Diagnostic Study

Internal mammary lymph nodal response to neoadjuvant chemotherapy on imaging and breast cancer prognosis

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ABSTRACT

Background: Pathologic complete response (pCR) to neoadjuvant chemotherapy (NAC) is an important prognostic indicator in breast cancer. Internal mammary lymph node involvement is not currently included in pCR determination, as sampling at the time of surgery is not routinely performed.

Methods: Pre and post neoadjuvant chemotherapy MRI or PET/CT imaging response of the internal mammary lymph node chain was utilized as a surrogate to pCR and imaging data was correlated with patient outcomes.

Results: Internal mammary lymph node response to NAC was associated with disease free survival over the course of this study, regardless of whether axillary nodal pCR was achieved.

Conclusion: Internal mammary lymph nodal response to NAC is an important prognostic indicator. Potential use of internal mammary lymph node resolution as an imaging data input for AI models that predict pCR post-NAC may improve accuracy and other metrics in pCR prediction.

1. Introduction

Several studies show a correlation between breast cancer response to NAC and outcome. Pathologic complete response (pCR) has been linked to a more favorable prognosis. Pathologic complete response (pCR) is defined as the complete disappearance of invasive cancer in the breast and axilla after neoadjuvant therapy.

[1] Specifically, 3 year recurrence free survival (RFS) is better in biologically high-risk invasive breast cancers that achieve pCR [2]. Currently internal mammary lymph nodes (IMLN) are not included in the determination of whether pCR has been achieved. Pathologic data on IMLN is lacking, as they are not routinely sampled at surgery, thus making inclusion of these lymph nodes in pCR estimation unfeasible. Prior studies have demonstrated that there is no survival advantage for patients who have internal mammary lymph node dissection, therefore this practice was abandoned [3]. Axillary lymph node regression at pathology and presumed initial pathologic N stage are independent prognostic factors, with number of completely-responsive LNs and the ratio of non-responsive LNs also demonstrating prognostic significance in breast cancer patients receiving NAC [4]. In this study, we seek to evaluate response of internal mammary lymph nodes to determine if IMLN response post NAC could play a role in determining prognosis.

2. Methods

207 patients with only invasive ductal breast cancer and with regional positive lymph nodes were identified over a 10 year period (1-1-20 through 12-31-20) who were clinical stage 2 and above prior to treatment and had NAC and surgery at our institution. 24 patients had regional positive lymph nodes that included IMLN on imaging (Fig 1a, 1b, 2a, 2b). Of these, 13 patients had pre NAC and post NAC PET/CT or MRI. One patient (pt 1) did not complete her therapy, so is excluded. There were 12 patients remaining who completed therapy and fulfilled criteria for inclusion in our retrospective study. Four of these patients already had metastatic disease beyond the regional lymph nodes (patients 2, 4, 5, and 8) and are excluded from the analysis of IMLN response as a determinant of prognosis, since prognosis would be worsened on the basis of already existing metastatic disease. The patients’ ages ranged from 25 to 76 years of age.

3. Results

Patient 1: excluded due to incomplete therapy.

Patient 2 (58 year old female, triple negative, poorly differentiated left IDC):

PET/CT showed axillary, interpectoral, internal mammary, and supraclavicular nodes and sternal (osseous) involvement. Post NAC...
PET/CT showed decrease in size of the primary breast tumor (from 4.9 to 3.8 and SUV decrease from 12.6 to 5.2), resolution of all nodes, healed sternal lesion (which became photopenic). Surgery (left mastectomy) revealed 1.5 cm residual tumor and 2 lymph nodes with macrometastatic disease (5 mm and 8 mm). Patient had radiation therapy. Patient had recurrence with progression on PET/CT 7 months after surgery and succumbed to disease 1 year after surgery.

Patient 3 (50 year old female, triple negative, poorly differentiated right IDC):
Breast MRI showed 5.7 cm right mass partially necrotic, axillary nodes (one necrotic), and right internal mammary node (Fig. 2a, 2b). Post NAC breast MRI showed resolution of breast mass, slightly prominent necrotic right axillary node, and resolution of remaining nodes (Fig. 2c, 2d). Lumpectomy revealed 5 foci of residual disease of 1–2 mm each in the breast with 3–4% cellularity, and 1 positive axillary node out of 8 axillary nodes (axillary sentinel node replaced by tumor 35 mm with extranodal disease). Patient had radiation therapy post-lumpectomy. Patient is disease free to the present, approximately 4 years post-surgery.

Patient 4 (69 year old female, triple negative, moderately differentiated left IDC):
PET/CT showed 4.3 cm left breast mass, left axillary, left subpectoral, and left internal mammary node involvement and extranodal disease in the form of a right lower lobe nodule in the lung pre NAC. Post NAC PET/CT showed improvement, but persistence of all of the lymph nodes and right lung nodule. Surgery was modified radical mastectomy with level 1 and level 2 axillary node dissection and revealed 3.5 cm residual tumor in the breast, 4 axillary nodes with macrometastases and extranodal extension, 3 axillary nodes with micrometastases, and 3 nodes with isolated tumor cells. Patient had radiation therapy. 4 months after surgery chest imaging showed new lung nodules; left breast and left axilla surgical beds were negative. 6 months after that patient showed iliac and sternal involvement on bone scan. Patient succumbed 1 year and 1 month after surgery.

Patient 5 (60 year old female with triple negative, moderate to well-differentiated right IDC):
PET/CT showed right axillary, supraclavicular, and internal mammary involvement as well as 4th rib and pectoralis major involvement. Post NAC PET/CT showed mass in right breast with SUV down from 6.4 to 2.4, mild right supraclavicular nodes, and resolution of axillary and internal mammary nodes and rib lesion. Surgery showed few foci of residual IDC 2–3 mm 5% cellularity with rare foci of DCIS and no LVI (lymphovascular invasion), macrometastasis in 1 LN with extranodal extension, micrometastasis in 1 LN, 12 negative nodes. Patient had radiation therapy. Imaging 2 years after surgery showed disease progression. No further studies and no further notes 3 years and 3 months after surgery. Patient was lost to follow-up.

Patient 6 (68 year old female with 2 site/multifocal both HER2 positive, both ER/PR negative, moderately differentiated and poorly differentiated left IDC):
PET/CT showed 2 left breast lesions, axillary nodes, and internal mammary node (Fig. 1a, 1b). Post NAC PET/CT showed resolution of breast lesions, axillary nodes, and internal mammary node. Surgery showed no residual tumor in breast and no tumor in LNs, with 0/3 lymph nodes (surgical pCR). Patient had radiation therapy. 5 and a half years post surgery patient has no recurrence.

Patient 7 (76 year old female with triple positive, moderately differentiated left IDC):
MRI showed internal mammary node resolution, residual improved axillary nodes, residual foci of enhancement in breast. Surgery showed 16 mm residual tumor in breast with 10–15% cellularity, +LVI, 3 out of 16 LN positive for tumor up to 8 mm focus. Patient had radiation therapy. CT scan was negative on follow up. No recurrence thus far 5 and a half years after surgery.

Patient 8 (61 year old female with triple negative, poorly differentiated left IDC):
PET/CT showed left breast mass, left axillary, subpectoral, internal mammary, supraclavicular, level 4 left neck, mediastinal lymph nodes. Post NAC PET/CT showed all nodes gone, decreased size but increased uptake of primary breast tumor. Left simple mastectomy showed 2 foci of IDC (4 cm and 1.5 cm) and 1 LN negative for tumor at pathology. Patient had radiation therapy. 7 months post surgery chest CT showed extensive progression of disease to multiple sites and patient succumbed to disease.

Patient 9 (40 year old female with poorly differentiated ER+/PR+/HER2- IDC):
MRI demonstrated 4.5 cm partially necrotic index right breast mass and 3 cm axillary lymph node and 1.5 cm right internal mammary lymph node. Post NAC MRI demonstrated 1.1 cm index mass and marked improvement of right axillary lymph node. No internal mammary lymphadenopathy was reported on MRI post NAC. Lumpectomy was performed. Surgery demonstrated 1.6 cm residual tumor bed with largest tumor focus measuring 6 mm, with 5% cellularity and with lymphovascular invasion. Lumpectomy revealed a 10 mm lymph node with micrometastatic foci of up to .25 mm in size. Four other smaller axillary nodes up to 4 mm in size were negative for tumor. The patient received radiation therapy. 2 years post surgery, the patient is disease free.

Patient 10 (51 year old female with ER+/PR+/HER2- ductal...
MRI demonstrated 2.6 cm right breast mass with ipsilateral axillary nodal and internal mammary nodal involvement. Post NAC MRI demonstrated no residual disease in the right breast or regional nodes. Mastectomy revealed no residual tumor in the breast, however lymphovascular invasion with 2 small foci of vascular tumor emboli was seen. 0 out of 9 lymph nodes were positive for tumor, indicating pCR. The patient had radiation treatment and remains disease free 5 years post surgery.

Patient 11 (25 year old BRCA1 female with poorly differentiated ER+/PR-/HER2- IDC):
MRI showed a 3.2 cm right breast mass with ipsilateral axillary and internal mammary lymph node involvement. Post-NAC MRI showed complete resolution of breast mass and regional lymph nodes. Mastectomy revealed no residual tumor in the right breast. 1 out of 20 lymph nodes revealed 1 cm macrometastatic disease. The remaining 19 lymph nodes were negative for tumor. The patient received radiation treatment and is disease free 7.5 years post surgery.

Patient 12 (37 year old female with poorly differentiated triple negative IDC):
7 cm mass in the right breast and abnormal right axillary and right internal mammary nodes were seen. Post NAC MRI revealed 4.3 cm residual index mass, with resolution of lymph nodal findings. Segmental resection was performed showing several foci of residual disease with individual focus measuring up to 8 mm. 1 out of 18 lymph nodes was positive for tumor, showing micrometastatic disease (under 2 mm). The patient had radiation treatment and remains disease free 9 years after surgery.

Patient 13 (37 year old BRCA2 female with poorly differentiated triple negative IDC):
PET/CT showed a 4.1 cm left breast mass with avid uptake. Ipsilateral axillary, subpectoral, supraclavicular, and internal mammary nodal involvement was also seen. Post NAC PET/CT demonstrated resolution of the breast and nodal findings. Mastectomies revealed 1 mm residual tumor in the left breast. Out of 18 lymph nodes, none were positive for tumor. Patient received radiation treatment and had 2.5 years of documented disease free survival and was then lost to follow-up.

3.1. Summary of results

Patients with involvement beyond regional lymph nodes at presentation:
4 patients had disease beyond regional lymph nodes (patients 2, 4, 5, and 8), all having triple negative disease and residual disease in the breast post NAC. Patients 2 and 8 demonstrated resolution of all nodal disease on imaging; however only patient 8 showed negative axillary lymph node at pathology. 3 patients succumbed to disease and one patient (patient 5) demonstrated disease progression, then lost to follow-up.

Patients with disease limited to breast and regional nodes at presentation:
8 patients (patients 3, 6, 7, 9, 10, 11, 12, and 13) had regional disease limited to the breast and regional nodes. Patients 6 and 10 had imaging resolution of all disease and demonstrated surgical pCR. Patients 3, 7, and 9 demonstrated imaging resolution of the internal mammary lymph node with partial imaging response of the axillary nodes. We presume that the internal mammary nodes achieved complete pathologic response, as all eight patients remain disease-free throughout their follow up.
prognosis. As no prior studies have sought to differentiate internal mammary lymph node dissection at surgery has been abandoned due to lack of pathologic data, since internal mammary lymph nodal response to NAC from axillary nodal response, or attempted to correlate imaging response to patient outcomes, the prognostic significance of IMC response to NAC remains unclear.

4.1. Internal mammary lymph node response relative to axillary lymph node response

In all of our patients, internal mammary lymph nodes demonstrated response to NAC equal to or better than the axillary nodes. This may be due to the fact that this area of the anatomy, where the internal mammary nodes reside, receives its blood supply from the medially located internal mammary artery which is the main vascular supply for the breast. We hypothesize that this may enhance delivery of chemotherapy to the medially situated internal mammary basin territory relative to the laterally situated axillary nodal basin territory, possibly increasing the efficacy of chemotherapy on the IMLN chain. The internal mammary artery is remarkably resistant to the development of atherosclerosis due to its unique properties, including more anti-thrombotic molecules like heparin sulfate and tissue plasminogen activator, and higher endothelial nitric oxide production, which has made it ideally suited for coronary bypass surgery, demonstrating greater long term patency and improved survival compared to saphenous venous grafts [5,6]. These unique biological features of the internal mammary artery would likely confer improved delivery of chemotherapy relative to other arteries. This is particularly relevant when one considers that the majority of breast cancers occur in post-menopausal women, a population that is at increased risk of developing atherosclerosis [7,8].

4.2. Analysis of IMLN response as a determinant of prognosis

In our patients with disease limited to the axillary and IM regional nodes, internal mammary lymph node resolution post NAC predicted good prognosis, even in the presence of residual axillary nodal disease post NAC. This may be due to a higher metastatic potential of the IMLN relative to the axillary nodes, such that resolution of IMLN alone would confer a more protective effect from disease dissemination than resolution of axillary nodal disease alone when both nodal basins are initially involved.

Eradication of axillary lymph node metastases as a result of NAC confers survival advantage to breast cancer patients, axillary nodal pCR with concomitant residual primary breast tumor confers greater survival benefit than pCR in the breast with concomitant residual axillary disease, and pCR in both breast and axilla show the greatest survival advantage [9-11]. These findings support the strength of axillary pCR as an indicator of outcome, as axillary pCR alone exerts a greater effect on disease free survival than breast pCR alone. It has been hypothesized that clearance of axillary metastases compared to clearance of disease in the breast exerts greater effect due to increased metastatic potential of axillary metastases [4]. Yet, residual axillary disease post NAC does not uniformly dictate a poor outcome. Recurrence free survival (RFS) over 10 years in patients with breast pCR and axillary pCR, axillary pCR and residual breast disease, residual axillary disease and breast pCR, and residual axillary disease and residual breast disease are 85%, 66%, 56%, and 49% respectively [4]. Clearly some patients with residual axillary disease have long term survival outcomes, with residual axillary disease/breast pCR demonstrating 56% RFS and residual axillary disease/residual breast disease demonstrating 49% RFS. This raises the question of whether there are any indicators that might allow us to differentiate patients who survive in spite of the presence of axillary nodal residual disease post NAC. Internal mammary lymph node dissection is not performed and is not included in the discussion of pCR. Inclusion of IMLN may strengthen prediction of pCR. Prior studies have demonstrated no survival advantage for patients who have internal mammary lymph node dissection, and therefore this practice was abandoned [3]. More recently, however, there has been a resurgence of interest in internal mammary node dissection, such that internal mammary lymph node response to NAC from axillary nodal response, or attempted to correlate imaging response to patient outcomes, the prognostic significance of IMC response to NAC remains unclear.

4. Discussion

Currently the internal mammary nodes are not included in pCR metrics. This is due to the lack of pathologic data, since internal mammary lymph node dissection at surgery has been abandoned due to lack of survival benefit [3]. Involvement on imaging mandates radiation to the IMC after surgery. Axillary and primary tumoral pCR have been shown to correlate to prognosis. Using imaging response of the internal mammary lymph node to NAC as a surrogate for pCR, we sought to gain insight into the significance of internal mammary chain (IMC) disease to prognosis. As no prior studies have sought to differentiate internal mammary lymph nodal response to NAC from axillary nodal response, or attempted to correlate imaging response to patient outcomes, the prognostic significance of IMC response to NAC remains unclear.

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Fig. 2b. Necrotic right axillary node and IM lymph nodes are demonstrated pre-NAC (pt 3).

Fig. 2c. 6 months later post NAC DCE MRI demonstrates complete resolution of right breast NME (pt 3).

Fig. 2d. Right IM nodal involvement is resolved, however residual right axillary nodal involvement is seen post-NAC on DCE MRI (pt 3). 1–2 mm of residual IDC and residual macrometastatic axillary lymph node were seen at surgery.
mammary node involvement is no longer deemed to be as detrimental a prognostic factor as previously thought [12]. This is, at least in part, due to selective radiotherapy regimens [12]. In addition to tumor regression at the site of IMLN involvement, an additional potential benefit of targeted radiation to the IMLN chain is the abscopal effect and radiation-induced bystander effect. The abscopal effect is explained by a systemic immune activation triggered by immunogenic cell death of irradiated target tumor tissue causing regression of tumor distant from the irradiated field [13]. A meta-analysis of 12,705 patients in 12 studies showed clinical benefit to N1-2 breast cancer patients from internal mammary lymph node radiation [14]. Andring et al showed 5 year locoregional recurrence free survival (RFS) of 89% in patients with nonmetastatic internal mammary lymph node (cN3B) disease, with treatment including NAC, surgery, and adjuvant radiation therapy [15]. Improved survival is a potential benefit, however toxicities of radiation also need to be considered [16]. Because of the risk of cardiac toxicity and lung injury from radiation, sentinel lymph node biopsy through the intercostal space has been proposed as a feasible technique for guiding individualized internal mammary nodal radiation [17–19]. Concurrent treatment regimens can also impact cardiac toxicity. Trastuzumab, which is associated with cardiac toxicity, increases disease free survival for HER 2+ breast cancer patients (20–21). This treatment usually is concurrent with adjuvant radiation therapy, raising cardiac safety concerns in treating left sided breast cancers [20–22]. Proximal positioning reduces lung and heart exposure during radiation treatment in breast cancer patients [23–26]. In addition modern techniques reduce radiation exposure, as older techniques increase dosage to heart and lungs [27–29]. Prophylactic radiation treatment for internal mammary nodes in early breast cancer is controversial [30].

Internal mammary chain (IMC) involvement is influenced by 3 factors: the presence of histological peritumoral vascular invasion in the primary carcinoma, the presence of axillary node metastases, and the size of the primary tumor [12]. Out of 68 patients demonstrating IMC involvement, S1 also showed axillary nodal disease, reflecting the strong association of IMC disease with axillary nodal disease [12]. Since axillary nodal disease is frequently seen in conjunction with IMC involvement, IMC response to NAC may provide insight into prognosis in patients with concomitant axillary nodal disease, particularly where axillary nodal status demonstrates partial response to NAC without pCR. In one study, patients with internal mammary metastases treated with radiotherapy and appropriate systemic therapy demonstrated 5 year survival of 95%, contradicting the previously held belief that IMC involvement is an ominous prognostic indicator [12]. The excellent survival was attributed to radiotherapy targeting the internal mammary nodes, which was deemed to be more beneficial than surgical dissection because of the wider treatable area with radiotherapy, potentially preventing pleural metastatization by eradicating cancer foci superficially involving the pleura [31]. Just as it has been hypothesized that clearance of axillary metastases is of greater prognostic significance compared to clearance of disease in the breast, due to the greater metastatic potential of axillary disease, it may be that clearance of internal mammary nodal metastases may be of greater prognostic significance than clearance of axillary metastases due to the higher metastatic/invasive potential of internal mammary metastases relative to the metastatic potential of axillary nodal disease.

4.3. pCR of primary tumor, pCR of axillary node, and complete clinical response of IMLN: patient outcomes and potential influence on prognosis

All eight of our patients with favorable outcomes (remission with no progression of disease on follow up) demonstrated resolution of IMC on imaging despite 4 of the 8 patients having residual primary tumor and residual axillary nodal disease post NAC. This may be due to the greater metastatic potential for IMLN compared to axillary nodes and would only be valid in regionally limited disease, explaining why remission of disease was short-lived in our patients with pre-existing metastatic disease, with uniformly unfavorable outcomes, in spite of good nodal response to NAC in some cases. Larger studies would need to be performed to further investigate the generalizability of our findings. Future directions would include the use of internal mammary lymph node resolution as an imaging data input for AI models that predict pCR post-NAC in order to improve accuracy and other metrics in pCR prediction.

4.4. Limitations

Limitations of our study include the small sample size of N = 12, which prohibits us from performing statistical analyses, and limited follow-up in some cases (the shortest being 2 years and the longest being 9 years). Another limitation would be the fact that data regarding internal mammary lymph node involvement and its subsequent response to NAC was based on imaging and not pathologic analysis (as resection of internal mammary lymph nodes is not typically performed). Another weakness of our study is that it was a retrospective study and not a prospective study.

5. Conclusion

Our results showed that internal mammary lymph nodal disease consistently demonstrated an equal or better response to NAC than axillary nodes. In all our patients with internal mammary nodal involvement in disease confined to regional lymph nodes, disease free survival was demonstrated, even when residual axillary disease was present at surgery. This implies that internal mammary lymph nodal response may exert a greater effect on prognosis than axillary nodal response. While internal mammary lymph node involvement is an important prognostic indicator, currently internal mammary lymph node data is not included in pCR metrics, as surgical removal is not commonly performed. We hypothesize that imaging response to NAC may serve as a substitute for pCR data, and may help in predicting outcomes and disease free survival.

Provenance and peer review

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Ethical approval

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Author contribution

All authors contributed to study concept and data analysis/interpretation.
All authors contributed to writing and/or editing of paper.

conflicts of interest

None.

Registration of research studies

1. Name of the registry: N/A. Study was retrospective and conducted purely through chart review. No information was collected directly from patients.
2. Unique Identifying number or registration ID:
3. Hyperlink to your specific registration (must be publicly accessible and will be checked):
Guarantor
Dr. Duong and Dr. Maldjian.

Consent
Consent was waived by IRB because study was retrospective and data was obtained through chart review, with no unique information disclosed in order to perform the study.

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