

Impact of Surgically and Radiologically Detected Incidental Internal Mammary Lymph Node Enlargement in Breast Cancer Patients Undergoing Free-Flap Breast Reconstruction

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Abstract

Background The internal mammary lymph node (IMLN) basin is considered the second most important regional nodal basin in breast cancer. IMLNs are often not detected radiologically and left untreated, with symptomatic recurrence being 0.1%. Challenges in accessibility have been an obstacle in achieving a comprehensive treatment plan, especially with undetermined and radiologically enlarged IMLN. Free autologous tissue breast reconstruction is considered the gold standard, and the familiarity of microvascular surgeons in using the internal mammary vessels (IMVs) puts them in a unique position to shed more light on the natural pathological process of IMLN metastases.

Materials and Methods A retrospective data analysis study was conducted evaluating 270 patients who underwent 307 free flaps for breast reconstruction using the IMV in the period between 2009 and 2017. Patient's demographics and clinicopathological data including IMLN harvest, radiological, operative details, adjuvant therapy, post-operative morbidity, and follow-up outcome data were analyzed.

Results Eighty-nine enlarged IMLNs were surgically retrieved from 30.7% (83/270) of the patients (73 delayed, 10 immediate breast reconstructions) with an age range of 29 to 77 years (mean: 45). Eighty six were incidentally encountered during surgery, whereas in three, the enlarged IMLN was preoperatively, radiologically determined and biopsied during computed tomography (CT) scan staging and was retrieved

Keywords

- ▶ internal mammary lymph node
- ▶ breast cancer
- ▶ breast reconstruction
- ▶ free flap

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subsequently during surgery. IMLN metastases were confirmed in 8.4% (7/83) of the patients in whom IMLNs were retrieved with subsequent modification of the proposed adjuvant therapy. The follow-up period ranged from 3 to 84 months (mean: 42) for the involved IMLN patients. Two patients (28% [2/7]) showed signs of disease progression with mortality.

Conclusion Microvascular surgeons in a multidisciplinary setting would provide a valuable role in improving outcomes of patients with IMLN metastases through better diagnosis and staging of incidentally enlarged metastatic IMLN and provision of an effective approach for locoregional disease control.

The internal mammary lymph node (IMLN) basin is considered the second most important regional nodal basin region in breast cancer.^{1,2} Lymphatic mapping studies revealed that pathological IMLN involvement enlargement could be in 10 to 15% of breast cancer patients, with up to 20% of these being positive for malignancy.^{3,4} Respectively, there have been contrasted views that had led to dilemma and controversy regarding the significance of sampling these nodes and their impact on staging, survival, and subsequent adjuvant therapy. Most of the studies have been limited to descriptive observations of early experiences and have led to inconsistent results with insufficient evidence in terms of efficacy and clinical significance.^{4–12} However, meta-analysis by the Early Breast Cancer Trialists' Collaborative Group showed poor outcomes in patients with IMLN involvement, leading to a resurgence of interest in the IMLN mapping and biopsy.^{9,13} Involved IMLNs are often not detected and left untreated, with symptomatic recurrence in this chain seen in 0.1% of breast cancer patients.¹⁴ The challenges in accessibility in terms of IMLN biopsy or dissection have been an obstacle in the widespread adoption of this technique. The familiarity of microvascular surgeons in using the internal mammary vascular pedicle (IMVP) as recipient vessels for free autologous tissue transfer for breast reconstruction puts them in a unique position to shed more light on the pathological process of IMLN metastases and recurrence.

We report our case series of incidentally diagnosed metastatic IMLN in breast cancer patients undergoing free-flap breast reconstruction using internal mammary vascular pedicle (IMVP) and the impact on their oncological management.

Materials and Methods

A retrospective analysis review of patients who underwent free autologous tissue transfer for breast reconstruction (immediate breast reconstruction [IBR] or delayed breast reconstruction [DBR] setting) postmastectomy in the period between January 2009 and March 2017 at Good Hope and Heartlands Hospitals, Birmingham, United Kingdom, was performed. The patients were identified from the department's audit database, and subsequently all patients who had incidentally enlarged IMLNs were identified from the operative details, and radiological and histopathology database. Patients were managed through a multidisciplinary team approach

(Breast Oncoplasty MDT) comprising an oncologist, a radiologist, breast surgeons, a reconstructive surgeon (H. K.), and a thoracic surgeon (M. K.). In addition, the demographic information and clinicopathological details, including timing of reconstruction, adjuvant therapy, postoperative morbidity, disease-free interval, survival, and follow-up period data, were collected from the electronic patient records and analyzed. As per the standard protocol for preoperative oncological staging, all immediate reconstruction patients underwent standalone sentinel lymph node biopsy (SLNB) of the axilla. On the other hand, patients requesting delayed reconstruction and who were deemed moderate or high risk for locoregional or distant metastases were candidates for staging computed tomography (CT) scan. If an incidental enlarged IMLN was detected radiologically, the patient was subjected to positron emission tomography (PET)/CT scan or mediastinoscope-guided biopsy prior to any definitive reconstruction (– Fig. 1). The IMVP was the recipient vessel of choice in all patients undergoing microvascular free-flap breast reconstruction either in an immediate or delayed setting. The IMVP was approached through dissection of the third costal cartilage, and any macroscopically enlarged IMLN was harvested and subjected to histopathological examination.

Results

Eighty-nine enlarged IMLNs were surgically retrieved from 30.7% (83/270) of the patients (73 in DBR and 10 in IBR) with an age range of 29 to 77 years (median: 45). Eighty six were incidentally encountered and surgically obtained during 307 free-flap reconstruction procedures in 270 patients (255 unilateral and 26 bilateral), with a flap success rate of 98.5%. Preoperative staging CT scan for patients mainly undergoing delayed reconstruction was performed in 27.7% (75/270). This detected isolated radiologically enlarged IMLNs in 4% (3/75) and confirmed on PET/CT scan (two warm spots and one hot spot). They were subsequently biopsied (two needle-guided CT scan and one mediastinoscope) with no evidence of metastases in any of them. No additional morbidity was associated when CT-guided biopsy was performed; however, when not feasible or deemed risky, biopsy under vision with mediastinoscope was performed (– Fig. 2). The median size of the IMLN was 1 cm (range: 0.5–2), with all lymph nodes retrieved from the second and third intercostal spaces, respectively (– Fig. 3).

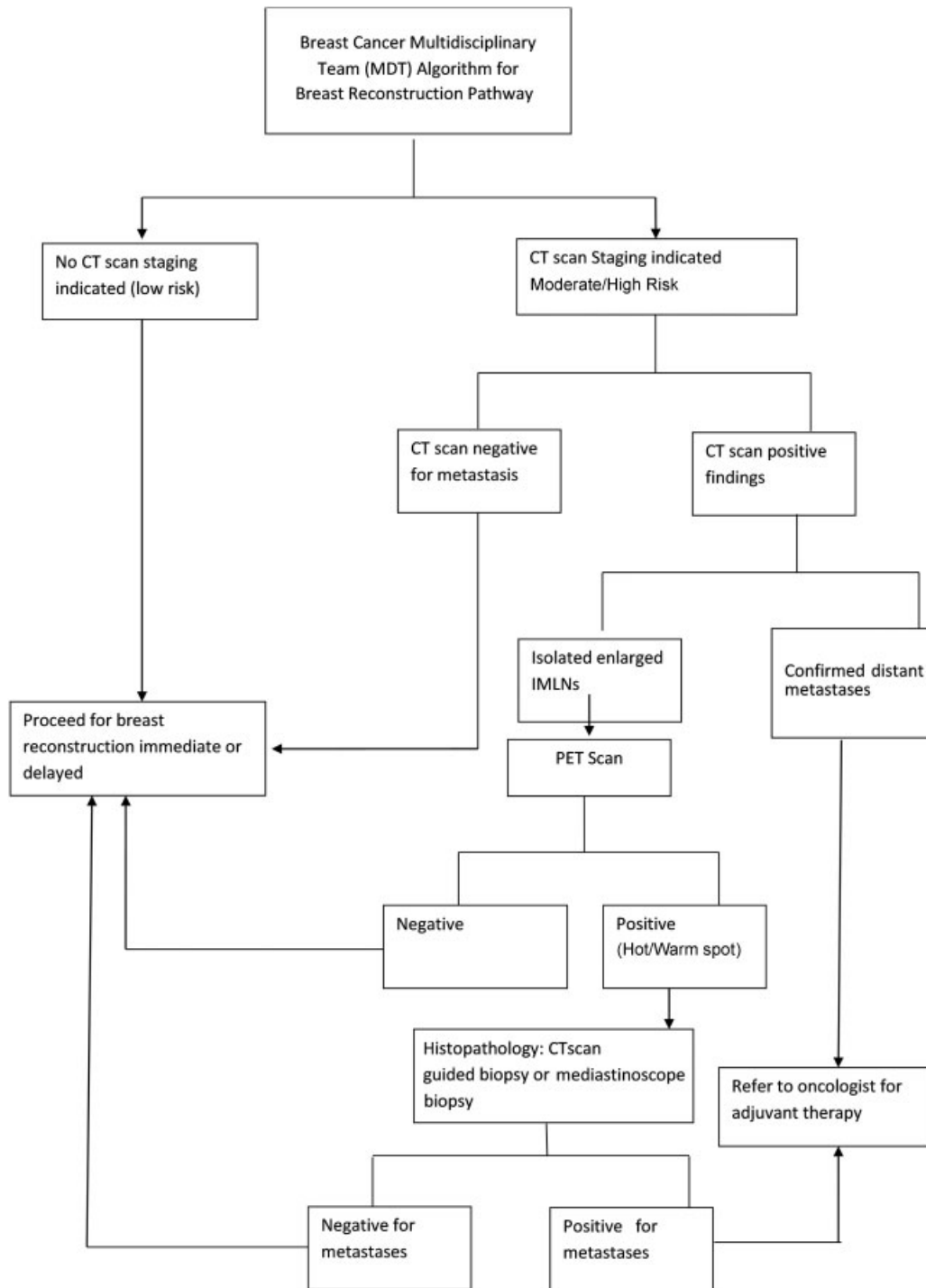


Fig. 1 Diagram demonstrating the Breast Cancer Multidisciplinary Team (MDT) Algorithm for Breast Reconstruction Pathway with special attention to the management plan for incidental radiologically detected internal mammary lymph node enlargement.

IMLN metastases were confirmed in 8.4% (7/83) of the patients in whom IMLNs were retrieved (5 DBR - 2 IBR) and 2.5% (7/270) of the whole cohort of breast cancer patients undergoing free-flap reconstruction with subsequent modification of the proposed adjuvant therapy. This included second-line chemotherapy and radiotherapy to the supraclavicular area and internal mammary chain, in addition to hormonal treatment. Other histopathological diagnosis included silicone granulomas from previous implant surgery ($n = 14$), sinus histiocytosis

($n = 8$), and reactive lymph nodes ($n = 60$). One node was harvested in 75 patients, two nodes in 4, and three nodes in 2. Macroscopically, there was no significant difference between the metastatic and benign retrieved IMLNs. The free autologous tissue transfer included free muscle-sparing transverse rectus abdominis myocutaneous (MSTRAM) type I/II flap ($n = 301$), superior gluteal artery perforator flap ($n = 3$), and transverse myocutaneous gracilis flap ($n = 3$) in an immediate setting ($n = 192$) or delayed setting ($n = 115$)

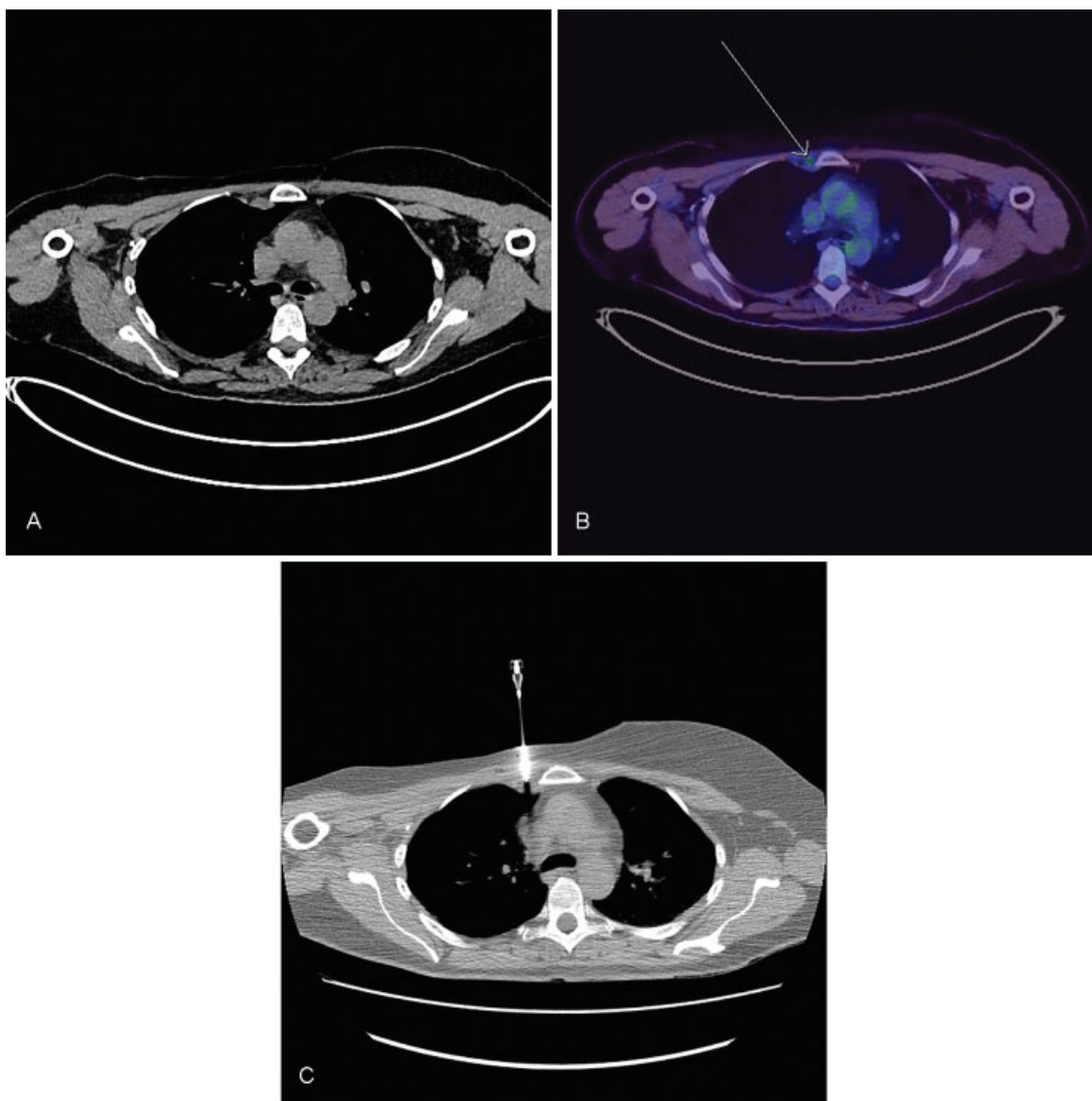


Fig. 2 (A) A preoperative computed tomography (CT) scan staging prior to delayed reconstruction revealing an isolated enlarged isolated internal mammary lymph node (IMLN). (B) A positron emission tomography (PET)/CT scan performed to determine the nature of the enlarged IMLN and also exclude any distant metastases; this scan revealed a hot spot that required further assessment with guide biopsy. (C) CT scan guided biopsy is performed to detect the nature of warm/hot spots on PET/CT scan.

postmastectomy. The IMVP was always the recipient pedicle of choice. The duration between the primary diagnosis and the DBR ranged from 12 to 84 months (median: 30).

The tumor, patient characteristics, and the follow-up outcomes for the seven patients (7/270) diagnosed with incidental positive IMLNs are summarized in **Table 1**. The original tumor site involved the medial quadrants of the breast in nearly 86% (6/7) patients with concurrent disease in the axilla also present in 86% (6/7) at their initial presentation. One patient showed signs of IMLN disease progression at 16 months with subsequent chest wall involvement despite adjuvant chemotherapy. Subsequently, she underwent palliative resection and reconstruction using sternal plates and pectoralis major muscle flap to control symptoms (fungation and pain) and improve quality of life. However, one patient died 14 months later due to systemic disease

progression within the follow-up period (**Fig. 4**). A second patient presented with stable bony metastases at 32 months with no evidence of disease progression at 55 months follow-up. The follow-up period ranged from 3 to 84 months (mean: 42) for the involved IMLN patients.

Discussion

IMLN metastases in breast cancer can occur at multiple levels; however, the most commonly encountered site in is the second or third intercostal space.¹⁵ The involvement of the IMLN at primary presentation is 3%^{16,17} whereas the recurrence rate is 0.1 to 1.5%.^{14,15,18} Clinical and radiological presentations vary from asymptomatic which could be incidentally found on CT scan during routine follow-up as a localized lump within the chain with or without musculoskeletal erosion or symptomatic

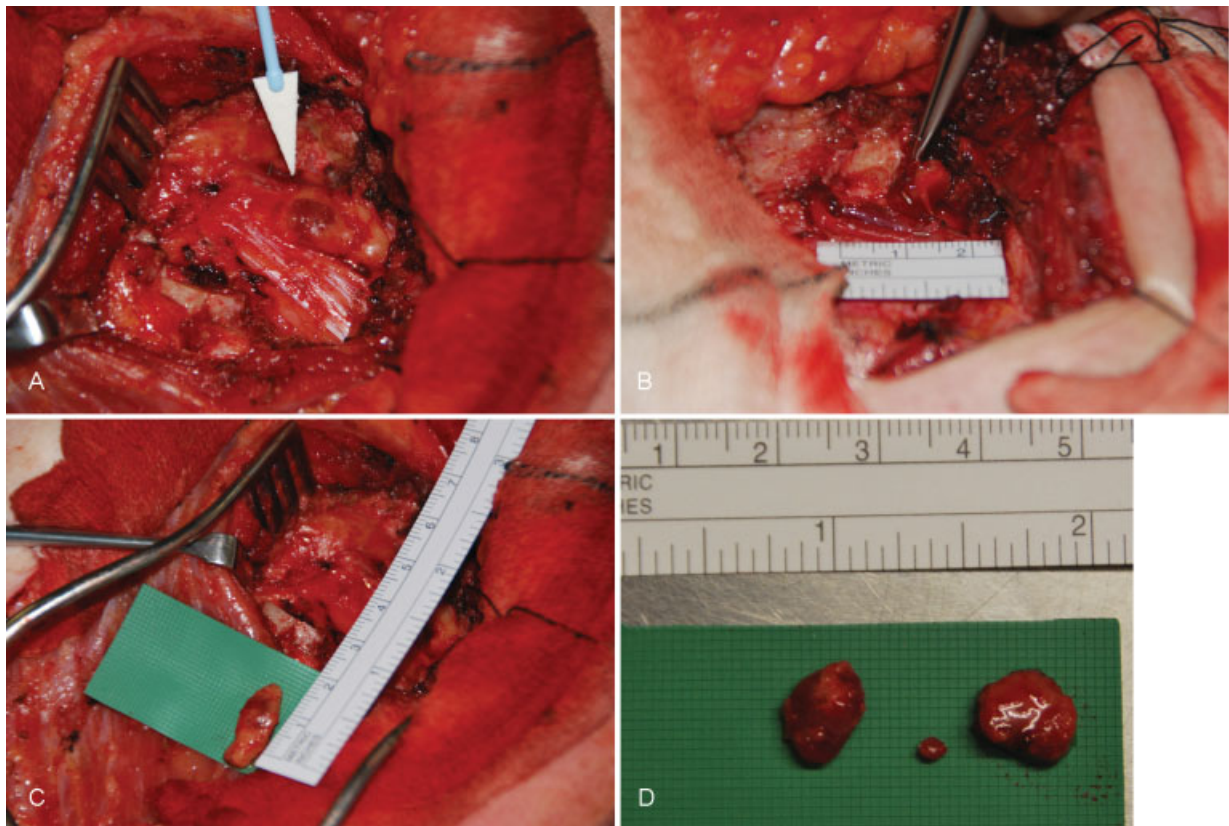


Fig. 3 (A) Intraoperative picture showing an incidental enlarged internal mammary lymph node (IMLN) within the perivascular fat of internal mammary vascular pedicle (recipient vessels) in the third intercostal space during the preparation for microvascular tissue transfer for breast reconstruction. (B) Intraoperative picture demonstrating the dissection of the IMLN with isolation and ligation of its vascular pedicle. (C) Intraoperative picture postretrieval of a 1 cm enlarged IMLN. (D) Intraoperative photo revealing multiple retrieved IMLNs with different sizes which could be occasionally encountered.

including sternal or parasternal swelling with concomitant pain or skin involvement including ulceration and fungation.^{15,19} IMLN metastasis is an important prognostic factor in breast cancer patients^{2,20,21}; however, concerns over accessibility, morbidity, and survival benefit from IMLN biopsy and dissection have contributed to poor uptake of this technique and lack of consensus regarding the most appropriate or effective forms of investigation and treatment in this group of patients.^{13,22,23} Even with the use of preoperative lymphoscintigraphy, the detection rates were only 25%,^{11,16,24} with even a lower successful biopsy rate (14%). Microvascular tissue transfer for breast reconstruction is considered the gold standard, and using the IMVP as the recipient pedicle serves a perfect setting for harvesting the IMLN without any additional morbidity.^{7,23,25-27} The outcome of our series correlates with these previously published studies in which 30% of the patients had enlarged incidental IMLN harvested of 83/270 (30.7%) with no additional morbidity. The IMLN metastases are considered forerunner for distant metastases and surrogate of systemic disease, hence the requirement of adjuvant systemic therapy.¹⁴ Historically, the routine dissection of IMLN has not been universally recommended due to the failure to demonstrate any survival benefit.^{28,29} On the other hand, several studies have demonstrated a significant statistical improvement in locoregional control and overall survival with systemic che-

motherapy and radiation to the IMLN chain.^{7,23,25-27,30} In our study, seven patients showed positive IMLN for metastasis, which respectively has had an impact on the overall treatment plan that included either adjuvant chemotherapy or locoregional targeted radiotherapy, highlighting the clinical value of incidentally detected positive IMLN, which has been reported consistently in previous studies.^{7,23,25-27} Within the follow-up period, six of these patients are still alive with no evidence of locoregional or distant metastasis, whereas one patient showed signs of disease progression despite adjuvant chemotherapy. Radiological evidence reported in the literature did show enlarged IMLN predominately detected in the second and third intercostal spaces; however, it can span from the first to fourth intercostal space.^{15,30} From the practical therapeutic point of view, the number of intercostal spaces involved did not have an impact on the locoregional control.³⁰ Similarly, the vast majority of the surgically encountered IMLNs were harvested from the second and third intercostal spaces after resecting the third costal cartilage.^{7,23,25-27} Zhang et al reported an overall incidence of 14% (112/809) of involved IMLN in advanced breast cancer by ultrasound (US) at their initial presentation. Biopsy of the IMLN was not routinely performed as most of his patients had simultaneously confirmed metastases in the axillary and supraclavicular region.³⁰ Nevertheless, 10/112 (9%) did undergo fine-needle aspiration cytology (FNAC),

Table 1 Patient and tumor characteristics for patients diagnosed with incidental positive IMLN

Case	Age and menopausal status	Diagnosis at the time of reconstruction	Previous treatment	Reconstruction timing, primary diagnosis (months)	IMLN Histopathology Diagnosis	Concurrent disease (clinical, CT staging)	Subsequent treatment	Follow-up from reconstruction and disease-free interval	Survival
1	41 y, premenopausal	Adenocarcinoma, 31 mm, ER-ve, PR-ve, HER2-ve, +ve ALND 3/12 +ve LV invasion Tumor site: UOQ left breast	Mastectomy + ALND + chemotherapy + radiotherapy	Delayed, MSTRAM type II (30 mo)	One node +ve metastatic adenocarcinoma (Macrometastases) 10 × 20 mm with extracapsular spread	Follow-up CT scan (hilar lymphadenopathy)	Chemotherapy, no response to disease progression at 16 mo with ulceration and fungation of skin Palliative chest wall resection and reconstruction followed by second-line chemotherapy	14 mo Systemic disease progression with mortality	Dead
2	48 y, postmenopausal	Multifocal IDC, 32 mm, ER +ve, PR +ve, HER2-ve +ve ALND 1/15 +ve LV invasion Tumor site: LIQ	Mastectomy+ ANC+ Chemotherapy + Radiotherapy + Hormonal treatment	Delayed, MSTRAM type II (37 mo)	One node +ve IDC (Macrometastases), 10 × 5 mm with extracapsular spread	No	Second-line chemotherapy + hormonal treatment	38 mo Disease-free	Alive
3	56 y, postmenopausal	ILC + DCIS, 60 mm, grade II, ER +ve, PR +ve, HER2-ve, +ve ALND 13/16 -ve LV invasion Tumor site: central	Neoadjuvant chemotherapy	SSM + ALND + immediate MSTRAM type I (5 mo)	One node +ve ILC (macrometastases) 15 mm	No	Radiotherapy (chest wall, internal mammary chain, and supraclavicular region) Hormonal treatment	55 mo Disease progression (iliac and rib bony metastases)	Alive
4	33 y, premenopausal	IDC + DCIS, 45 mm, grade III, ER +ve, PR +ve, HER2-ve +ve ALND 3/10 -ve LV Tumor site: central and LIQ	Mastectomy + ALND Chemotherapy Radiotherapy Hormonal therapy	Delayed (19 mo)	One node +ve IDC (micrometastases) 10 mm	No	Second-line chemotherapy + hormonal treatment	28 mo Disease-free	Alive
5	52 y, postmenopausal	IDC, 60 mm, grade II, ER +ve, PR +ve, HER2-ve, +ve ALND 13/16 -ve LV Tumor site: central + medial quadrant	Mastectomy + ALND Chemotherapy Radiotherapy Hormonal therapy	Delayed, MSTRAM type I (22 mo)	One node +ve (macrometastases) 8 mm	No	Second-line chemotherapy Hormonal treatment	34 mo Disease-free	Alive
6	50 y	ILC + LCIS, 50 mm, grade II, ER +ve, PR +ve, HER2 +ve -ve standalone axillary SLNB Tumor site: central	Previous standalone SLNB (-ve)	SSM, immediate MSTRAM type I	Micrometastases 9 mm	No	Radiotherapy (chest, internal mammary chain, and supraclavicular region) Chemotherapy hormonal therapy	14 mo Disease-free	Alive
7	49 y	IDC, 30 mm, grade III, ER +ve, PR +ve, HER2-ve +ve ALND 5/14 -ve LV invasion Tumor site: LIQ	Mastectomy + ALND Chemotherapy Radiotherapy Hormonal therapy	Delayed, MSTRAM II (60 mo)	Macrometastases + invading intercostal muscle with extranodal spread	No	Hormonal therapy only	10 mo Disease-free	Alive

Abbreviations: ALND, axillary lymph node dissection; CT, computed tomography; DCIS, ductal carcinoma in situ; ER, estrogen receptor; HER, herceptin receptor; IDC, invasive ductal carcinoma; ILC, invasive lobular carcinoma; IMLN, internal mammary lymph node; LCIS, lobular carcinoma in situ; LIQ, lower inner quadrant; LV, lymphovascular invasion; MSTRAM, muscle-sparing mastectomy; UOQ, upper outer quadrant; progesterone receptor; SLNB, sentinel lymph node biopsy; SSM, skin-sparing mastectomy.

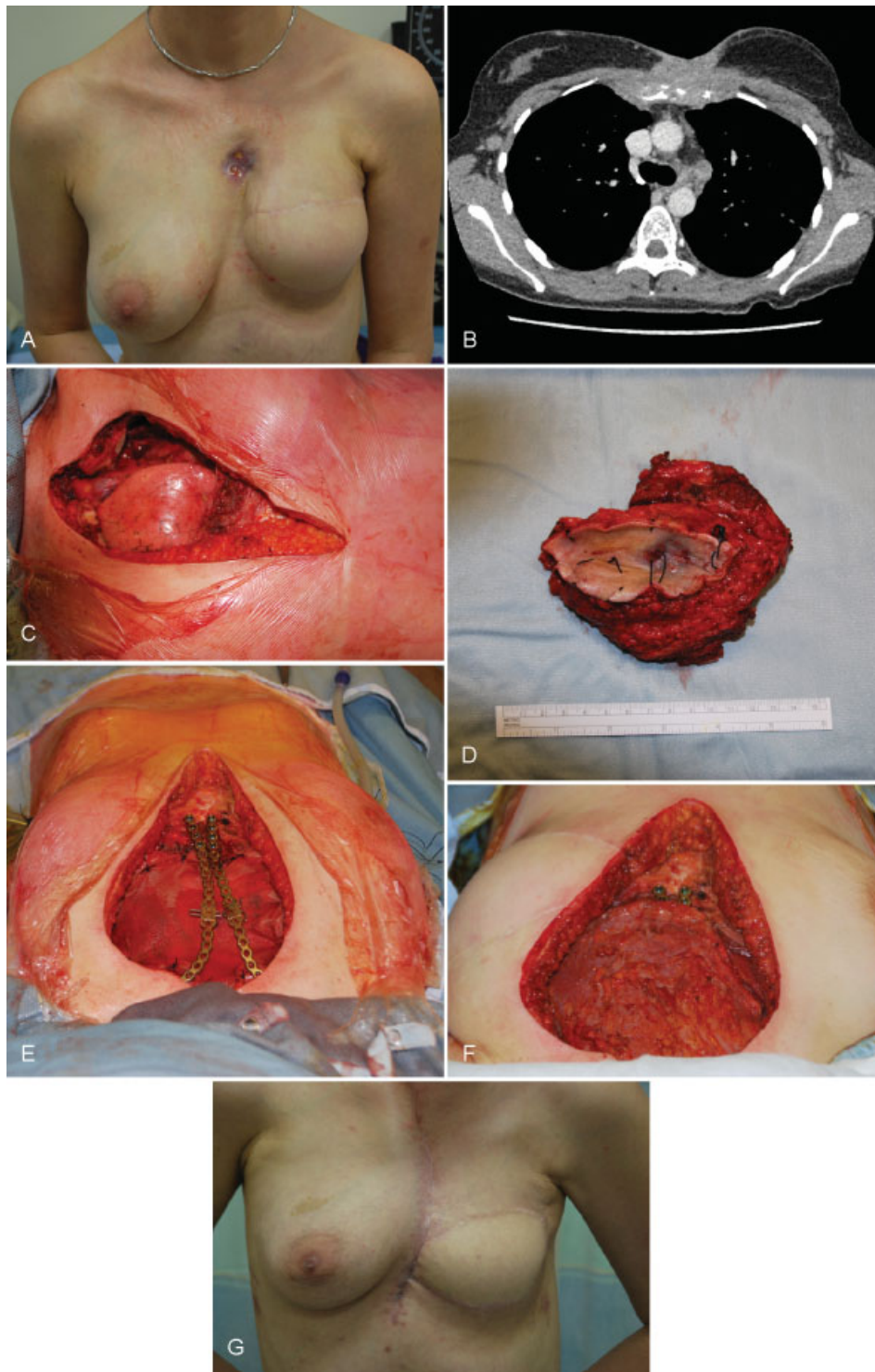


Fig 4 (A) Preoperative picture showing a triple-negative breast cancer patient who underwent mastectomy and delayed reconstruction with free muscle-sparing transverse rectus abdominis myocutaneous (MSTRAM) muscle with an incidental finding of positive malignant internal mammary lymph node (IMLN) during dissection of the internal mammary vascular pedicle. Despite postoperative chemotherapy, disease progression occurred 16 months later with ulceration/skin breakdown discharge and intractable sternal pain. (B) Computed tomography (CT) scan image showing IMLN mass invading the sternum and the adjacent costochondral junctions. (C) Intraoperative picture showing the extent of palliative resection including near total sternectomy and bilateral adjacent costochondral junction with exposure of the intrathoracic contents. (D) Intraoperative picture showing the pathological specimen post en bloc resection. (E) Intraoperative picture showing skeletal chest wall reconstruction achieved with sternal titanium plates + polypropylene mesh. (F) Intraoperative picture showing soft tissue achieved with unilateral left rotational pectoralis major muscle flap followed by primary closure. (G) Post-operative picture (5 months) with complete healing of the sternal wound with primary intention and despite the resection the vascularity of the free MSTRAM flap appeared not to be jeopardized.

representing the rare group of patients who had suspicious IMLN metastases as the only regional nodal involvement. Their study had too few IMLN metastases detected on CT or PET scan, and it was difficult to compare their sensitivity to that of the US, which was proven to be sensitive and cost-effective. Comparatively, worldwide, the majority of the performed breast reconstructions are implant-based³¹; however, they would not benefit from the advantage of surgical accessibility of the IMLN basin. Therefore, radiological investigations depending on the available expertise, including US, CT/PET scan, magnetic resonance imaging (MRI), lymphoscintigraphy, and radiological guided FNAC or biopsy, would be a reasonable approach to assess the IMLN basin without any additional morbidity. That is to provide more accurate staging for therapeutic purposes, especially in medial breast cancers and high-risk patients.^{29,30} In our study, 3/75 (4%) staging CT scans showed incidental isolated enlarged IMLN, and following our algorithm, subsequent PET/CT scan determined whether a biopsy would be required or not. Cold spots are regarded negative, and those patients would proceed for breast reconstruction as they would be considered nonmetastatic. On the other hand, warm or hot spots underwent CT-guided biopsy and mediastinoscope, which was negative for metastasis in all three patients. If IMLN biopsy had turned out to be positive, then these patients would have been candidates for multimodality adjuvant chemoradiotherapy, and the reconstruction would have deferred to a later stage. Emerging evidence has demonstrated that patients with positive IMLN who were managed with multimodality treatment had more than 50% disease-free survival and acceptable rates of locoregional control at the IMLN basin.³⁰ This correlates with our findings as 2/7 patients (28%) with positive metastatic IMLN showed signs of disease progression despite multimodality treatment.

Reconstructive surgeons play an important role in treating patients with chest wall involvement facilitating chest wall resection (CWR) and immediate reconstruction in terms of managing pain control, skin involvement, and preventing uncontrolled tumor growth, thereby optimizing long-term outcomes and quality of life in this group of patients. Surgery is considered the cornerstone in isolated locoregional metastases as the effectiveness of chemotherapy and/or radiotherapy as a first line remains unclear.^{32,33} In this study, one patient who previously underwent free MSTRAM for DBR and was proven to have an incidental positive IMLN required palliative CWR and reconstruction with sternal plates and pectoralis major muscle to control locoregional IMLN recurrence 2 years later. Observation from previously published reports demonstrated that proximate collaboration between several disciplines with a multidisciplinary thoracic oncoplastic approach is of paramount importance in devising a comprehensive and safe outcome for this challenging group of patients.^{34,35} Few studies reported a strong relationship between tumor location and the lymphatic drainage, with medial tumors lymphatic drainage been higher to IMLN^{1,34}; however, it was not emphasized by other studies.^{9,32} This has led to an ongoing debatable issue that patients with medially located tumors are understaged and receive inadequate oncological treat-

ment.^{36–38} It is worth noting that 88% (6/7) patients presented initially with medial tumors. Endorsement of a proposition plan for diagnosis and management of IMLN metastases remains an undetermined multidisciplinary dilemma, which emphasizes the role of microvascular surgeons to exuviate a better understanding on the natural course and implications on treatment and outcomes. There are limitations to this study. This is a single-institution retrospective study design with a relatively small number of patients with positive IMLN and radiologically detected enlarged IMLN on prereconstruction CT scan staging, possibly as a result of the rarity of the presentation. This may indicate that the cohort is underpowered to achieve any statistical results. Furthermore, more studies are required to objectively highlight the indications for prebreast reconstruction radiological investigations as there is no actual consensus to date for performing preoperative radiological based staging in patients undergoing IBR or DBR.

This study is driven to imperatively emphasize the significance of correlating the clinicopathological and radiological features, focusing on the importance of sampling any incidentally enlarged IMLN encountered during microvascular tissue transfer using the IMVP for breast reconstruction and performing preoperative CT scan staging prior to breast reconstruction, especially in high-risk patients and medial tumors. Eventually, this will enable better assessment of the IMLN basin, especially with the growing evidence of the impact of IMLN metastases in determining a comprehensive oncological treatment plan including chemotherapy, radiotherapy, and CWR with reconstruction.

Note

Part of this work has been presented as an oral presentation in the Association of Breast Surgery Meeting, 2015, Bournemouth, United Kingdom, with the abstract published in the official journal, *European Journal of Surgical Oncology*, June 2015, Vol.41(6):55–58.

Conflict of Interest

None.

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