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CLINICAL INVESTIGATION

Response to Neoadjuvant Chemotherapy as a Potential Indicator of Internal Mammary Node Involvement in Early Breast Cancer

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Purpose: Internal mammary lymph node (IMN) irradiation has the potential to improve the overall survival in patients with nodal-positive breast cancer. Nevertheless, achieving these benefits while keeping treatment-related morbidity low is technically complex and requires careful patient selection and treatment planning. For this, detection of IMN involvement is of particular importance. This study aims to investigate the response of visible IMN to neoadjuvant chemotherapy (NACT) as a potential surrogate for initial IMN involvement.

Methods and Materials: We analyzed 298 patients with nonmetastatic breast cancer who underwent high-resolution pretreatment magnetic resonance imaging (MRI) and follow-up MRI after NACT. If visible IMNs were present, diameters were measured in axial and coronal planes on both pre- and post-NACT MRIs. Differences in size were assessed, and response was systematically classified and correlated with clinical and histopathological response, axillary lymph node (AXN) metastasis (AXN+), and tumor characteristics.

Results: Out of 298 patients with breast cancer, 175 (58.7%) had visible IMN on pretreatment MRI and 158 patients had a histopathological response of the primary tumor. Among these, 62 patients (39.3%) had a response of visible IMN. In patients with AXN+, the rate of IMN response was particularly high at 48.6%. In patients without AXN metastasis, 21.8% of patients with visible IMN showed a response to NACT. Response of visible IMN correlated significantly with medial tumor location and predominant tumor contact with internal mammary perforator vessels. The large majority (76.3 %) of IMN with response to NACT were initially rated as nonsuspicious during initial staging and in the interdisciplinary tumor board consensus.

Conclusions: Clinical IMN response to NACT may serve as an indicator of previously undetected IMN involvement in a relevant proportion of patients with early breast cancer. The observation that approximately 20% of patients without AXN

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metastases demonstrated a radiologic IMN response warrants further investigation, as this subgroup is not routinely considered for IMN irradiation. These findings highlight the need for prospective validation in larger, well-characterized cohorts using standardized imaging protocols to better define the clinical significance of IMN response to systemic therapy.

Introduction

The presence and extent of nodal involvement is 1 of the most important prognostic factors in patients with breast cancer. It is known that survival rates are significantly lower with increasing burden of lymphatic metastases.[1]

While assessment of the axillary lymph node(s) (AXN) is typically performed through standardized clinical, radiological, and surgical methods, evaluation of the internal mammary lymph node(s) (IMN) region is more challenging: Due to the small size of these lymph nodes, the general principles used for radiological evaluation of lymph node involvement are not applicable, and no universally accepted standard exists for diagnosing IMN metastases.[2] Furthermore, the IMN region is generally not surgically addressed, as earlier studies demonstrated no oncologic benefit but a high risk of morbidity.[3,4]

Involvement of the IMN has significant implications for the prognosis and management of breast cancer, and its accurate diagnosis is essential for ensuring optimal and individualized treatment.

It is known that IMN metastases are associated with a significantly increased rate of distant metastases and reduced disease-free survival (DFS) even in patients without axillary lymph node metastases.[5,6] Consequently, detection of IMN involvement may lead to upstaging and alter the approach to both systemic and locoregional therapy, especially in patients with negative AXN.

Irradiation of the IMN region (IMNI) can improve overall survival (OS) and decrease the risk of distant metastases for patients with high-risk breast cancer.[7-9] Since IMNI leads to higher doses in the organs at risk such as the heart,[10] careful consideration of risk and benefits is necessary. While inclusion of the IMN region in the target volume is undisputed in patients with confirmed IMN involvement, the optimal selection criteria for elective IMNI in the absence of clinically apparent metastases are controversial.[11,12] Thus, in clinical routine, IMNI is usually based on a risk assessment using tumor location and extent of axillary metastases. In patients without axillary nodal disease, IMNI is usually not performed. Although IMN involvement is less likely without involvement of axillary lymph nodes, the incidence of isolated IMN metastases ranged from 1.2% to 17.9%.[4] Hence, the correct diagnosis of IMN is inevitable, as it has a direct impact on the outcome of patients with breast cancer.

The increasing use of neoadjuvant chemotherapy (NACT) in patients with high-risk breast cancer adds an additional dimension to the assessment of lymph node metastases, namely the evaluation of treatment response. In patients with detected IMN involvement, it has been recently shown that the response of IMN metastases to NACT is an independent prognostic factor.[13] However, reliable detection of IMN involvement during initial imaging is challenging.

While older studies with surgical assessment of the IMN region indicate that approximately one-third of patients with axillary lymph nodes have additional IMN metastases,[6] the number of detected IMN metastases in patients with axillary lymph node metastases is significantly lower, at approximately 10%. This "diagnostic" gap indicates insufficient sensitivity of initial imaging. This is worrying considering the implications of IMN metastases for treatment planning and the potential impact on the prognosis. In this context, assessment of the response of visible IMN to NACT could help to identify patients with initially undetected IMN involvement.

Therefore, the aim of this study was to investigate the frequency of visible IMN in patients with breast cancer and evaluate the response to NACT.

Methods and Materials

Assessment and analysis of all patient data were performed pseudonymized in our institution. The study was approved by the local institutional review board (2024-373-S-CB).

Patient collective

For patient selection, we screened our institutional picture archiving and communication system for patients with histologically confirmed invasive breast cancer who underwent pretreatment magnetic resonance imaging (MRI) of the breast between 2013 and 2023. Patients were excluded if they did not receive NACT, if there was not at least 1 follow-up MRI after onset of NACT, if the follow-up MRI was less than 2 months after onset of NACT, or if there was a primary metastatic disease.

In all patients, response assessment to NACT was performed at our institutional specialized breast imaging center using pre- and post-treatment high-resolution, contrast-enhanced breast MRI and ultrasound. However, ultrasound examinations were exclusively focused on the primary breast tumor and potentially regional axillary lymph nodes but did not include systematic evaluation of the IMN region. Accordingly, IMN assessment was based on MRI, which also provides superior soft tissue contrast and higher sensitivity than ultrasound and contrast-enhanced CT for the detection of particularly small IMN metastases.[2,14]

All 175 patients additionally underwent pretreatment contrast-enhanced staging CT, whereas only 7 patients received a repeat contrast-enhanced CT after completion of NACT. Positron emission tomography-computed tomography (PET-CT) was available in 22 patients at baseline, but only 5 patients underwent PET-CT both before and after NACT. Given the limited availability of paired PET-CT and contrast-enhanced CT examinations, additional response analyses based on these imaging modalities were not feasible.

Basic patient characteristics and outcomes were assessed for all patients including tumor stage, biological subtype, grading, treatment information as well as histopathological and radiological findings of the primary tumor (PT) and AXN. In addition, known risk factors for IMN involvement were analyzed, including involvement of AXN, tumor site, as well as the predominant contact of the tumor to the ipsilateral internal mammary perforator vessel (IMPVc) on pretreatment MRI according to Behzadi et al.[15] Moreover, it was evaluated whether IMN involvement was identified by a dedicated breast radiologist and confirmed by a consensus of the interdisciplinary tumor board. Diagnosis relied on contrast enhancement, visibility in diffusion-weighted imaging sequences, and asymmetry of IMN on contrast-enhanced MRI alongside relevant clinicopathological tumor characteristics. If IMN metastasis was not mentioned either in the interdisciplinary tumor board consensus or in the radiological findings, it was considered clinically uninvolved at the initial stage of diagnosis.

We screened 527 patients with pretreatment MRI of the breast and excluded 182 patients who did not undergo NACT, 43 patients without a follow-up MRI at least 2 months after the onset of NACT, and 4 patients with primary metastatic disease. Among the remaining 298 patients, 175 patients with primary breast cancer and visible IMN on pretreatment MRI were included in this study. Because of missing data on pathological results after surgery, 8 patients were excluded from the final analysis. Further details are depicted in Figure 1.

Response assessment of the PT and axillary lymph nodes to NACT

Histopathological tumor response was extracted from histopathological reports. Response evaluation was classified by the reported and at that time guideline-concordant regression criteria using the semiquantitative scoring system defined by Sinn et al,[16] considering any value ≥1 (defined as resorption and tumor sclerosis) as response to NACT. Clinical response of the PT and AXN was defined based on the imaging reports (clinical response vs no clinical response).

Internal mammary node evaluation pre- and post-NACT

In all pretreatment MRIs, we evaluated the presence of visible IMN. IMN assessment followed a highly standardized study protocol with strict predefined criteria for lymph node measurements in order to reduce the potential impact of interobserver variability. To maximize measurement accuracy and reproducibility, an experienced second observer conducted frequent spot checks, which revealed no significant discrepancies. All patients with visible IMN were included in further analyses irrespective of whether the IMN was rated as suspicious or not during initial radiological assessment. Due to the shape of IMN and variable presentation depending on the viewed plane, each IMN was measured in axial and coronal planes using both the axis of

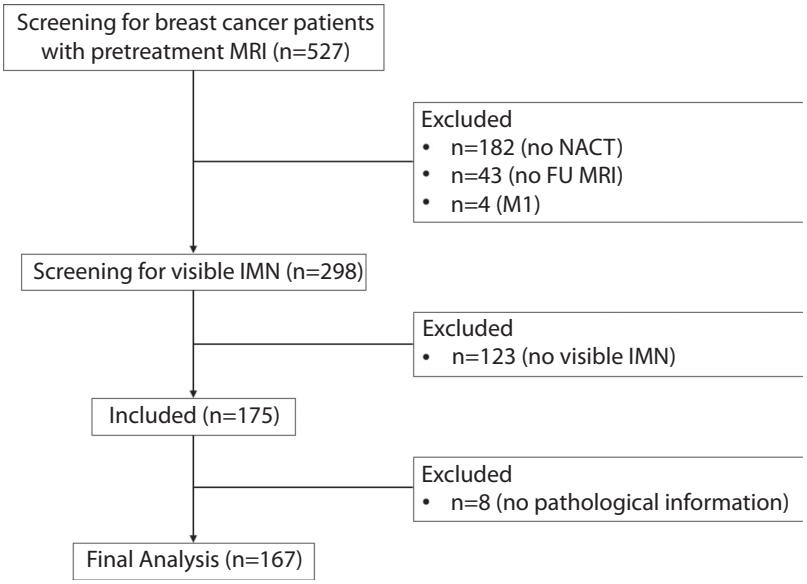

Fig. 1. Selection of study patients. *Abbreviations*: FU = follow up; IMN = internal mammary lymph node metastasis; M1 = metastatic disease; MRI = magnetic resonance imaging; NACT = neoadjuvant chemotherapy.

the longest dimension and its orthogonal axis (long and short-axis diameters; LAD and SAD). For each IMN, the location (intercostal space [ICS]) was assessed. If more than 1 IMN was visible in 1 patient, all visible IMN were measured, and the IMN with the largest dimension was used as the index lesion.

In the next step, the IMN dimensions were assessed in post-NACT MRIs using the same methodology and then compared with pre-NACT MRIs. Clinical response of IMN to the NACT was evaluated by the change in size of at least 1 axis (LAD and/or SAD) in both axial and coronal planes (see Fig. 2). The clinical response of IMN to NACT was classified in analogy to Response Evaluation Criteria In Solid Tumors (RECIST) 1.1[17] as follows:

- IMN response: IMN with either
  - complete response (CR; disappearance of lymph node) or
  - partial response (PR; at least 30% decrease of at least 1 axis in both axial and coronal planes) or
- No IMN response: IMN with either
  - progressive IMN (progressive disease (PD); at least 20% increase of at least 1 axis in both axial and coronal planes) or
  - stable disease (SD; neither partial response no PD).

Likewise, the diameters of pre- and post-treatment size of ipsilateral AXN were assessed in case if clinical pretreatment involvement. In addition, in all patients, contralateral axillary lymph nodes were assessed as "negative control."

To evaluate possible associations with prior interventions, the date of PT biopsy was assessed and correlated with IMN response.

Evaluation of follow-up

For each patient, clinical and radiological follow-up data were assessed for occurrence of locoregional recurrence, distant metastasis, or death. Moreover, DFS, OS, and locoregional control (LRC) were evaluated. In case of IMN metastases occurring in follow-up imaging, we correlated the location of IMN metastases with the location of initially visible IMN.

Statistical analysis

The primary endpoint of this study was to evaluate the frequency of clinical IMN response in patients with pathological tumor response to NACT. The second endpoint was to evaluate whether IMN response correlated with established risk factors of IMN involvement as well as the occurrence of distant metastasis.

Continuous variables are reported as mean ± SD for normally distributed data and as median (IQR) for skewed data. Categorical variables are presented as total numbers with the corresponding percentage. The difference between groups (IMN response rates across subgroups such as PT response [yes vs no], axillary lymph node involvement [yes vs no], internal mammary perforating vessel contact [IMPVc; predominant vs minor/no contact], and tumor location [medial vs central/lateral]) was assessed using Chi-

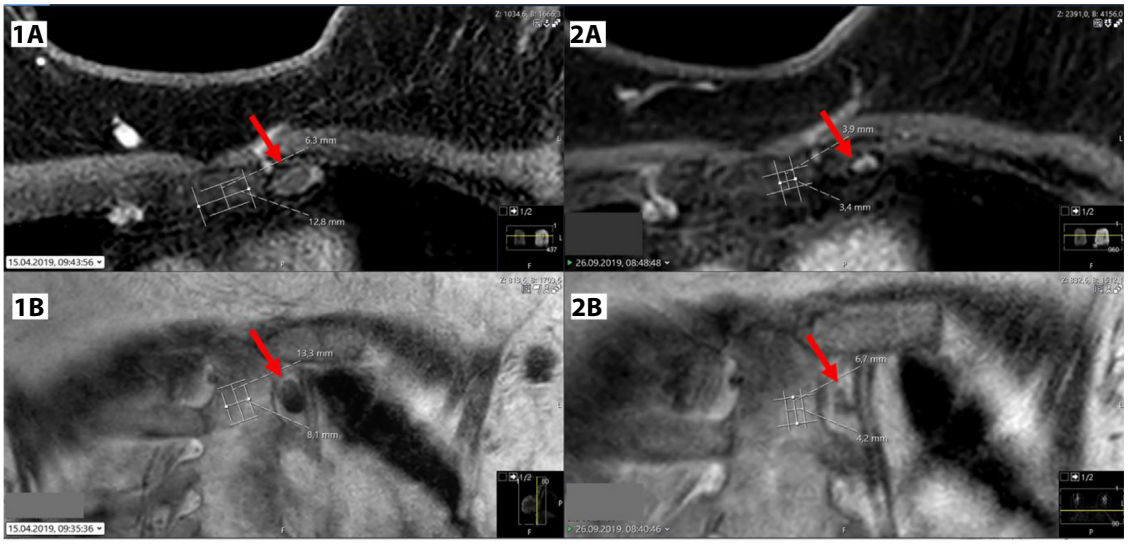

Fig. 2. Measurement of visible IMN for response evaluation before and during/after NACT: 1-left-sided breast cancer patient with visible IMN in the left second intercostal space in axial (A) and coronal (B) planes of pretreatment MRI. 2-same patient after 5 months of NACT with clinical complete response of primary tumor and axillary metastasis and relevant decrease of the visible IMN in axial (A) and coronal (B) planes. For better clarity, measurements were placed next to the relevant lymph nodes. Red arrows indicate the internal mammary lymph nodes. *Abbreviations*: IMN = internal mammary lymph node(s); MRI = magnetic resonance imaging; NACT = neoadjuvant chemotherapy. A color version of this figure is available at [10.1016/j.ijrobp.2026.07.050].

square or Fisher's exact test, depending on sample size. Statistical significance was defined as $P < .05$.

Data collection, statistical analysis, and graphical visualization were conducted using IBM SPSS Statistics (version 28.0.0.1; IBM SPSS Statistics) and GraphPad Prism software (version 10.2.3; GraphPad Software Inc.).

Results

Patient characteristics

Median age was 46 years (24-81) at the time of breast cancer diagnosis. Initial tumor size of the PT was ≤5 cm (T-Stage: T1/T2 > 80%) in most cases and located in the lateral part of the breast (40%). More than half of the tumors had a positive hormone receptor (HR) status, and one-third was triple negative. In total, 62.9% of patients had initially diagnosed, histologically confirmed axillary lymph node metastasis (AXN+). Median time between NACT onset and follow-up MRI was 5.8 months (2-10 months). Detailed information on patient characteristics is summarized in Table 1.

In total, 64.6% of patients had 2 visible IMN and 33.7% had 3 visible IMN. The visible IMN were mostly located in the second (57.1%) or third (26.9%) ICS, less frequently in the first (13.1%) or fourth (2.9%) ICS.

Response of PT and axillary lymph nodes to NACT

Of 167 patients in the final analysis cohort, 94.6% (n = 158) had a histopathological response of the PT (NACT-responder), whereas 5.4% (n = 9) did not respond to NACT based on histopathological findings. According to the imaging reports, clinical response of the PT was seen in 97.5% of those patients (n = 154), whereas 2.5% (n = 4) did not have any radiological response of the PT. Stratified by tumor subtype, patients with negative HR had a higher rate of histopathological response in the PT compared with patients with positive HR (95.8% vs 93.7%; $P = .542$).

Of the patients with initially involved ipsilateral AXN, 56.9% had a histopathological CR in the AXN (ypN0). The contralateral AXN, used as a "negative control," did not show any change in size in any included patient.

IMN response in responders to NACT

Median size of visible IMN was 5.4 mm (2.1-25.4; LAD) and 3.9 mm (2.0-15.0; SAD) in axial planes and 7.5 mm (2.3-29.7; LAD) and 4.6 mm (2.0-23.7; SAD) in coronal planes in pretreatment MRI. Nine patients had visible IMN with ≥1 cm in at least 1 imaging plane (n = 8 in coronal and n = 4 in axial plane), all of whom had suspected IMN metastasis according to radiological findings or interdisciplinary tumor board consensus.

Among patients with response in the PT (n = 158 of n = 167), IMN response was seen in 39.3% (n = 62, see Fig. 3A), even though IMN metastasis was initially described in only 8.3% of these patients.

Initial SAD in axial planes was significantly associated with IMN response ($P = .031$).

Stratified by nodal status, IMN response was seen in 48.5% of patients with positive lymph nodes and 21.8% in node-negative patients (P value of <.001, see Fig. 3B). After stratification by tumor location, IMN response was seen in 52.3% in medial tumors and 34.2% in central and lateral tumors ($P = .037$, see Fig. 3C). IMN response was rare in patients without predominant IMPVc (6.5%), whereas patients with IMN response had in 75.8% predominant IMPVc ($P < .001$; see Fig. 3D). In small tumors (T1-T2), 34% showed IMN response, whereas in larger tumors (T3-T4), 65.4% showed IMN response ($P = .002$). Stratified by subtype, IMN response was seen in 30.5% of patients with HR+ and 45.8% HR− ($P = .031$).

In initially patients with AXN+, we observed a radiologic response of AXN in 89% of cases. No significant differences in response of AXN were observed between patients with and without IMN response (94% vs 85%, $P = .141$).

Median time interval between biopsy of the PT and pretreatment MRI was 16.5 days (68-77 days). A comparative analysis of patients with up to 16.5 days versus more than 16.5 days between biopsy and pretreatment MRI revealed no significant association between the time of biopsy and IMN response (Chi-square test: $P = .378$, Cramer's V = .068; see Fig. E1).

Time differences between pretreatment and follow-up MRI were not associated with response to NACT in PT ($P = .469$) or visible IMN ($P = .484$).

Local treatment

Surgery of the breast consisted of lumpectomy in 47.3% and mastectomy in 52.7% of patients. Axillary surgery included sentinel lymph node biopsy (SLNB) in 37.7%, targeted axillary dissection (TAD) in 10.8%, and axillary lymph node dissection (ALND) in 51.5% of patients. In total, 64.7% received radiation therapy of the breast or chest wall. Regional nodal irradiation (RNI) was performed in 58.9% of patients, of which 45.6% included IMNI. Information on irradiation was missing in 19.8% of patients.

Follow-up

Median follow-up was 46.0 months (5-180). Among the 175 included patients, local recurrence occurred in 12 patients (6.9%), whereas distant metastasis occurred in 29 patients (16.6%) according to imaging reports and/or tumor board consensus. Overall, 13 patients died (7.4%) during the observed time interval. A total of 31 DFS events were observed (17.7%), whereas 144 patients (82.3%) were censored at last follow-up. The mean DFS time was 48.39

Table 1 Patient characteristics of the total patient cohort (n = 175, left) and the patient cohort for the final analysis (n = 167, right)

Patient characteristics		Total n = 175		Final analysis n = 167	
		n	%	n	%
Tumor location	medial	51	29.1	48	28.7
	central	53	30.3	52	31.1
	lateral	71	40.6	67	40.1
Molecular subtype	HR+/HER2−	67	38.3	65	38.9
	HR+/HER2+	33	18.9	30	18.0
	HR−/HER2+	24	13.7	24	14.4
	TNBC	51	29.1	48	28.7
Initial tumor size (T)	1	49	28.0	46	27.5
	2	97	55.4	93	55.7
	3	17	9.7	17	10.2
	4	12	6.9	11	6.6
	cN+	110	62.9	109	65.3
	cN-	65	37.1	58	34.7
Axillary lymph nodes	0/is	81	46.2	81	48.5
	1	46	26.3	46	27.5
	2	34	19.4	33	19.8
ypT	3	7	4.0	7	4.2
	missing	7	4.0	-	-
	No response	9	5.1	9	5.4
Histological response of primary tumor (Sinn)	Grade 1	54	30.9	54	32.3
	Grade 2	22	12.6	22	13.2
	Grade 3	20	11.4	20	12.0
	Grade 4	62	35.4	62	37.1
	Missing	8	4.6	-	-
	cN+/ypN0	62	35.4	62	37.1
	cN+/ypN+	48	27.4	47	28.1
Histological Response of AXN	cN0	65	37.2	58	34.8
		Mean	1.0	Mean	1.0
Number of ypN+		SD	2.5	SD	2.5
Resected nodes		Mean	8.5	Mean	8.4
		SD	6.7	SD	6.4
Differentiation (G)	1	4	2.3	4	2.4
	2	77	44.0	71	42.5
	3	92	52.6	90	53.9
	missing	2	1.1	2	1.2
Affected breast	left	103	58.9	101	60.5
	right	72	41.2	66	39.5
Age (y)	Median		46.0		46.0
	Min-Max		24-81		24-81

Abbreviations: AXN+ = positive axillary lymph node metastasis; AXN− = no axillary lymph node metastasis; HR = hormone receptor status; HER2 = human epidermal growth factor receptor status; Max = maximum; Min = minimum; TNBC = triple negative breast cancer; cN+ = clinically positive lymph nodes; cN-/0 = clinically negative lymph nodes; ypN+ = amount of positive axillary lymph nodes after neoadjuvant chemotherapy; ypT = extent of primary tumor after neoadjuvant chemotherapy.

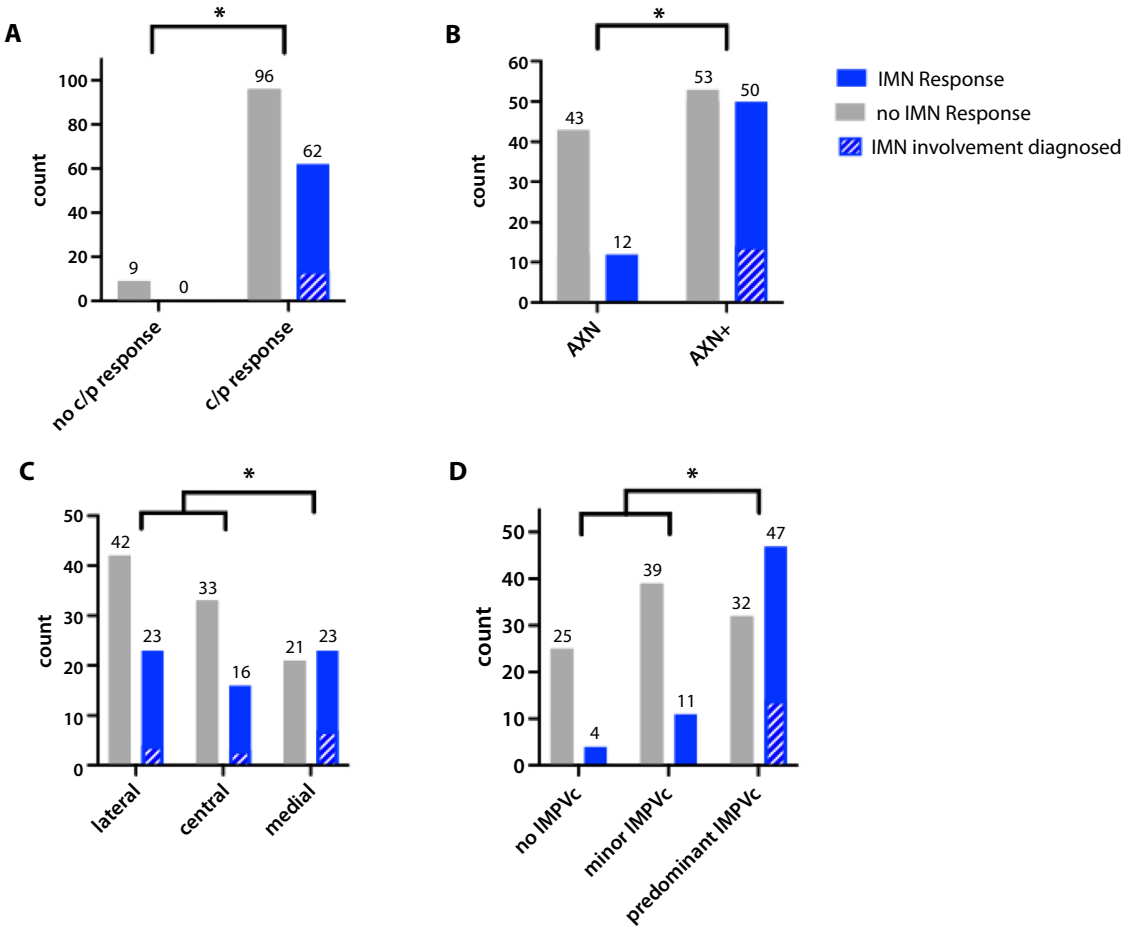

Fig. 3. Response in visible IMN after NACT; IMN response is demonstrated as blue bar; no IMN response is demonstrated as gray bar. The hatched area demonstrates the number of patients with initially diagnosed IMN metastasis in the pretreatment MRI. (A) IMN response in patients without clinical and pathological response vs. with clinical and pathological response to NACT (n = 167). (B) IMN response in patients without vs. with axillary lymph node metastasis in patients with response to NACT (n = 158). (C) IMN response in NACT responders with lateral, central and medial tumor site in patients with response to NACT (n = 158). (D) IMN response in patients without, with minor and with predominant IMPV-contact in patients with response to NACT (n = 158). * statistically significant. *Abbreviations*: AXN+ = positive axillary lymph node metastasis; AXN− = no axillary lymph node metastasis; c/p response = clinical and pathological response; IMN = internal mammary lymph node(s); IMPVc = contact to the internal mammary perforator vessels; NACT = neoadjuvant chemotherapy; MRI = magnetic resonance imaging. A color version of this figure is available at [10.1016/j.ijrobp.2026.07.050].

months (SD, 33.96), with a median DFS time of 40 months (range, 0-180). The mean OS time was 51.14 months (SD, 34.52), with a median OS time of 45 months (range, 5-180). Mean LRC was 50.77 months (SD, 33.94), with a median LRC of 44 months (5-180). Patients with IMN response showed a trend toward poorer outcomes with regard to LRC, DFS, and OS. Kaplan-Meier curves for DFS, OS, and LRC are shown in Figure E2. Patients with IMN response had significantly more distant metastasis than patients without IMN response (24.6% vs 12.4%; Chi-square test: P = .022, Cramer's V, .361).

Among patients with distant metastasis,14 patients had available MRIs and/or PET-CT during follow-up. Six of those patients showed IMN metastases, and in 3 cases, the IMN metastases occurred at the same site as the initially visible IMN that had shown an IMN response under NACT (see Fig. 4). Only 1 of those patients had IMNI with simultaneously integrated boost to a diagnosed IMN metastasis (up to 58.8 Gy in 28 fractions), whereas the other 5 patients did not undergo IMNI during initial treatment.

Discussion

For personalized radiation therapy of regional lymph nodes in patients with early breast cancer, detection of IMN involvement is essential. In the current study, we demonstrate that visible lymph nodes in the IMN region show response to NACT in approximately 40% of patients, even though in only 8% of cases

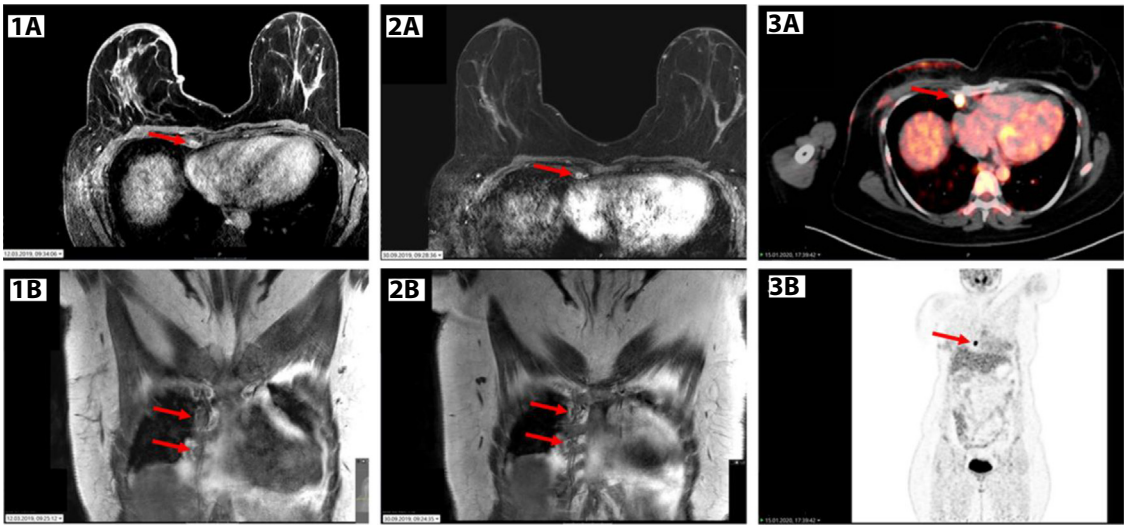

Fig. 4. IMN dynamics before/after NACT under consideration of follow-up imaging: 1-right-sided breast cancer patient with visible IMN in the second and third intercostal spaces in axial (A) and coronal (B) planes of pretreatment MRI. 2-same patient after 6 months of NACT with clinical complete response of primary tumor and axillary metastasis and response of the visible IMN in axial (A) and coronal (B) planes. 3-recurrence of initially visible IMN with response after NACT, subsequently increasing 6 months later in axial (A) and coronal (B) planes of PET/CT. Red arrows indicate the internal mammary lymph nodes. *Abbreviations*: IMN = internal mammary lymph node(s); MRI = magnetic resonance imaging; NACT = neoadjuvant chemotherapy; PET/CT = positron emission tomography/computed tomography. A color version of this figure is available at [10.1016/j.ijrobp.2026.07.050].

IMN involvement was suspected. Knowing from surgical studies that there is a high number of undetected IMN metastases, our study highlights IMN response as a potential additional characteristic for evaluating IMN involvement.

Our hypothesis of IMN response to NACT indicating initial IMN involvement is supported by 4 separate findings:

First, the measured IMN response was only observed in patients who also had a response of the PT.

Second, IMN response was strongly associated with established risk factors for IMN involvement such as AXN involvement, larger tumors, medial tumor site, and predominant contact with the IMPVc.[15]

Third, the percentage of patients with IMN response in our study is similar to the rates of IMN metastases found in older surgical studies.[6] Earlier trials with use of extended mastectomy or Halsted mastectomy, including surgical removal of IMN, revealed incidences of 33% IMN metastases and even 44% to 65% in patients with medial tumors and axillary lymph node involvement.[18] Even though surgical assessment of IMN has been abandoned due to its morbidity, it should be noted that these numbers are more accurately reflected by the count of IMN with treatment response rather than by the number of initially suspected IMN metastases, thereby strengthening our hypothesis.[3,18]

Fourth, patients with IMN response had significantly more distant metastasis than patients without IMN response and showed a trend toward poorer outcomes with regard to locoregional recurrences, DFS, and OS. This further supports the hypothesis of IMN response as a potential indicator for initial IMN involvement, which is known to be associated with poorer outcomes and especially a higher rate of distant metastasis. Moreover, during follow-up, patients developed IMN metastases at the exact location of an initially visible IMN identified as potentially suspicious based on IMN response to NACT. Nearly all those patients (83%) had not received local therapy with radiation therapy to the IMN during primary treatment.

A decrease in lymph nodes in the tumor environment does not necessarily imply metastatic involvement. Reactive axillary lymphadenopathy following breast interventions is a well-recognized phenomenon. Imaging studies have demonstrated that lymph node enlargement and cortical thickening can occur in the postoperative setting in up to 10% of patients and may persist for several months without evidence of malignancy.[19,20] Importantly, staging MRI is often performed within a short interval after biopsy, frequently within 1-2 weeks, which corresponds to the expected time frame of acute inflammatory response. Therefore, biopsy-related reactive nodal changes are biologically plausible and may overlap with imaging features suggestive of metastatic involvement. However, in our cohort, the exploratory analysis of the association between the time interval from biopsy to MRI and IMN response (see Fig. E1) did not demonstrate a significant relationship. While this finding argues against a dominant effect of biopsy-related reactivity, it cannot fully exclude a potential confounding influence. Moreover, in a subgroup analysis of patients with clinically apparent AXN, we found high rates of patients with clinically measurable AXN response both in patients with and without visible IMN response. This further supports the assumption that IMN response is not a purely nonspecific or reactive phenomenon but rather reflects genuine treatment-related changes within the lymphatic system.

Adequate detection of IMN involvement is highly relevant for patients with early breast cancer since IMN involvement in the absence of sufficient treatment is associated with an increased rate of distant metastasis.[5,6] Despite the potential risk of serious toxicity in organs at risk, IMNI has a significant impact on the outcome of patients with high risk of (sub-)clinical IMN involvement[7-9]: large randomized trials such as the EORTC 22922 or MA.20 trials demonstrated an OS benefit following regional nodal irradiation in high-risk patients[21,22] and the EBCTCG meta-analysis with more than 10,000 patients even found a reduced risk of breast cancer mortality after RNI in patients with clinically node-negative disease.[8] Moreover, the DBCG IMN2 trial recently demonstrated an OS benefit in patients with node-positive breast cancer even though more than 60% of patients received modern systemic therapy.[23] Although chemotherapy was explicitly given in an adjuvant setting, the survival benefit may have also been related to patients with an undetected subclinical IMN involvement. Subgroup analysis revealed no differences between the evaluated groups in this trial. This highlights the relevance of subclinical metastasis and the need for adequate local treatment despite the use of effective systemic therapies. However, optimal patient selection remains challenging, particularly due to the lack of histopathological evaluation of IMN. Consequently, treatment decisions in this region largely rely on imaging-based assessment and risk stratification. In the context of treatment de-escalation strategies, there is a critical need to better identify patients with subclinical IMN involvement who may benefit from targeted irradiation. Emerging imaging-based approaches may help to refine this selection. For example, predominant tumor contact with the IMPVc on MRI has been shown to be associated with an increased likelihood of IMN involvement,[15] highlighting the potential of imaging biomarkers to identify patients at risk of occult IMN metastases. Furthermore, in patients with clinically positive IMN metastases, recent data suggest an OS benefit for patients receiving escalated radiation doses of more than 60 Gy to persistent IMN after NACT.[13] Together, these findings emphasize the importance of accurate detection and the value of an appropriately tailored radiation therapy after correct diagnosis. While questions regarding treatment adaptation are inherently linked to the detection of occult IMN involvement, the present study was designed to address the diagnostic rather than the therapeutic aspect of this issue. Our findings therefore do not support specific recommendations regarding IMN irradiation but suggest that the prevalence of clinically unrecognized IMN involvement may be underestimated and warrants further prospective investigation.

A clinical response to NACT has been demonstrated previously in diagnosed IMN metastases equivalent to a response in AXN metastases and the PT.[24] Given this background, the response of a large number of initially nonsuspicious IMN in our study is striking. The clinical distinction between suspicious and nonsuspicious IMN in pretreatment imaging can be challenging and leads to a diagnostic dilemma about whether to report or not report visible IMN. In this trial, only 8% of NACT responders had imaging reports or interdisciplinary tumor board consensus with suspicious IMN, suggesting a potential understaging in a considerable number of patients. This is critical, given the prognostic relevance of IMN involvement.[6]

In our study, IMN response was more likely with the presence of axillary metastases (80.6% AXN+), which is consistent with the fact that AXN metastases are a strong risk factor for IMN involvement. Correspondingly, in the large trials on IMNI, patient cohorts included patients with AXN metastases only,[7-9] suggesting that a high incidence of unidentified IMN metastases in these cohorts may have contributed to the enormous benefit of IMNI.

Alternatively, IMN response to NACT in accordance with the response of the PT occurred in 21.8 of patients without AXN metastases. Despite the elevated risk of IMN involvement in the presence of AXN metastases, the prevalence of isolated IMN metastases can be up to 18%, depending on initial tumor site and depth.[4] This is crucial, given that patients without proof of axillary metastases will most likely not receive any regional nodal irradiation. Thus, with the risk of understaging these patients, unrecognized IMN also implies the risk of inadequate treatment.

Interestingly, we observed a significantly higher incidence of IMN response in patients with medial tumors compared with those with central or lateral tumors. While it is well established that IMN metastases occur more frequently in medial than in lateral tumors due to specific lymphatic drainage patterns,[25-27] central tumors are often reported to behave similarly to medial tumors and are therefore often grouped together as mediocentral tumors in the literature. However, lymphoscintigraphic data have demonstrated lymphatic drainage to the IMN chain in up to 57% of patients with medial tumors, 21% to 33% of patients with central tumors, and even 26% to 42% of those with lateral tumors,[26] which may explain the differences seen in the current study. In fact, the anatomical definition of “medial,” “central,” and “lateral” tumors in the randomized trials on RNI lacks clearly defined boundaries, and particularly central tumors might overlap with both medial and lateral tumors.

Although recent trials did not show an oncologic benefit from RNI in nodal-positive patients with a CR after NACT, this association cannot be transferred to patients with extensive nodal involvement.[28,29] Both the RAPCHEM and the NSABP-B51 trial included patients with limited axillary involvement (cN1) only, so the results cannot be extrapolated to patients with IMN involvement, even if a clinical response can be seen in IMN after NACT. Adding the diagnosis of an IMN metastasis to a patient’s tumor stage will result in RNI including irradiation of the IMN instead of omission of RNI or even radiation therapy at all. In fact, for patients with clinical IMN involvement, there remains a strong clinical rationale for local therapy such as radiation therapy. Therefore, a thorough assessment of all lymphatic basins is highly relevant for all patients even if axillary lymph nodes are uninvolved. Moreover, even small IMN on preoperative MRI might be relevant for further treatment.

The sole presence of an IMN does not necessarily indicate metastatic involvement, since IMN can also be detected in screening MRIs of healthy women with a high incidence of up to 46%.[30] However, the definitive clinical differentiation between benign and malignant nodes remains unclear. Radiological studies evaluating IMN metastases in patients with breast cancer found a higher possibility of IMN metastases in IMN with a larger size,[31-34] although there is disagreement on the exact threshold of the size and axis that should be used for this assessment.[2,35] While a short-axis diameter of 5 mm is a commonly used cut-off value, there is clear evidence of metastatic IMN starting from 2-mm-sized lymph nodes.[32,33] Thus, it seems questionable to rely only on the size criterion in malignancy assessment. In a CT-based investigation of patients with locally advanced breast cancer, patients with visible IMN had a significantly higher rate of subsequent metastatic disease compared with those without visible IMN, irrespective of size or other malignancy assessment criteria.[36]

It should be noted that the patient cohort evaluated in this study most likely represents a subgroup of patients with high-risk breast cancer. Patients were included if they received NACT and pretreatment MRI, which is usually indicated in younger patients with larger tumors, lymph node metastases, and aggressive histopathological features. Accordingly, the mean age of the included patients was 46 years; 30% of tumors were triple negative breast cancer and 97% were G2/G3. This could explain the relatively high incidence of 58.7% visible IMN and 20.8% suggested IMN metastases in this study compared with previous trials (17%-37% IMN metastases[18]; 42% visible IMN[37]).

Interestingly, we observed metachronous distant metastasis precisely at the location of previously responsive IMNs in a small subset of patients with follow-up imaging. Earlier trials show a high rate of distant metastasis in patients with IMN recurrence.[38,39] This again supports the hypothesis of unrecognized IMN metastases with a strongly associated risk of distant metastases later on and highlights the need for accurate identification of IMN involvement for adequate treatment.

This study has 3 relevant limitations. First, our suspected IMN metastases could not be verified by histopathological results of IMN biopsies, which prevents a definitive confirmation of our hypothesis. However, IMN biopsy is no longer recommended or routinely performed because previous studies have failed to demonstrate a survival benefit while carrying a significant risk of postinterventional morbidity.[3,40] Precisely for this reason, improvement of noninvasive diagnostic approaches is essential to better identify patients who will most likely benefit from IMNI. While our results suggest a potential prognostic role of IMN response to NACT, they require prospective validation in larger, well-characterized cohorts with standardized MRI-based imaging and, ideally, histopathological confirmation where feasible.

A further limitation is the lack of systematic multimodality imaging, particularly the absence of paired PET/CT, contrast-enhanced CT or ultrasound, and MRI data for the majority of patients due to the retrospective design of our study. While all patients underwent contrast-enhanced CT at baseline, only 7 patients received a repeat CT after NACT. Likewise, baseline PET/CT was available in only 22 patients and in merely 5 patients both before and after NACT, precluding a formal concordance analysis between metabolic and morphological response. Ultrasound examinations were performed before and after NACT in all patients; however, these assessments were focused on the primary breast tumor and did not include systematic evaluation of the IMN region. An example of a patient with both MRI and PET/CT can be found in Figure E3. Diagnostic use of PET/CT can improve detection of IMN metastases, reaching a specificity of at least 80% and a positive predictive value of 87%.[41-43] Nonetheless, it is known that the sensitivity of PET/CT falls rapidly in small lesions.[44,45] One study found a sensitivity of only 53% of ^{18}F-fluorodeoxyglucose (FDG)-PET/CT in lesions of $\leq$5 mm in patients with breast cancer.[46] Given the fact that the IMN with response in our cohort had an average diameter of 5.4 $\times$ 3.9 mm, the additional value of PET/CT for IMN evaluation is questionable.[32,33] Consequently, while systematic multimodality imaging would have strengthened the validation of our imaging-based surrogate endpoint, the available evidence suggests that MRI remains a suitable modality for the response assessment of visible IMN metastases in this setting.

Moreover, the use of histopathological response assessment based on the Sinn regression grading system[16] represents a limitation of the study. While this approach was guideline-concordant and widely used at the time of patient treatment, it may limit direct comparability with internationally more commonly applied systems such as Miller-Payne or Residual Cancer Burden.[47] However, the prognostic value of various histopathological regression grading systems remains heterogeneous across studies, which is why there is currently no definitive international consensus on the use of a specific regression grading system.[12] Nevertheless, the observed association between radiological and histopathological response supports the biological relevance of treatment response patterns and provides additional evidence for the underlying hypothesis of our study.

Conclusion

In this study, IMN response to NACT was seen in 40% of patients with visible IMN, suggesting that the prevalence of initial IMN involvement may be underestimated by current imaging criteria. This observation is consistent with historical surgical series, which reported significantly higher rates of IMN metastases than are seen today. Notably, IMN response was also observed in approximately 20% of patients without axillary lymph node metastases, indicating that occult IMN involvement may occur even in patients who are not conventionally considered high risk and thus

generally do not undergo IMNI. These findings support further investigation of MRI-based IMN assessment as a potential tool for improving the detection of clinically relevant IMN involvement. Prospective validation in larger, well-characterized cohorts with standardized imaging protocols is warranted to confirm this hypothesis, ideally complemented by histopathological confirmation where feasible.

Declaration of Generative AI and AI-Assisted Technologies in the Writing process

During the preparation of this work, the authors used the language model ChatGPT (OpenAI) in order to support linguistic editing and improve clarity of the text. After using this tool, the authors reviewed and edited the content as needed and take full responsibility for the content of the publication.

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