0.72-2.49)	0.36	-	-
IMN size (Normal-IMN vs. cMet-IMN)	1.90 (1.07-3.37)	0.03	1.91 (1.08-3.39)	0.03

UICC, Union for International Cancer Control; ER, estrogen receptor; PR, progesterone receptor; HER2, human epidermal growth factor receptor 2; IMN, internal mammary node; cMet-IMN, clinically metastatic IMN; Mild-IMN, mild IMN enlargement; Normal-IMN, clinically normal IMN; UVA, univariate analysis; MVA, multivariate analysis; HR, hazard ratio; FDG, fluorodeoxyglucose.

P=0.92). In multivariate analysis, age (HR, 1.90; 1.03-3.50; P=0.04) and IMN status (Normal-IMN vs. cMet-IMN; HR, 1.93; 95% CI, 1.01-3.68; P=0.05) remained significant factors for OS. These findings are presented in Table II.

Furthermore, for the patients with cMet-IMN, the use of IMN boost did not yield a significant impact on OS (IMN boost vs. IMN no boost; HR, 1.12; 95% CI, 0.37-3.34; P=0.84; Fig. 1C). Similarly, among patients with large cMet-IMN (size of ≥1.0 cm), the IMN boost did not significantly impact OS (IMN boost vs. IMN no boost; HR, 2.02; 95% CI, 0.25-16.50; P=0.51).

Disease-free survival and IMN. The median follow-up duration for DFS was 74.1 months (range, 4.0-147.6 months). The 7-year DFS rate was 73.0% (Normal-IMN, 78.8%; Mild-IMN, 64.2%; cMet-IMN, 57.6%; Fig. 2A and B). Sixty-three patients experienced recurrence and 57 experienced simultaneous recurrence in multiple locations. The most frequent site of recurrence was distant metastases (n=54).

In univariate analysis, HER2 status (positive vs. negative) and IMN status (Normal-IMN vs. cMet-IMN) were identified as significant factors for DFS. However, in terms of IMN status, Mild-IMN did not have an influence on

the DFS (Normal-IMN vs. Mild-IMN; HR, 1.34, 95% CI, 0.72-2.49; P=0.36). In multivariate analysis, IMN status (Normal-IMN vs. cMet-IMN; HR, 1.91; 95% CI, 1.08-3.39; P=0.03) remained a significant factor for DFS. These findings are presented in Table III.

In addition, for the patients with cMet-IMN, IMN boost did not have a significant impact on DFS (IMN boost vs. IMN no boost; HR, 1.20; 95% CI, 0.44-3.30; P=0.73; Fig. 2C). Similarly, for the patients with large cMet-IMN (size of ≥1.0 cm), the IMN boost did not have a significant impact on DFS (IMN boost vs. IMN no boost; HR, 1.13; 95% CI, 0.24-5.31; P=0.88).

IMN recurrence-free survival. The median follow-up duration for IRF was 65.4 months (range, 1.0-145.4 months). The 7-year IRF rate was 93.4% (Normal-IMN, 95.5%; Mild-IMN, 95.2%; cMet-IMN, 83.7%; Fig. 3A and B). The number of first recurrences with IMN was 13.

In univariate analysis, clinical N stage (0-1 vs. 2-3; HR, 5.42; 95% CI, 1.47-20.01; P=0.01), ER status (positive vs. negative; HR, 4.45; 95% CI, 1.41-14.03; P=0.01), and IMN status (Normal-IMN vs. cMet-IMN; HR, 3.84; 95% CI, 1.17-12.61; P=0.03) were significant factors for IRF. However, concerning IMN status, Mild-IMN did not impact IRF (Normal-IMN vs. Mild-IMN; HR, 1.47; 95% CI, 0.18-12.24; P=0.72). In the multivariate analysis, ER status (positive vs. negative; HR, 4.18; 95% CI, 1.20-14.53; P=0.02) remained a significant factor for IRF. These results are presented in Table IV.

Furthermore, among patients with cMet-IMN, the application of an IMN boost (10 Gy in 5 fractions) did not yield a significant impact on IRF (IMN boost vs. IMN no boost; HR, 1.94; 95% CI, 0.22-17.47; P=0.55; Fig. 3C). Similarly, for the patients with large cMet-IMN (size of ≥1.0 cm), the application of an IMN boost (10 Gy in 5 fractions) did not significantly impact IRF (IMN boost vs. IMN no boost; HR, 1.38; 95% CI, 0.14-13.46; P=0.78).

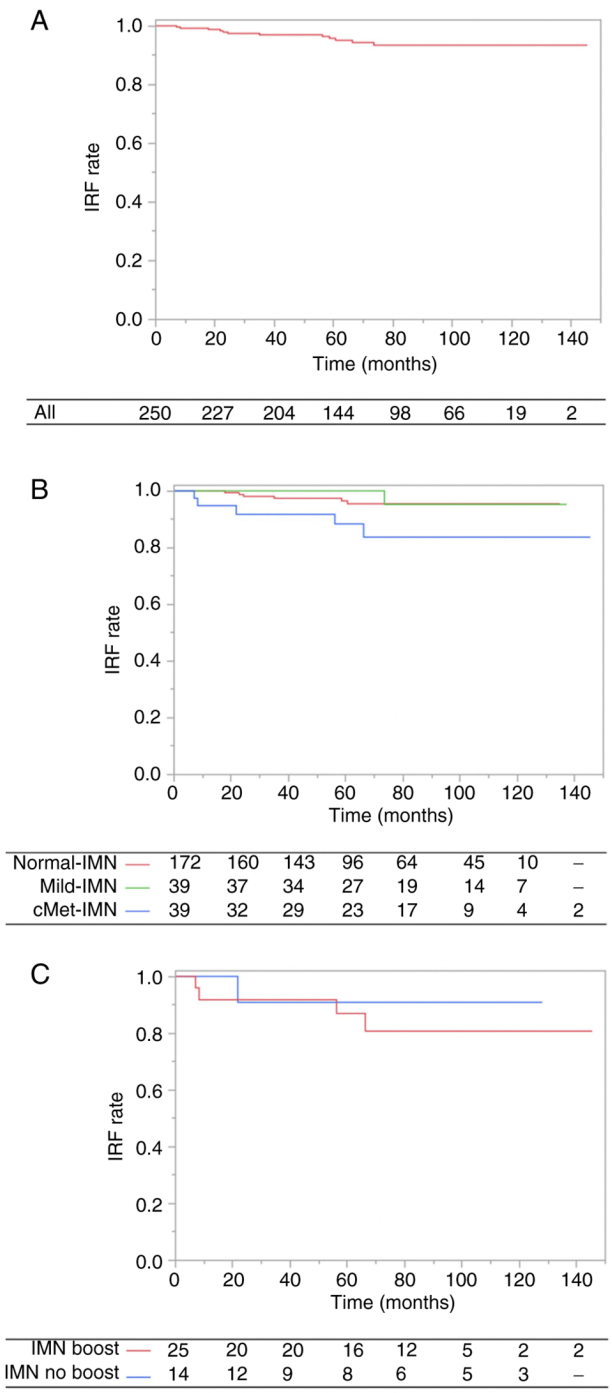

Figure 3. IRF rate of patients with breast cancer. (A) Kaplan-Meier curve of IRF. (B) Kaplan-Meier curves of IRF according to IMN status. (C) Kaplan-Meier curves of IRF in patients with cMet-IMN according to whether or not IMN boost was applied. In patients with cMet-IMN, 2 Gy x5 fraction IMN boost did not improve IRF (IMN boost vs. IMN no boost; HR, 1.94; 95% CI, 0.22-17.47; P=0.55). cMet-IMN, clinically metastatic IMN; IMN, internal mammary node; IRF, IMN recurrence-free survival; Mild-IMN, mild IMN enlargement; Normal-IMN, clinically normal IMN.

Discussion

In patients with breast cancer treated with systemic therapy and PMRT, the use of Mild-IMN without FDG uptake was not a significant adverse factor for OS and DFS. By contrast, cMet-IMN with FDG uptake emerged as a significant adverse factor for both OS and DFS. In addition, the application of an IMN boost (10 Gy in 5 fractions) for cMet-IMN did not lead to improvements in the OS, DFS, and IRF.

Although the diagnostic accuracy of lymph node metastasis by magnetic resonance (MR) or FDG-PET/CT is very high, there is not always complete concordance between the clinical N stage and pathological N stage (21). In some studies, the size of IMN of ≥0.5 cm has been considered indicative of IMN metastasis (16-18). Therefore, the cut-off size for IMN metastasis was notably small. Mild-IMN, characterized by IMN enlargement (<0.5 cm) without FDG uptake and larger size compared to the contralateral IMN, is occasionally identified in clinical practice. Distinguishing whether this Mild-IMN represents a microscopic metastatic lymph node or a reactive enlargement is difficult to diagnose in imaging studies alone. In our study, patients with Mild-IMN achieved similar treatment outcomes as patients with Normal-IMN, even without IMN irradiation. This suggests that Mild-IMN may be a reactive enlargement or could be effectively managed by systemic therapy without IMN irradiation even if it harbors micro-metastasis.

Furthermore, in our study, the application of an IMN boost (10 Gy in 5 fractions) did not improve the OS, DFS, and IRF for patients with cMet-IMN. Limited studies have explored the optimal RT dose for the IMN region (21-23). Yang *et al* (24)

Table IV. UVA and MVA for IMN recurrence-free survival.

	UVA		MVA	
Variables	HR (95% CI)	P-value	HR (95% CI)	P-value
Age (<55 years vs. ≥55 years)	1.01 (0.32-3.12)	0.99	-	-
cT stage (UICC 8th) (1-2 vs. 3-4)	2.00 (0.44-9.14)	0.37	-	-
cN stage (UICC 8th) (0-1 vs. 2-3)	5.42 (1.47-20.01)	0.01	2.85 (0.59-13.80)	0.19
Nuclear grade (1-2 vs. 3)	1.33 (0.42-4.20)	0.63	-	-
Laterality (left vs. right)	1.02 (0.32-3.22)	0.98	-	-
Tumor location (medial/central vs. lateral)	0.80 (0.26-2.49)	0.70	-	-
ER status (positive vs. negative)	4.45 (1.41-14.03)	0.01	4.18 (1.20-14.53)	0.02
PR status (positive vs. negative)	3.22 (0.97-10.71)	0.06	-	-
HER2 status (positive vs. negative)	3.97 (0.51-30.80)	0.19	-	-
IMN status (Normal-IMN vs. Mild-IMN)	1.47 (0.18-12.24)	0.72	-	-
IMN status (Normal-IMN vs. cMet-IMN)	3.84 (1.17-12.61)	0.03	1.66 (0.41-6.78)	0.48

UICC, Union for International Cancer Control; ER, estrogen receptor; PR, progesterone receptor; HER2, human epidermal growth factor receptor 2; IMN, internal mammary node; cMet-IMN, clinically metastatic IMN; Mild-IMN, mild IMN enlargement; Normal-IMN, clinically normal IMN; UVA, univariate analysis; MVA, multivariate analysis; HR, hazard ratio.

suggested that a higher RT dose (biologically equivalent dose in 2 Gy fractions of >63.5 Gy) might improve the DFS, particularly for IMN size ≥1.0 cm. In contrast, our study found that the IMN boost (10 Gy in 5 fractions IMN boost; total biologically equivalent dose in 2 Gy fractions of 60 Gy) did not improve OS, DFS, and IRF for patients with IMN size of ≥1.0 cm and ≥0.5 cm. Given that the RT doses required for cMet-IMN were higher than those used in our study, it is possible that the IMN boost dose in our study may have been insufficient to improve treatment outcomes. Considering the only factor affecting IRF was ER status, it could be an option to irradiate cMet-IMN boost with higher RT dose may be an option in ER-negative cases in clinical practice. Further large-scale studies are needed to assess the impact of the IMN boost dose on enhancing treatment outcomes.

This study has some limitations due to its retrospective nature. First, the limited number of patients with Mild-IMN and cMet-IMN reduced the statistical power of our study. Second, we only assessed the clinical T and N stages, as obtaining pathological T and N stages was not possible for patients treated with NAC. Additionally, we were unable to evaluate the prognostic impact of the NAC response on OS, DFS, and IRF as many patients in our study received AC without NAC. Third, differences by surgeon's surgical skills could not be analyzed. However, at our institutions, because total mastectomy is generally performed by breast surgeons, we believe that the quality of surgical procedures is adequate. Finally, in our study, because of the wide age range, the median age was used as a cutoff value to examine the impact on treatment outcome. Because hormone therapy for breast cancer depends not only on estrogen/progesterone status but also on menopausal status, this may not be the optimal age cutoff value. In the future, a prospective study adjusting for age will be warranted. Despite these limitations, as the first study to examine the clinical significance of Mild-IMN, these results are meaningful for optimizing IMN irradiation in routine clinical practice. Future large-scale studies are needed to determine the appropriate IMN irradiation and IMN boost dose.

In conclusion, the impact of Mild-IMN on OS, DFS, and IRF was minor. The presence of Mild-IMN does not significantly warrant IMN irradiation. Furthermore, while irradiating cMet-IMN is important, an IMN boost of 10 Gy in 5 fractions may not significantly improve treatment outcomes, and only ER status appears to be a factor influencing cMet-IMN control.

Acknowledgements

Not applicable.

Funding

No funding was received.

Availability of data and materials

The data generated in the present study may be requested from the corresponding author.

Authors' contributions

KM, YH, HK, KN and KA had full access to the data in the study, confirm the authenticity of all the raw data, and take responsibility for the integrity of the data and the accuracy of the data analysis. KM, YH, HK, KN and KA designed the study. KM, YH, HK, KN and KA collected patient data, and collaborated on discussions. KM prepared the manuscript and YH edited the manuscript. KM, YH, HK, KN and KA drafted the manuscript. All authors have read and approved the final version of the manuscript.

Ethics approval and consent to participate

All procedures performed in the present study were in accordance with the ethical standards of the Institutional Research Committee and the 1964 Declaration of Helsinki and its later amendments. The patients treated at our institutions consented in writing to the use of their anonymous data for research in general. Opt-out consent was applied due to the retrospective nature of the present study, and there was no non-consent for the present study. The present study was approved by the Ethics Committee of National Hospital Organization Shikoku Cancer Center (Matsuyama, Japan; approval. no. 2023-526) and the Ethics Committee of Ehime Prefectural Central Hospital (Matsuyama, Japan; approval. no. gai 2023-13).

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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