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An evaluation of incidental metastases to internal mammary lymph nodes detected during microvascular abdominal free flap breast reconstruction☆

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Summary *Background:* The significance of internal mammary lymph nodes (IMLNs) encountered during dissection of internal mammary vessels (IMVs) for microvascular free flap breast reconstruction (FFBR) remains uncertain. We report our experience with the opportunistic harvest of IMLNs during FFBR. Therapeutic implications and patient outcomes are explored.
Methods: All IMV anastomoses for delayed (DBR) or immediate breast reconstruction (IBR), between 1997 and 2009 were recorded. Opportunistic IMLN harvests were identified and patient characteristics and outcomes recorded from review of case records.
Results: Of the 293 FFBRs, 43 patients had 46 IMLNs harvested during 20 immediate and 26 delayed FFBRs. Six patients had positive nodes (4 IBR and 2 DBR), and were offered post operative chemotherapy. Four received radiotherapy to the internal mammary chain. Three of the four IMLN+ve IBR patients have died of metastatic disease at 23, 33 and 55 months after reconstruction. The two IMLN+ve DBR patients were alive at 4 and 20 months.
Discussion and Conclusion: Although routine biopsy of IMLNs for staging in breast cancer is not

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standard practice, if identified during IMV recipient site preparation for microvascular anastomosis, opportunistic biopsy should be performed due to the additional staging information provided and subsequent effect upon the predicted prognosis.

Introduction

Microvascular free tissue transfer is considered the gold standard for autologous tissue breast reconstruction.[1] The internal mammary vessels (IMVs) are an increasingly used recipient site for microvascular anastomosis.[2] In our institution the preferred methods of autologous reconstruction are deep inferior epigastric perforator (DIEP) flap or muscle-sparing transverse rectus abdominis myocutaneous (ms-TRAM) flaps, with anastomosis to the IMVs.

Isolation of the IMVs during free flap breast reconstruction (FFBR) occasionally results in the incidental identification of enlarged internal mammary lymph nodes (IMLNs) which can then be easily removed. Three previous studies have reported opportunistic IMLN biopsy in 13/98 delayed breast reconstructions (3 contained metastasis),[3] 11/54 mixed reconstructions (1 contained metastasis)[4] and 25/232 mixed reconstructions (5 of which contained metastases).[5]

We report our institution's experience with opportunistic IMLN biopsy, and its impact on the oncological management of the patients.

Methods

All patients who underwent immediate or delayed free flap breast reconstruction for breast cancer between 1997 and 2009 at Addenbrooke's University Hospital, Cambridge were identified from the unit's audit database. Patients who had IMLN biopsy were then identified from the histology database and clinical and pathological data were retrospectively collected.

Exposure of the IMVs required resection of the medial 2–3 cm of the 3rd costal cartilage. When obvious lymph nodes were encountered, these were harvested and submitted for histological examination. All IMLN pathology slides were reviewed by a single histopathologist (EP) to verify the accuracy of the diagnosis, to identify possible causes for 'enlargement' of the lymph node, and to remeasure lymph node size. As well as the outcome of IMLN histology, patient details, tumour characteristics, axillary nodal staging, adjuvant treatment, and patient and flap outcomes were recorded.

Axillary staging was performed as per the standard protocol; prior to 2006 this consisted of a level II axillary lymph node dissection for invasive cancers. This changed in early 2006 to sentinel lymph node biopsy (SLNB) using blue dye and isotope for axillary staging for T1 and T2 tumours, with subsequent axillary dissection for patients with involved SLNB. SLNB is undertaken as a day case procedure before definitive surgery, with axillary clearance at the time of mastectomy and reconstruction if required.

Results

Between 1997 and 2009 a total of 293 free DIEP and TRAM flap breast reconstructions were performed (196 immediate and 97 delayed) by two reconstructive plastic surgeons. Internal mammary lymph nodes (IMLNs) were encountered in 43 patients, 19 during immediate breast reconstruction (IBR) and 24 during delayed breast reconstruction (DBR). A single node was removed in 40 patients. The remaining 3 patients had 2 nodes harvested each.

The median age of patients was 48.2 years, (47.2 for IBR and 50.0 for DBR). In the delayed reconstruction group, the median time between primary diagnosis and surgery was 33 months (range = 11–154). In the immediate group, 4 of 19 patients were confirmed to have IMLN metastases histologically (21%) compared to 2 of 24 patients (8.3%) in the delayed group. In the IBR internal mammary node positive group, two of the four mastectomies were performed for recurrence in breasts previously treated with breast conservation.

The treatment for positive IMLNs was radiotherapy to the chest wall and IMLN chain in four patients found to have metastases, with two of these patients also receiving radiotherapy to their supraclavicular fossae. Of the remaining two patients, one received chemotherapy alone and the other received endocrine therapy alone. Although one patient has been lost to follow-up (moved abroad) the remaining three patients with positive IMLN in the IBR group have died after survival of 23, 33 and 55 months, versus none in the negative biopsy group. The tumour and nodal characteristics, treatments and outcomes in the positive patients are summarised in Table 1.

In the 37 IMLN-negative patients, 38 lymph nodes (LNs) were excised. Five LNs had silicone granulomas from previous implant-based breast reconstructions whereas the remaining 33 nodes showed reactive changes only. There were no significant macroscopic differences between the metastatic and the non-involved nodes. Of the seven positive IMLNs (in 6 patients), 6 contained macrometastases (three were completely replaced by tumour). The seventh node contained a micrometastasis; this was one of two nodes from the same patient, the second of which was completely replaced by tumour.

Discussion

Free abdominal flap breast reconstruction is a standard reconstructive technique that is associated with superior aesthetic results when compared to pedicled flaps. Microvascular anastomosis of the free flap to the internal mammary vessels (IMVs) has many advantages over the thoracodorsal pedicle, and gives the surgeon an excellent

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Table 1 Summary of treatment implications and outcomes in patients with positive IMLNs during abdominal free flap breast reconstruction.

Case	Age (yrs)	Diagnosis at reconstruction	Recon timing	IMLN		Previous treatment	Subsequent treatment	Recurrence and treatment post reconstruction	Survival	Follow-up from recon (months)
				No. biopsied (+ve)	Maximum ø; metastasis size (mm)					
1	38	Prophylactic Lt mastectomy − fibrocystic change only LN − metastatic carcinoma with similar histological features to original tumour	DBR (Rt) IBR (Lt) DIEP	2 (1)	1) 12; 12 2) 5; 0 No metastasis	- WLE (4 mm, UIQ GIII IDC, ER+, HER2−, PG−, LVI−, high grade DCIS) and SLNBx (−ve) 12 months previously - Completion mastectomy	6/52 post reconstruction: AD − 0/20 nodes involved - Cytotoxic chemotherapy - Chest wall and SCF radiotherapy	Nil	Alive	20
2	54	20 mm, UIQ GIII IDC, ER−, HER2−, PG-R−, LVI−. 0/1 nodes involved	IBR TRAM	2 (2)	1) 5; 0.6 Micro-metastasis 2) 6; 6	- WLE + AD (15 mm, GII IDC. 4/6 nodes involved) 7 yrs 5 m previously - Cytotoxic chemotherapy - Chest wall radiotherapy	- Cytotoxic chemotherapy	12 months: Contralateral axillary recurrence; GIII IDC with necrosis, PR+. Multiple gross axilla LN Rx: • Radiotherapy to axilla and SCF • Third line endocrine therapy	Alive	20 (lost to follow-up)
3	48	26.5 mm, UOQ GIII IDC, ER+, HER2−, PG−, LVI−, high grade comedo DCIS	IBR DIEP	1 (1)	18; 11	- WLE + AD (10 mm, GIII IDC. 0/14 nodes involved) 6yrs 11 m previously - Cytotoxic chemotherapy - Chest wall radiotherapy	- Cytotoxic chemotherapy - IMLN radiotherapy	19 months: Multiple bony, liver, lung and skull base metastases Rx: • Palliative treatment	Dead	23
4	62	90 mm, OQ GII ILC, ER−, HER2+, PG−, LVI+, high grade DCIS. 13/14 nodes involved	IBR TRAM	1 (1)	5; 5	Nil	- Cytotoxic chemotherapy - IMLN, chest wall and SCF radiotherapy - Endocrine therapy	24 months: Multiple brain metastases Rx: • Palliative treatment	Dead	33

(*continued on next page*)

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Table 1 (*continued*)

Case	Age (yrs)	Diagnosis at reconstruction	Recon timing	IMLN		Previous treatment	Subsequent treatment	Recurrence and treatment post reconstruction	Survival	Follow-up from recon (months)
				No. biopsied (+ve)	Maximum ø; metastasis size (mm)					
5	33	73 mm, UOQ GIII IDC, ER−, HER2−, LVI+, high grade comedo DCIS. 19/24 nodes involved	IBR TRAM	1 (1)	5; 4	Nil	- Cytotoxic chemotherapy - IMLN and chest wall radiotherapy	47 months: Cervical and parotid LN metastasis. Developed multiple cerebral metastases. Rx: Palliative treatment	Dead	55
6	62	LN − 4 mm, well differentiated, ER+ metastatic adenocarcinoma	DBR DIEP	1 (1)	14; 4	- Mastectomy + AD (16 mm, LOQ GII IDC, ER+, HER2−, PG−, LVI−, intermediate grade DCIS. 2/14 nodes involved) 23 m previously - Cytotoxic chemotherapy - Endocrine therapy - Chest wall radiotherapy	Second line endocrine therapy	Nil	Alive	4

AD − Axillary dissection, DCIS − Ductal carcinoma *in situ*, DIEP − Deep inferior epigastric perforator, ER − oestrogen receptor, G − grade, HER2 − Human epidermal growth factor receptor 2, IDC − Infiltrating Ductal Carcinoma, ILC − Infiltrating Lobular Carcinoma, LVI − lymphovascular invasion, LOQ − lower outer quadrant, OQ − outer quadrants, PR − progesterone receptor, Rx − treatment, SCF − supraclavicular fossa, SLNBx − sentinel lymph node biopsy, TRAM − transverse rectus abdominis myocutaneous, UIQ − upper inner quadrant, UOQ − upper outer quadrant, ø − diameter.

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opportunity to harvest visible internal mammary lymph nodes (IMLNs) between the second and fourth ribs without an additional procedure.[6–8] This is the most frequent site for positive internal mammary sentinel lymph node (IM SLN) biopsy with 77% found in the 3rd intercostal space.[9]

The primary site for nodal metastasis in breast cancer is the axilla followed by the IMLN.[10] Although the importance of IMLN metastasis has long been established,[11] routine IMLN dissection was abandoned after studies failed to show significant survival benefit of Halsted mastectomy with IMLN dissection over Halsted mastectomy alone where no adjuvant chemotherapy or radiotherapy was given.[12] Management of IMLNs has since been a matter of great debate with little consensus regarding the most appropriate or effective forms of investigation or treatment.[13,14]

Where IMLN biopsy is performed as part of management, IMLNs have been reported as the primary site of nodal metastasis in up to 7% of patients.[9,15,16] Paredes et al. performed IMLN biopsy in 32/391 patients, with subsequent upstaging of disease in 5 of these, and Veronesi et al. showed involvement in 68/663 cases with upstaging of 17 patients.[16,17] IMLN metastasis is associated with increasing tumour size, peritumoural vascular invasion and axillary metastases but is unaffected by tumour grade or receptor positivity.[16]

The presence of IMLN metastasis is an indicator of a poorer prognosis in women with breast cancer independent of axillary lymph node positivity.[10,11,18,19] In axillary node-negative breast cancer, positive IMLNs convey a 2-fold greater risk of recurrence or death at 10 years compared to negative IMLNs.[10] In contrast, however, Veronesi et al. suggested that IMLN involvement alone had a similar prognostic value as axillary metastasis alone in a 10-year survival follow-up study.[16]

Although there is no proven survival advantage in performing elective IMLN dissection,[12] evaluating IM SLNs provides more accurate staging of patients,[16] such that if sampling is not performed, patients may be under-staged.[10] Radiotherapy may improve local disease control for IMLNs and thus prolong the disease-free interval or overall survival, especially if combined with chemotherapy.[14,16,18]

The optimal timing of radiotherapy, whether as an adjuvant or neoadjuvant therapy, is unclear with pros and cons for both treatment options.[20] With regards to scenarios encountered by reconstructive plastic surgeons, adjuvant radiotherapy affects the quality of the reconstruction, and may cause flap contraction, shrinkage and hyperpigmentation to variable degrees,[20,21] but its effect on the microvascular anastomoses if given to the IMLN chain is unknown. On the contrary microvascular reconstruction after neoadjuvant radiation therapy, if administered to the chest wall, may be problematic as the vessels may be friable or sclerosed (especially the artery) and thus are not ideal for microvascular anastomoses.[22] However, this finding is contrary to our unit's experience.[23,24]

Whether or not to perform IMLN biopsy has been the subject of recent discussion.[13,16] However, surgical sampling and histological analysis remains the best way to identify micrometastases in LN chains. Imaging methods, such as lymphoscintigraphy have demonstrated variable isotope drainage to the IMLN, between 4% and 41%.[9,16,17,25] Patients with inner quadrant tumours, especially lower quadrant, predominately drain to the IMLNs, and it has been suggested that this patient group should therefore be particularly considered for IM SLN biopsy.[26] Yao et al. assessed 5-year prognosis based on IMLN drainage and found an almost three-fold increase in mortality risk in axillary node-positive patients with IMLN drainage.[25] Major barriers to the routine use of this technique are difficult access and potential morbidity associated with IMLN biopsy.[27]

In our study we found IMLN metastasis in 6 patients, similar to published series. Two patients (both undergoing IBR) had very extensive axillary nodal involvement (>9 positive nodes each) and it is unlikely that the information from IMLNs significantly altered the course of their diseases. The two other IBR patients had had previous breast conservation treatment for cancer in the ipsilateral breast and had been disease-free for over six years before presentation; since reconstruction, one went on to develop contralateral recurrence after 12 months and the other developed extensive systemic metastases after 19 months. The finding of IMLN metastatic disease during two delayed reconstructions after completion of treatment dramatically altered the management of these patients with one patient receiving both chemotherapy and radiotherapy and the other, endocrine therapy alone.

The suitability of major reconstructive procedures may be called into question in patients with extensive disease, for example, patients 4 and 5 in Table 1. However, in our opinion there are few exclusion criteria for offering IBR due to its well documented psychological advantages.[1,28,29] In our unit, contraindications would include the presence of visceral metastases or severe co-morbidities making the patient unsuitable for prolonged surgery.[23]

IMLN biopsy currently does not form part of the routine assessment of patients with breast cancer. Our study identified 6 patients with IMLN metastases. The information from IMLNs altered therapeutic decisions in a single patient in whom axillary nodal staging was not available due to previous axillary dissection. Our findings did not contradict the current practice of excluding IMLN from routine staging of breast cancer. However, opportunistic biopsy of these nodes during IMV dissection can be achieved with minimal additional morbidity. We therefore advocate that surgeons should remain aware of these nodes during IMV exposure, and any nodes identified should be removed and submitted for histology. The nature of this study precludes the calculation of the incidence of positive IMLNs and we do not support extending or prolonging IMV dissection in order to specifically identify such nodes.

Conflict of interest

None.

Sources of funding

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