Ann Surg Oncol (2024) 31:7420–7428
https://doi.org/10.1245/s10434-024-15708-9

Annals of
SURGICAL ONCOLOGY
OFFICIAL JOURNAL OF THE SOCIETY OF SURGICAL ONCOLOGY

ORIGINAL ARTICLE – BREAST ONCOLOGY

Internal Mammary Lymphadenopathy Does Not Impact Oncologic Outcomes in Patients Treated with Neoadjuvant Chemotherapy: Results from the I-SPY2 Clinical Trial

Mara A. Piltin, DO, FACS[1], Peter Norwood, PhD[2], Velle Ladores, BS[2], Rita A. Mukhtar, MD[3], Candice A. Sauder, MD[4], Mehra Golshan, MD[5], Julia Tchou, MD[6], Roshni Rao, MD[7], Marie Catherine Lee, MD[8], Jennifer Son, MD[9], Chantal Reyna, MD[10], Kelly Hewitt, MD[11], Henry Kuerer, MD, PhD[12], Gretchen Ahrendt, MD[13], Ian Greenwalt, MD[9], Jennifer Tseng, MD[14], Lauren Postlewait, MD[15], Marissa Howard-McNatt, MD[16], Nora Jaskowiak, MD[17], Laura J. Esserman, MD, MBA[3], and Judy C. Boughey, MD[1], ISPY2 Locoregional Working Group

[1]Division of Breast and Melanoma Surgical Oncology, Department of Surgery, Mayo Clinic, Rochester, MN; [2]Quantum Leap Healthcare Collaborative, San Francisco, CA; [3]Division of Surgical Oncology, Department of Surgery, University of California San Francisco, San Francisco, CA; [4]Department of Surgery, UC Davis Comprehensive Cancer Center, Sacramento, CA; [5]Department of Surgery, Yale Medicine, New Haven, CT; [6]Division of Breast Surgery, Penn Medicine at University of Pennsylvania, Philadelphia, PA; [7]Division of Breast Surgery, Columbia University Medical Center, New York, NY; [8]Moffitt Cancer Center Comprehensive Breast Program, Tampa, FL; [9]Breast Surgical Oncology, MedStar Georgetown University Hospital, Washington, DC; [10]Division of Surgical Oncology, Department of Surgery, Loyola University Medical Center, Mayowood, IL; [11]Division of Surgical Oncology and Endocrine Surgery, Vanderbilt University Medical Center, Nashvilee, TN; [12]Department of Breast Surgical Oncology, MD Anderson Cancer Center, Houston, TX; [13]Breast Surgical Oncology, UC Health, Highlands Ranch, CO; [14]Department of Surgery, City of Hope Orange County, Irvine, CA; [15]Division of Surgical Oncology, Department of Surgery, Emory University, Atlanta, GA; [16]Department of Surgical Oncology, Wake Forest, Winston-Salem, NC; [17]Department of Surgery, University of Chicago, Chicago, IL

ABSTRACT

Background. Internal mammary lymphadenopathy (IML) plays a role in breast cancer stage and prognosis. We aimed to evaluate method of IML detection, how IML impacts response to neoadjuvant chemotherapy (NAC), and oncologic outcomes.

Methods. We evaluated patients enrolled in the I-SPY-2 clinical trial from 2010 to 2022. We captured the radiographic method of IML detection (magnetic resonance imaging [MRI], positron emission tomography/computed tomography [PET/CT], or both) and compared patients with IML with those without. Rates of locoregional recurrence (LRR), distant recurrence (DR) and event-free survival (EFS) were compared by bivariate analysis.

Results. Of 2095 patients, 198 (9.5%) had IML reported on pretreatment imaging. The method of IML detection was 154 (77.8%) MRI only, 11 (5.6%) PET/CT only, and 33 (16.7%) both. Factors associated with IML were younger age ($p = 0.001$), larger tumors ($p < 0.001$), and higher tumor grade ($p = 0.027$). Pathologic complete response (pCR) was slightly higher in the IML group (41.4% vs. 34.0%; $p = 0.03$). There was no difference in breast or axillary surgery ($p = 0.41$ and $p = 0.16$), however IML patients were more likely to undergo radiation (68.2% vs. 54.1%; $p < 0.001$). With a median follow up of 3.72 years (range 0.4–10.2), there was no difference between IM+ versus IM− in LRR (5.6% vs. 3.8%; $p = 0.25$), DR (9.1% vs. 7.9%; $p = 0.58$), or EFS (61.6% vs. 57.2%; $p = 0.48$). This was true for patients with and without pCR.

Conclusions. In this large cohort of patients treated with NAC, outcomes were not negatively impacted by IML. We demonstrated that IML influences treatment selection but is

First Received: 11 April 2024
Accepted: 16 June 2024
Published online: 9 July 2024

M. A. Piltin, DO, FACS
e-mail: Piltin.mara@mayo.edu

not a poor prognostic indicator when treated with modern NAC and multidisciplinary disease management.

Significant improvements in systemic therapy for breast cancer have continued to drive re-evaluation of locoregional treatment techniques and considerations. Historically, patients with internal mammary (IM) chain lymphadenopathy have been identified as having worse prognosis compared with those with the same disease biology, tumor size (cT), and clinical nodal category (cN) without IM involvement.[1–4] The three most common lymphatic draining nodal basins of the breast are well described and include the ipsilateral axilla, IM chain, and supraclavicular regions.[5,6] Utilizing lymphatic mapping, the ipsilateral axilla has been clearly defined as the dominant draining basin for breast cancer and thus remains the location for sentinel lymph node (SLN) biopsy when surgically staging the regional nodes in a patient with primary breast cancer. In addition to the axilla, sentinel lymphatic drainage to the IM chain occurs in approximately 13–37% of cases.[4,7–9] However, it is far less common to identify isolated IM node involvement in the absence of concomitant axillary nodal involvement.[4,10–12] Surgical resection of the IM lymph nodes has been explored historically but has not shown to provide oncologic benefit, and therefore it has been largely abandoned.[13–15] Current National Comprehensive Cancer Network (NCCN) recommendations support locoregional treatment of involved IM nodes with adjuvant radiation strategies but does not endorse routine surgical resection.[16] For these reasons, attention to IM nodal involvement in the literature has been limited.

Cross-sectional imaging with breast magnetic resonance imaging (MRI) and positron emission tomography/computed tomography (PET/CT) are frequently employed in the work-up and staging algorithm for breast cancer,[17,18] especially when neoadjuvant chemotherapy (NAC) is being considered. Percutaneous biopsy of IM nodes is not commonly employed and thus IM lymphadenopathy (IML) detected by imaging is utilized as a surrogate for metastatic involvement by breast cancer. The presence or suspicion of abnormal IM nodes on imaging can raise a patient's clinical N category from N0 to N2b in the absence of axillary disease, or from N1 or N2 to N3b in the presence of concomitant axillary involvement.[19,20] This ultimately impacts the patient's clinical stage, treatment recommendations, prognosis, and outcomes. In the context of modern systemic therapy utilizing neoadjuvant treatment approaches, prognosis and adjuvant therapy recommendations are largely impacted by response to treatment. We sought to evaluate the frequency of detection of IM nodes on imaging and the impact of IML on oncologic outcomes in a large cohort of patients treated with NAC in a prospective clinical trial.

METHODS

I-SPY-2 Clinical Trial

We performed a retrospective analysis of patients enrolled in the I-SPY-2 multicenter clinical trial.[21] This is an ongoing randomized controlled trial that utilizes adaptive randomization to test novel systemic agents in the neoadjuvant setting. Subjects are stratified by risk as determined by 70-gene signature (Mammaprint) testing on the diagnostic core biopsy. All patients proceed to surgical intervention after neoadjuvant treatment. Enrolled patients are ≥18 years of age, tumor size ≥2.5 cm by clinical examination or ≥2 cm by imaging, and have an Eastern Cooperative Oncology Group performance status of 0 or 1. Eligible tumor subtypes include luminal breast cancer if high risk by 70-gene signature (Mammaprint), triple negative, or human epidermal growth factor receptor 2-positive (HER+) disease. All patients enrolled in the trial have a baseline dynamic contrast-enhanced MRI prior to NAC, and utilization of PET/CT or other systemic staging techniques, such as CT of the chest, abdomen and pelvis plus bone scan, is at the discretion of the providers. After the completion of NAC, all patients proceed to surgical treatment in the form of breast-conserving surgery or mastectomy with SLN surgery and/or axillary lymph node dissection. All patients must achieve negative surgical margins and radiation delivery is at the discretion of the treating providers. The primary endpoint of the trial is the rate of pathologic complete response (pCR) in each arm, while secondary endpoints are event-free survival (EFS) and distant recurrence-free survival (DRFS).[21]

Study Population

We evaluated all patients enrolled in the I-SPY-2 clinical trial from March 2010 to October 2022. We utilized radiographic IML as a surrogate for involvement of IM nodes by malignancy, as is standard in current clinical practice. IML was defined as abnormal nodes by MRI, abnormal uptake on PET/CT, or both, as these were the only two imaging modalities with IM node assessment captured on the trial. This was obtained from a baseline assessment form submitted for each patient enrolled at the time of diagnosis. Abnormal is not explicitly defined with a size measurement, but determination is at the discretion of the treating facility. Tumor biology was categorized as hormone receptor-positive (HR+) if estrogen receptor (ER) and/or progesterone receptor (PR) were positive (≥1% positively staining cells by immunohistochemistry). HER2+ was defined as expression of HER2 staining intensity of IHC 3+ or IHC 2+, and positive by fluorescence in situ hybridization (FISH). Approximated biologic subtypes were categorized as HR+/HER2-negative (HER2−), HER2+, and HR-negative (HR−)/HER2−. We

evaluated the position of the tumors within the breast and defined inner breast location as those positioned in the upper inner quadrant, lower inner quadrant, 12 o'clock position, 6 o'clock position, and left breast 9 o'clock position or right breast 3 o'clock position. Percutaneous sampling of axillary nodes was performed in the setting of suspicious axillary nodes. Pathology from breast and nodal surgery was captured to assess for response and extent of any residual disease, with residual cancer burden (RCB) calculated by centrally trained study pathologists. From imaging studies at presentation, the size of the largest abnormal IM node was collected when available. We also identified performance of PET/CT, the occurrence of radiographically abnormal IM node(s), and maximum standardized uptake value (SUV_{max}) of IM node(s) when available. Rates of pCR were recorded in each group. We then evaluated locoregional recurrence (LRR), distant recurrence (DR), and estimated cumulative EFS in those with IML compared with those without IML overall, as well as within the group who achieved a pCR and the group who did not achieve a pCR separately. An event impacting EFS was defined as any LRR, DR, or death from any cause. LRR was defined as the presence of invasive disease involving the breast and regional lymph nodes, including the axilla, chest wall and/or skin ipsilateral to the primary diagnosis. DR was any recurrence except LRR or contralateral new breast cancer. The date of treatment consent was utilized for survival and patients without an event were censored at the last follow-up date.

Statistical Methods

Statistical analyses compared distributions of key variables between the IM nodal cohorts. For non-survival distributions, *p*-values were generated from the Fisher's exact test for categorical variables and Student's *t*-test for continuous variables. The log-rank test was used for survival distributions; associated survival curve figures were also presented. R[22] was used for all statistical analyses, the survival package[23,24] was used to run log-rank tests, and the ggsurvfit package[25] was used to generate survival figures.

RESULTS

A total of 2096 patients were identified from the I-SPY-2 clinical trial from March 2010 to October 2022, with a median follow up of 3.72 years (range 0.4–10.2). 199 patients (9.5%) were found to have abnormal IM lymph nodes by MRI and/or PET/CT. One patient later classified as M1 was excluded due to progression to metastatic disease while receiving neoadjuvant therapy, resulting in 198 (9.5%) patients with IM lymphadenopathy (IM+) in our study cohort of 2095 total patients. The remaining 1897 patients (90.5%) did not have abnormal IM nodes by either of the imaging modalities (IM−). Mean age at diagnosis was 48.4 years, with the IM+ patients being younger (mean age 46.0 years vs. 48.6 years; $p = 0.001$). There was no difference in race, ethnicity, tumor laterality, or approximated biologic subtype between the IM+ and IM− groups (Table 1). Patients with IM+ nodes were more likely to have larger clinical T category at presentation ($p < 0.001$) and grade III disease (60.1% vs. 48.6%; $p = 0.027$). Of the 198 patients with IM+ disease, 47% ($n = 94$) had inner breast tumors; 107 IM+ patients had axillary lymph node imaging abnormalities and were biopsied, with 89 being positive for malignancy, for a rate of concomitant axillary and IM nodal involvement of 45%. Use of adjuvant radiation therapy was higher (68.2% vs. 54.1%; $p < 0.001$) in patients with IM+ disease, however there was a high rate of missing radiation data (31.3% overall), higher in the IM− group (Table 1).

Evaluation of the breast and axillary surgical procedures performed, rate of pCR, RCB class, and pathologic tumor and nodal categories was performed. There were no statistically significant differences between IM+ and IM− in any of these measures, except for pCR rate; the IM+ patients had a higher rate of pCR (41.4% vs. 34%; $p = 0.031$) [Table 2].

Internal Mammary-Positive Imaging Findings

Of the 198 IM+ patients, 154 patients had IML by MRI only, 11 by PET/CT alone, and 33 by both modalities (Table 3). Since all patients had an MRI, the rate of IM+ on MRI was 188/2095 (8.97%). A total of 505 patients in the entire study cohort underwent PET/CT as a component of their work-up, and the rate of IM+ on PET/CT was 44/505 (8.71%). Use of PET/CT was higher in patients who were IM+ (43.3%, $n = 86$) than in patients who were IM− (22.1%, $n = 419$).

On MRI, the majority of IM+ patients had one abnormal IM node ($n = 112$, 56.6%) and the mean size of the largest IM lymph node was 7.52 mm (standard deviation [SD] 3.18). The average size increased when both imaging modalities detected IML (8.37 mm vs. 7.34 mm). Among IM+ cases by PET/CT, the mean SUV_{max} of the IM node(s) was 4.39 (SD 3.8) [Table 3].

Oncologic Outcomes

Evaluating oncologic outcomes, we found no differences between IM+ and IM− patients with respect to LRR (5.6% vs. 3.8%; $p = 0.200$), DR (9.1% vs. 7.9%; $p = 0.200$), or EFS (61.6% vs. 57.2%; $p = 0.600$) [Table 4]. Figure 1A shows the Kaplan–Meier estimates of the probability of EFS by the presence or absence of IML. Looking specifically at patients who achieved a pCR, there was also no significant difference in oncologic outcomes between the IM+ and IM− groups (Fig. 1B). While these event rates became quite small, the

TABLE 1 Patient demographics, clinical and pathologic characteristics of the overall cohort and by the presence or absence of IM lymphadenopathy on imaging

	IM−[*n* = 1897]	IM+[*n* = 198]	Overall [*n* = 2095]	*p* value
Age at screening				
Mean (SD)	48.6 (11.2)	46.0 (11.0)	48.4 (11.2)	0.00136
Median [min, max]	48.0 [19.0, 78.0]	45.0 [24.0, 80.0]	48.0 [19.0, 80.0]	
Missing	2 (0.1)	0 (0)	2 (0.1)	
Race				
American Indian/Alaska Native	6 (0.3)	0 (0)	6 (0.3)	0.448
Asian	138 (7.3)	17 (8.6)	155 (7.4)	
Black	237 (12.5)	17 (8.6)	254 (12.1)	
Native Hawaiian/Pacific Islander	9 (0.5)	0 (0)	9 (0.4)	
White	1468 (77.4)	158 (79.8)	1626 (77.6)	
Missing	39 (2.1)	6 (3.0)	45 (2.1)	
Ethnicity				
Hispanic	263 (13.9)	27 (13.6)	290 (13.8)	1
Non-Hispanic	1615 (85.1)	169 (85.4)	1784 (85.2)	
Missing	19 (1.0)	2 (1.0)	21 (1.0)	
Laterality				
Left	941 (49.6)	108 (54.5)	1049 (50.1)	0.205
Right	950 (50.1)	90 (45.5)	1040 (49.6)	
Missing	6 (0.3)	0 (0)	6 (0.3)	
T category				
T1	47 (2.5)	1 (0.5)	48 (2.3)	< 0.001
T2	1156 (60.9)	105 (53.0)	1261 (60.2)	
T3	431 (22.7)	75 (37.9)	506 (24.2)	
T4	54 (2.8)	16 (8.1)	70 (3.3)	
Missing	209 (11.0)	1 (0.5)	210 (10.0)	
Grade				
1	22 (1.2)	0 (0)	22 (1.1)	0.027
2	387 (20.4)	32 (16.2)	419 (20.0)	
3	921 (48.6)	119 (60.1)	1040 (49.6)	
Missing	567 (29.9)	47 (23.7)	614 (29.3)	
Subtype				
HR−/HER2−	665 (35.1)	71 (35.9)	736 (35.1)	0.944
HR−/HER2+	136 (7.2)	16 (8.1)	152 (7.3)	
HR+/HER2−	817 (43.1)	84 (42.4)	901 (43.0)	
HR+/HER2+	273 (14.4)	27 (13.6)	300 (14.3)	
Missing	6 (0.3)	0 (0)	6 (0.3)	
Radiation				
No	266 (14.0)	12 (6.1)	278 (13.3)	< 0.001
Yes	1026 (54.1)	135 (68.2)	1161 (55.4)	
Missing	605 (31.9)	51 (25.8)	656 (31.3)	

Data are expressed as *n* (%) unless otherwise specified

IM internal mammary, *SD* standard deviation, *min* minimum, *max* maximum, *T* tumor, hormone receptor, *HER2* human epidermal growth factor receptor 2

group who achieved pCR had LRR rates for IM+ versus IM− of 2.4% versus 0.6% ($p = 0.10$), DR of 4.9% versus 2.6% ($p = 0.40$), and EFS of 70.7% versus 68.4% ($p = 0.06$) [Table 5]. Similarly, for patients who did not achieve a pCR, we saw no statistical differences in LRR, DR, or EFS (Table 6, Fig. 1C).

DISCUSSION

For the infrequent finding of IML identified on imaging in the clinical work-up of breast cancer, we utilized a large cohort of patients from a multicenter clinical trial, I-SPY-2, to show the impact of IM+ nodes in patients treated with

TABLE 2 Surgical intervention and pathologic response of patients categorized by the presence or absence of IM lymphadenopathy on imaging

	IM−[n = 1897]	IM+[n = 198]	Overall [n = 2095]	p Value
Breast surgery performed				
Lumpectomy	834 (44.0)	78 (39.4)	912 (43.5)	0.405
Mastectomy with reconstruction	476 (25.1)	52 (26.3)	528 (25.2)	
Mastectomy without reconstruction	413 (21.8)	50 (25.3)	463 (22.1)	
Mastectomy unknown reconstruction	101 (5.3)	7 (3.5)	108 (5.2)	
Missing	73 (3.8)	11 (5.6)	84 (4.0)	
Nodal surgery performed				
SLN surgery only	1336 (70.4)	126 (63.6)	1462 (69.8)	0.171
ALND only	72 (3.8)	8 (4.0)	80 (3.8)	
SLN surgery + ALND	329 (17.3)	40 (20.2)	369 (17.6)	
Missing	160 (8.4)	24 (12.1)	184 (8.8)	
PCR				
No	1173 (61.8)	106 (53.5)	1279 (61.1)	0.031
Yes	645 (34.0)	82 (41.4)	727 (34.7)	
Missing	79 (4.2)	10 (5.1)	89 (4.2)	
RCB class				
0	645 (34.0)	82 (41.4)	727 (34.7)	0.148
I	256 (13.5)	23 (11.6)	279 (13.3)	
II	646 (34.1)	55 (27.8)	701 (33.5)	
III	271 (14.3)	28 (14.1)	299 (14.3)	
Missing	79 (4.2)	10 (5.1)	89 (4.2)	
Pathological N category				
N0	1180 (62.2)	118 (59.6)	1298 (62.0)	0.759
N1	402 (21.2)	46 (23.2)	448 (21.4)	
N2	136 (7.2)	12 (6.1)	148 (7.1)	
N3	59 (3.1)	8 (4.0)	67 (3.2)	
NX	10 (0.5)	0 (0)	10 (0.5)	
Missing	110 (5.8)	14 (7.1)	124 (5.9)	
Pathological T category				
T0	552 (29.1)	72 (36.4)	624 (29.8)	0.169
Tis	127 (6.7)	15 (7.6)	142 (6.8)	
T1	582 (30.7)	43 (21.7)	625 (29.8)	
T2	344 (18.1)	35 (17.7)	379 (18.1)	
T3	160 (8.4)	17 (8.6)	177 (8.4)	
T4	18 (0.9)	2 (1.0)	20 (1.0)	
TX	5 (0.3%)	0 (0%)	5 (0.2%)	
Missing	109 (5.7%)	14 (7.1%)	123 (5.9%)	

Data are expressed as *n* (%)

IM internal mammary, *SLN* sentinel lymph node, *ALND* axillary lymph node dissection, *PCR* pathologic complete response, *RCB* residual cancer burden, *N* nodal, *T* tumor, *Tis* carcinoma in situ

NAC in a modern context. Prior studies have identified patient and tumor factors that are associated with a higher likelihood of IM nodal involvement, including a study evaluating 1697 patients who underwent extended radical mastectomy in the absence of preoperative systemic therapy from 1956 to 2003. They found that more than four positive axillary nodes, medially located T2 tumors, medial tumors of any size with concomitant axillary involvement, T2 tumors in any location with concomitant axillary involvement, and age <35 years with a T3 tumor were all associated with a >20% risk of having IM nodal involvement pathologically at surgery.[26] In a study published in 2023 by Qiu et al., predictive modeling was used to identify factors associated with IM+ metastasis. In their validated nomogram, Qiu et al. found that tumor size, location, presence of lymphovascular invasion, and number of involved axillary nodes all had a significant relationship with IM nodal metastasis on multivariate analysis.[27] We similarly identified that our

TABLE 3 MRI and PET/CT imaging assessment for patients with IM+ nodes detected, evaluated by method of detection

	IM+ by both [$n = 33$]	IM+ by MRI only [$n = 154$]	IM+ by PET only [$n = 11$]	Overall [$n = 198$]
Number of abnormal IM nodes by MRI [n (%)]				
1	21 (63.6)	91 (59.1)	NA	112 (56.6)
2	3 (9.1)	22 (14.3)	NA	25 (12.6)
3 or more	9 (27.3)	41 (26.6)	NA	50 (25.3)
Missing	0 (0)	0 (0)	NA	11 (5.6)
Largest IM node by MRI, mm				
Mean (SD)	8.37 (3.76)	7.34 (3.10)	NA	7.52 (3.18)
Median [min, max]	9.50 [2.20, 13.0]	8.00 [1.00, 15.0]	NA	8.00 [1.00, 15.0]
Missing [*n* (%)]	27 (81.8)	125 (81.2)	NA	163 (82.3)
IM nodes SUV max				
Mean (SD)	4.24 (3.23)	NA	4.98 (5.71)	4.39 (3.80)
Median [min, max]	3.06 [1.10, 13.6]	NA	2.90 [0, 18.0]	3.06 [0, 18.0]
Missing [*n* (%)]	3 (9.1)	NA	3 (27.3)	160 (80.8)

IM internal mammary, *SD* standard deviation, *min* minimum, *max* maximum, *SUV* standard uptake value, *MRI* magnetic resonance imaging, *PET/CT* positron emission tomography/computed tomography

TABLE 4 Locoregional recurrence, distant recurrence, and event-free survival comparing patients with and without IM lymphadenopathy

	IM−[$n = 1897$]	IM+[$n = 198$]	Overall [$n = 2095$]	*p* Value
LRR				
No	1824 (96.2)	187 (94.4)	2011 (96.0)	0.200
Yes	73 (3.8)	11 (5.6)	84 (4.0)	
DR				
No	1747 (92.1)	180 (90.9)	1927 (92.0)	0.200
Yes	150 (7.9)	18 (9.1)	168 (8.0)	
EFS				
No	205 (10.8)	27 (13.6)	232 (11.1)	0.600
Yes	1086 (57.2)	122 (61.6)	1208 (57.7)	
Missing	606 (31.9)	49 (24.7)	655 (31.3)	

Data are expressed as *n* (%)

IM internal mammary, *LRR* locoregional recurrence, *DR* distant recurrence, *EFS* event-free survival

IM+ patients were more likely to be younger, have larger tumors, and higher grade (all $p < 0.05$). Of the IM+ patients in our study, 47.5% of the tumors were located in the inner breast ($n = 94/198$) and 45% of the IM+ patients had biopsy-proven axillary nodal involvement ($n = 89/198$).

Due to the reduced frequency of surgical resection of IM nodes, as well as minimal instances of percutaneous sampling in current clinical practice, we utilized abnormal IM lymph nodes detected by MRI and/or PET/CT as a surrogate for involvement by metastatic malignancy, an approach that has been utilized in prior studies.[28–30] We identified 9.5% of the total study population had abnormal IM nodes by imaging, which is similar to previous reports.[28,31,32] Since utilization of PET/CT in this study was at the discretion of the treating physicians, we were unable to perform a head-to-head analysis of MRI and PET/CT for the detection of IML; however, all patients underwent MRI per study protocol. Prior publications have shown that the performance of MRI in detecting IML is not inferior to PET/CT,[17,33,34] although head-to-head analyses are limited. Interestingly, we found that use of PET/CT was higher in patients who were IM+, which may be related to the baseline disease characteristics or may be secondary to findings from an MRI and could be further explored in future studies.

Historically, IM nodal involvement has indicated worse prognosis and outcomes for patients. This was largely investigated prior to the significant utilization of NAC. Furthermore, cross-sectional imaging modalities have continued to improve over time, thus identifying small and possibly less clinically significant disease. We sought to identify whether the clinical detection of IML in a modern cohort of high-risk patients treated with neoadjuvant therapies remained a poor prognostic predictor. In our cohort, we found that oncologic outcomes were not negatively impacted by the presence of IML. This finding remained statistically true when evaluating patients with or without IML who achieved a pCR and those who did not achieve a pCR. Interestingly, we identified a higher rate of pCR within the IM+ group. This could be attributed to a higher proportion of grade III disease within the IM+ group, resulting in a better response to NAC.[35,36] We saw no difference in the types of breast or axillary surgery performed. Importantly, we did note a significantly higher use of radiation therapy in the IM+ group, as expected. This illustrates that the presence of IML is

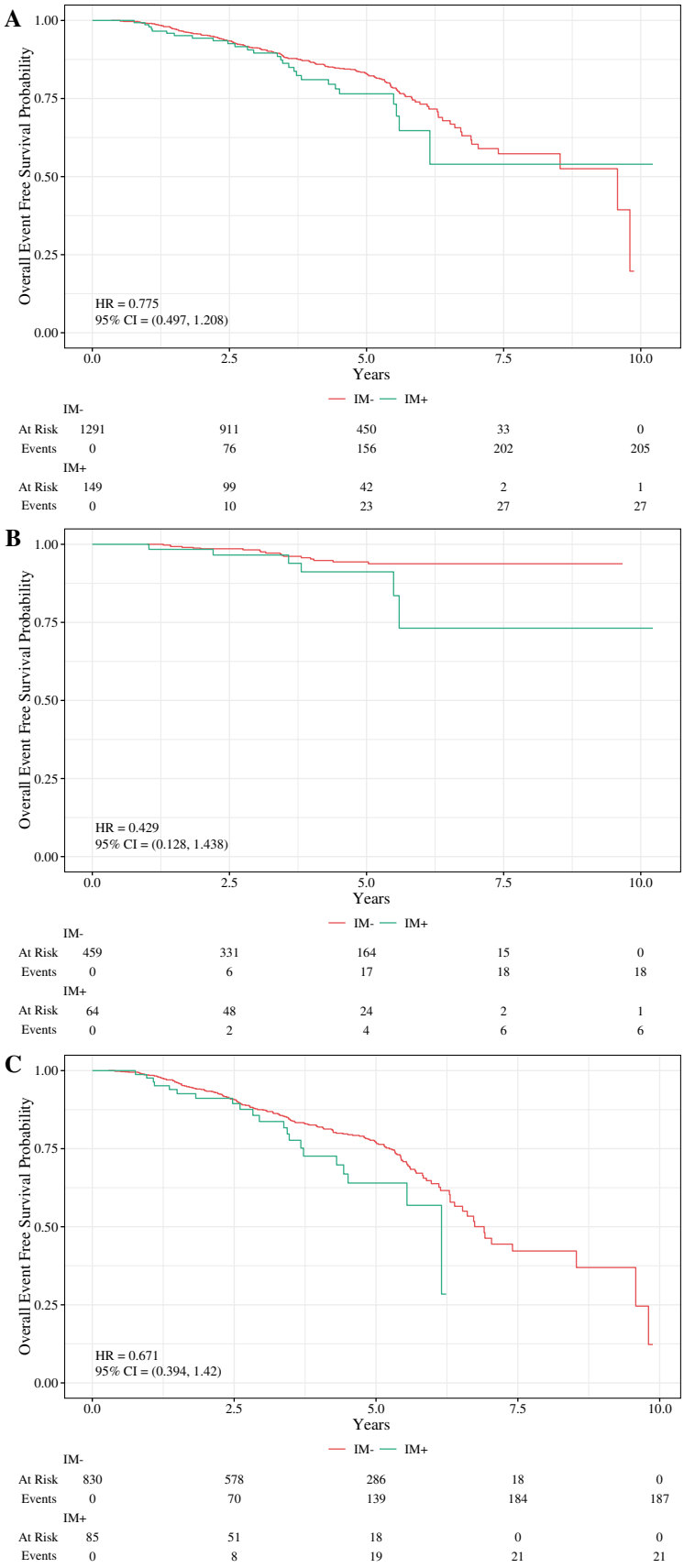

FIG. 1 Kaplan–Meier estimate of event-free survival probability by the presence or absence of IM lymphadenopathy on **A** imaging; **B** imaging in only those patients who achieved a pathologic complete response; and **C** imaging in only those patients who did not achieve a pathologic complete response. *CI* confidence interval, *HR* hazard ratio, *IM* internal mammary

TABLE 5 Locoregional recurrence, distant recurrence, and event-free survival comparing patients with and without IM lymphadenopathy who achieved a pCR

	IM−[$n = 645$]	IM+[$n = 82$]	Overall [$n = 727$]	p value
LRR				
No	641 (99.4)	80 (97.6)	721 (99.2)	0.10
Yes	4 (0.6)	2 (2.4)	6 (0.8)	
DR				
No	628 (97.4)	78 (95.1)	706 (97.1)	0.4
Yes	17 (2.6)	4 (4.9)	21 (2.9)	
EFS				
No	18 (2.8)	6 (7.3)	24 (3.3)	0.06
Yes	441 (68.4)	58 (70.7)	499 (68.6)	
Missing	186 (28.8)	18 (22.0)	204 (28.1)	

Data are expressed as *n* (%)

IM internal mammary, *pCR* pathologic complete response, *LRR* locoregional recurrence, *DR* distant recurrence, *EFS* event-free survival

TABLE 6 Locoregional recurrence, distant recurrence, and event-free survival comparing patients with and without IM lymphadenopathy who did not achieve a pCR

	IM−[$n = 1173$]	IM+[$n = 106$]	Overall [$n = 1279$]	p value
LRR				
No	1104 (94.1)	97 (91.5)	1201 (93.9)	0.10
Yes	69 (5.9)	9 (8.5)	78 (6.1)	
DR				
No	1040 (88.7)	92 (86.8)	1132 (88.5)	0.20
Yes	133 (11.3)	14 (13.2)	147 (11.5)	
EFS				
No	187 (15.9)	21 (19.8)	208 (16.3)	0.08
Yes	643 (54.8)	64 (60.4)	707 (55.3)	
Missing	343 (29.2)	21 (19.8)	364 (28.5)	

Data are expressed as *n* (%)

IM internal mammary, *pCR* pathologic complete response, *LRR* locoregional recurrence, *DR* distant recurrence, *EFS* event-free survival

influencing treatment strategies effectively. Of note, at least 6% of the patients with IML in our cohort did not receive radiation, which would be recommended by the NCCN guidelines. We suspect that this is a combination of shared decision making between patients and providers, or, potentially, that the IML documented on imaging at diagnosis was not ultimately felt to be clinically meaningful by the treating team after completion of NAC and surgery.

While our study utilized a large cohort of patients to obtain relatively high numbers of an uncommon clinical finding, the number of patients with involved IM nodes remains limited. Further follow-up is necessary to comment on long-term oncologic outcomes with confidence, specifically in patients with luminal breast cancer. Additionally, in the I-SPY-2 trial, utilization of PET/CT was at the discretion of the treating team, and other systemic staging techniques such as CT chest were not captured. Additionally, there was no standardized definition of abnormal IM node, such as minimum size criteria on MRI or SUV_{max} on PET. While this introduces some heterogeneity in the patient population, this is reflective of real-world practice. This evaluation would benefit significantly from more complete information on the delivery, dose, and treatment plans of radiation therapy.

As the multidisciplinary care of breast cancer evolves, improvements in imaging techniques, systemic therapy, surgery and radiation have changed the way we diagnose and treat IML. This study presents a valuable addition to the literature as an update on the oncologic impact of IML in the context of a rapidly advancing field. Historically, IML was associated with poor prognosis, and in this study we show that with our current clinical practice, other factors such as response to neoadjuvant therapy likely have a stronger impact on oncologic outcomes.

CONCLUSION

While IM nodal involvement is a relatively uncommon clinical finding in the staging work-up of breast cancer that impacts treatment decisions, we report on a large cohort of patients treated in a randomized controlled trial over a period of >10 years of enrollment and identify no prognostic impact from the presence of IML at a median follow-up of 3.72 years.

DISCLOSURE The corresponding author has no relevant disclosures to declare related to this work. Individual author disclosures have been submitted through the Annals of Surgical Oncology Manuscript Central website.

REFERENCES

1. Livingston SF, Arlen M. The extended extrapleural radical mastectomy: its role in the treatment of carcinoma of the breast. *Ann Surg*. 1974;179(3):260–5.
2. Veronesi U, Cascinelli N, Greco M, et al. Prognosis of breast cancer patients after mastectomy and dissection of internal mammary nodes. *Ann Surg*. 1985;202(6):702–7.
3. Donegan WL. The influence of untreated internal mammary metastases upon the course of mammary cancer. *Cancer*. 1977;39(2):533–8.
4. Chen RC, Lin NU, Golshan M, et al. Internal mammary nodes in breast cancer: diagnosis and implications for patient management: a systematic review. *J Clin Oncol*. 2008;26(30):4981–9.
5. Tanis PJ, Nieweg OE, Valdés Olmos RA, Kroon BB. Anatomy and physiology of lymphatic drainage of the breast from

the perspective of sentinel node biopsy. *J Am Coll Surg*. 2001;192(3):399–409.
6. Suami H, Pan WR, Taylor GI. Historical review of breast lymphatic studies. *Clin Anat*. 2009;22(5):531–6.
7. Madsen E, Gobardhan P, Bongers V, et al. The impact on post-surgical treatment of sentinel lymph node biopsy of internal mammary lymph nodes in patients with breast cancer. *Ann Surg Oncol*. 2007;14(4):1486–92.
8. Tan C, Caragata R, Bennett I. Is sentinel node biopsy of the internal mammary lymph nodes relevant in the management of breast cancer? *Breast J*. 2017;23(4):410–4.
9. Estourgie SH, Nieweg OE, Olmos RA, et al. Lymphatic drainage patterns from the breast. *Ann Surg*. 2004;239(2):232–7.
10. Braue K, Baker C, Lippey J. Internal mammary node involvement in patients with axilla-negative early breast cancer: a narrative review. *ANZ J Surg*. 2023;93(1–2):59–64.
11. Morrow M, Foster RS Jr. Staging of breast cancer: a new rationale for internal mammary node biopsy. *Arch Surg*. 1981;116(6):748–51.
12. Cserni G, Szekeres JP. Internal mammary lymph nodes and sentinel node biopsy in breast cancer. *Surg Oncol*. 2001;10(1–2):25–33.
13. Veronesi U, Marubini E, Mariani L, et al. The dissection of internal mammary nodes does not improve the survival of breast cancer patients. 30-year results of a randomised trial. *Eur J Cancer*. 1999;35(9):1320–5.
14. Lacour J, Le M, Caceres E, et al. Radical mastectomy versus radical mastectomy plus internal mammary dissection: ten year results of an international cooperative trial in breast cancer. *Cancer*. 1983;51(10):1941–3.
15. Meier P, Ferguson DJ, Karrison T. A controlled trial of extended radical versus radical mastectomy. Ten-year results. *Cancer*. 1989;63(1):188–95.
16. National Comprehensive Cancer Network (NCCN). NCCN Clinical Practice Guidelines in Oncology. Breast Cancer Version 2.;2024.
17. Jochelson MS, Lebron L, Jacobs SS, et al. Detection of internal mammary adenopathy in patients with breast cancer by PET/CT and MRI. *AJR Am J Roentgenol*. 2015;205(4):899–904.
18. Cho SM, Cha JH, Kim HH, et al. Assessing internal mammary lymph node metastasis by breast magnetic resonance imaging in breast cancer. *Medicine (Baltimore)*. 2023;102(47):e36301.
19. Plichta JK, Ren Y, Thomas SM, et al. Implications for breast cancer restaging based on the 8th edition AJCC staging manual. *Ann Surg*. 2020;271(1):169–76.
20. Giuliano AE, Edge SB, Hortobagyi GN. Eighth edition of the AJCC cancer staging manual: breast cancer. *Ann Surg Oncol*. 2018;25(7):1783–5.
21. Barker AD, Sigman CC, Kelloff GJ, Hylton NM, Berry DA, Esserman LJ. I-SPY 2: an adaptive breast cancer trial design in the setting of neoadjuvant chemotherapy. *Clin Pharmacol Ther*. 2009;86:97–100.
22. R Core Team. R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria; 2022. Available at: https://www.R-project.org/.
23. Therneau T. A Package for Survival Analysis in R. R package version 3.5-8. 2024. Available at: https://CRAN.R-project.org/package=survival.
24. Therneau TM, Grambsch PM. Modeling survival data: extending the cox model. New York: Springer; 2000.
25. Sjoberg D, Baillie M, Fruechtenicht C, Haesendonckx S, Treis T. ggsurvfit: Flexible Time-to-Event Figures. R package version 1.0.0; 2024. Available at: https://www.danieldsjoberg.com/ggsurvfit/; https://github.com/pharmaverse/ggsurvfit.
26. Huang O, Wang L, Shen K, 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 Cancer Res Treat*. 2008;107(3):379–87.
27. Qiu PF, Lv Q, Zhao WH, et al. Development and validation of a nomogram for predicting internal mammary sentinel node metastasis in breast cancer patients. *Eur J Surg Oncol*. 2023;49(10):107040.
28. Zhang YJ, Oh JL, Whitman GJ, 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(4):1113–9.
29. Adam R, Duong TQ, Hodges L, Lu J, Maldjian T. Internal mammary lymph nodal response to neoadjuvant chemotherapy on imaging and breast cancer prognosis. *Ann Med Surg (Lond)*. 2022;84:104900.
30. Chung HL, Shin K, Sun J, Leung JWT. Extra-axillary nodal metastases in breast cancer: comparison of ultrasound, MRI, PET/CT, and CT. *Clin Imaging*. 2021;79:113–8.
31. Madsen EV, Aalders KC, van der Heiden, van der Loo M, et al. Prognostic significance of tumor-positive internal mammary sentinel lymph nodes in breast cancer: a multicenter cohort study. *Ann Surg Oncol*. 2015;22(13):4254–62.
32. Wang W, Qiu P, Li J. Internal mammary lymph node metastasis in breast cancer patients based on anatomical imaging and functional imaging. *Breast Cancer*. 2022;29(6):933–44.
33. Samreen N, Dhage S, Gerber NK, et al. Imaging and management of internal mammary lymph nodes. *J Breast Imaging*. 2020;2(6):530–40.
34. Cheon H, Kim HJ, Lee SW, et al. Internal mammary node adenopathy on breast MRI and PET/CT for initial staging in patients with operable breast cancer: prevalence and associated factors. *Breast Cancer Res Treat*. 2016;160(3):523–30.
35. Müller C, Schmidt G, Juhasz-Böss I, et al. Influences on pathologic complete response in breast cancer patients after neoadjuvant chemotherapy. *Arch Gynecol Obstet*. 2021;304(4):1065–71.
36. Jarząb M, Stobiecka E, Badora-Rybicka A, et al. Association of breast cancer grade with response to neoadjuvant chemotherapy assessed postoperatively. *Pol J Pathol*. 2019;70(2):91–9.