FEASIBILITY OF THE INTERNAL MAMMARY LYMPH NODE FLAP AS A VASCULARIZED LYMPH NODE TRANSFER: A CADAVERIC DISSECTION STUDY

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Background: We performed cadaveric dissections to examine the feasibility of an internal mammary-based lymph node flap as a donor site for vascularized lymph node transfer. *Methods*: Internal mammary vessels and adjacent nodes were dissected in ten fresh cadaver specimens. Surgeon inspection and palpation identified the number of nodes in the specimen. Specimens were examined macro- and microscopically by a pathologist for correlation of lymph node counts. Kappa statistic correlated surgeon- and pathologist-reported node counts. *Results*: Surgeon- and pathologist-reported node counts were moderately correlated (kappa 0.57). Inspection and palpation correctly predicted node presence or absence in 80% of specimens. Sixty percent of flaps contained between 1 and 3 nodes, with a mean of 2.0 nodes when nodes were present. *Conclusions*: Inspection and palpation predicts the presence or absence of nodes in 80% of flaps. Nodes were present in 60% of internal mammary-based flaps, and one to three nodes can be transferred. © 2015 Wiley Periodicals, Inc. Microsurgery 00:000–000, 2015.

Lymphedema is a devastating complication of surgical treatment for breast cancer estimated to affect up to 40% of women having axillary lymph node dissection and 3% of women having sentinel lymph node biopsy.[1] Systematic reviews with pooled data from 30 studies have shown that 21% of all women who survive breast cancer will develop lymphedema.[2] Nearly 1.4 million women are diagnosed with breast cancer worldwide each year. Annually, over 295,000 women will receive a new diagnosis of arm lymphedema.[2] The rate of lymphedema diagnosis rises steadily in the first two years after surgery, and new cases can be diagnosed five years from surgery and beyond.[2–4]

Body image disturbance is common among women with lymphedema. Breast cancer patients with lymphedema are known to have significantly lower quality of life scores than breast cancer patients without lymphedema.[5] In a qualitative study, one lymphedema patient was quoted as saying "Cancer changed me for a short time. Lymphedema changed me for the rest of my life."[6]

There are many recognized risk factors for lymphedema, including increased body mass index, mastectomy, and breast cancer metastatic to the axilla.[4] Axillary lymph node dissection is recognized as one of the most important risk factors,[2] as it removes the entire nodal basin draining the upper extremity. Vascularized lymph node transfer (VLNT) is a surgical intervention for lymphedema which has recently experienced a resurgence. This free-flap based technique brings a vascularized packet of lymph nodes from a distant site to replace lymph nodes removed during oncologic extirpation.

Regardless of the donor lymph node site, many patients have fewer infections, decreased limb circumference, and can discontinue lymphedema therapy after VLNT.[7–12] As improvements with lymphedema severity have been achieved with many different vascularized lymphatic packets, the challenge remains to identify which donor site is most acceptable. An ideal donor site would leave minimal or no scar, would not place additional critical structures at risk, and would not needlessly transect named vessels.

To our knowledge, the internal mammary lymph node chain has not previously been used as a donor site for VLNT. The internal mammary vessels are familiar to reconstructive microsurgeons as a common recipient vessel for free flap breast reconstruction. Importantly, an internal mammary-based flap could be harvested through a standard approach for microvascular breast reconstruction, and would be based on vessels otherwise transected during that operative procedure. Thus, no additional donor site scar or vessel morbidity would be incurred by flap harvest. Here, we provide an anatomic and microscopic description of the internal mammary lymph node flap.

MATERIALS AND METHODS

This study was approved by the University of Pennsylvania's Cadaver and Body Part Operational Committee (Approval # 5387/01). Ten dissections, including five right and five left specimens, were performed in cadavers

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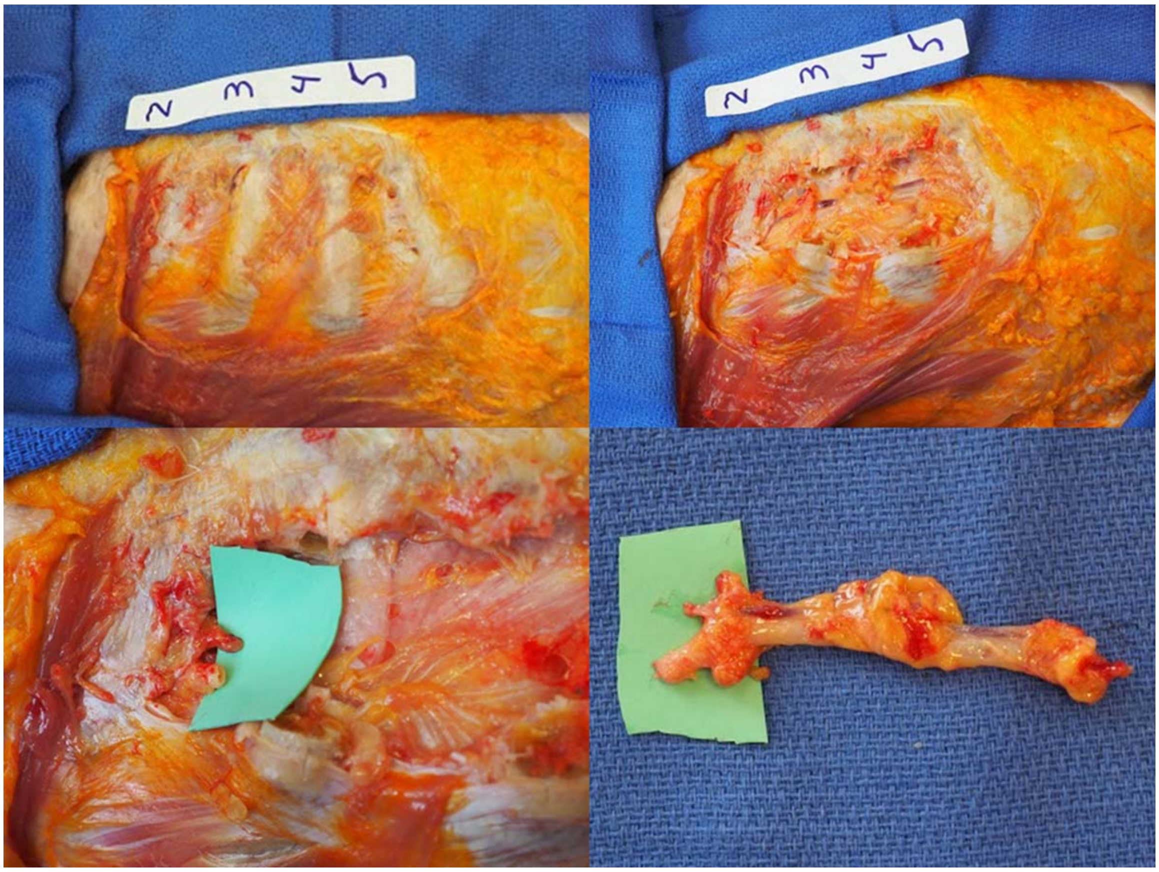

Figure 1. Cadaveric dissection of internal mammary lymph node flap showing removal of the pectoralis major (top left), dissection of the internal mammary vessels and adjacent lymph nodes (top right), 8 mm residual stump of internal mammary artery and vein after flap harvest (bottom left), and harvested internal mammary lymph node flap (bottom right). [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

obtained from an approved vendor (ScienceCare, Denver CO). All cadaveric specimens were females and had no history of surgery on the neck, breast, chest wall, or axilla. Cadavers ranged in age from 70 to 90.

Dissection

The skin overlying the chest wall was removed. The pectoralis major muscle was identified and reflected. A subperiosteal dissection was performed around the cartilaginous portion of the third and fourth ribs. The ribs were then removed using a rongeur, taking care not to violate the posterior perichondrium. The posterior perichondrium and intercostal muscles were incised and reflected medially and the internal mammary vessels were identified deep to these structures. The internal mammary vessels and the adjacent lymphatic tissue and lymph nodes were dissected from the inferior border of the second rib to the superior border of the fifth rib. The specimen, including the internal mammary artery and vein(s) and adjacent lymphatic tissue and nodes was removed, leaving an 8 mm stump of internal mammary vessels superiorly. This was done to simulate the length of internal mammary vessels required for planned free flap anastomoses (Fig. 1). Axillary dissection was performed to identify the thoracodorsal pedicle and its serratus branch.

Vessel and Specimen Quantification

Internal mammary and serratus branch vessels were dissected and transected at clinically appropriate locations. Standard microsurgical instruments were used to prepare and dilate vessel ends. Pedicle vessel size was measured to a 0.5 mm standard using the coupling gauge from a Synovis vein coupling set (Baxter International, Minneapolis, MN). Measurements of specimen length, width, and height were made using a digital caliper (Neiko 01407A, Neiko Tools, USA). These measurements were made to the nearest one tenth of a millimeter.

Lymph Node Quantification

The dissecting surgeon (CJP or SKK) examined the specimen in vivo including inspection and palpation. Surgeon-reported estimate of number of lymph nodes

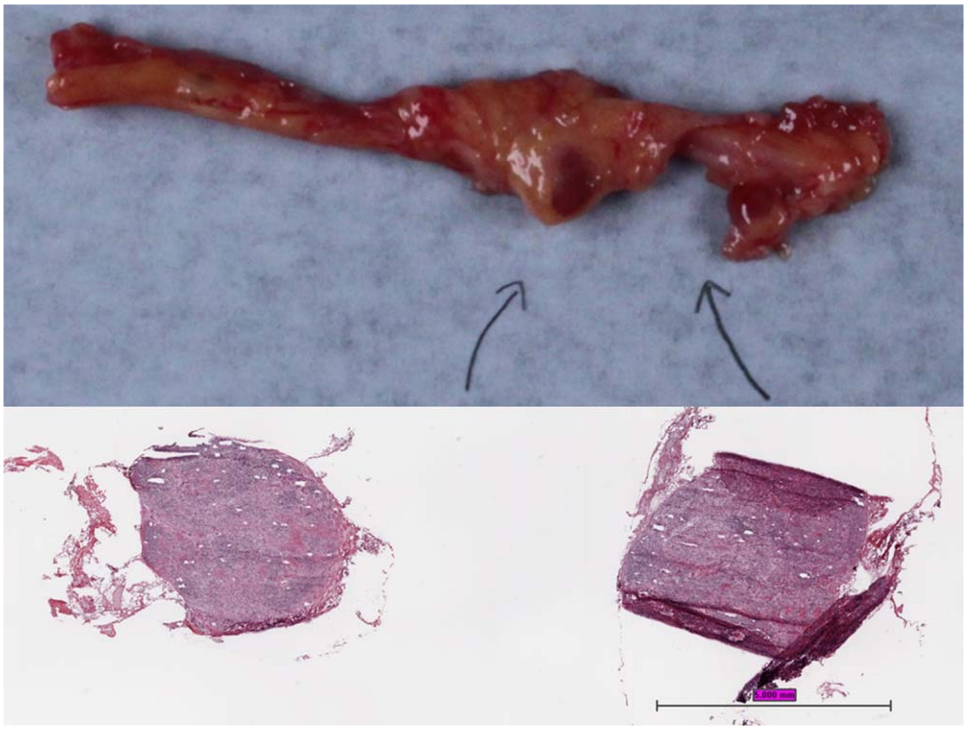

Figure 2. Gross-micro image showing visible lymph nodes within the flap (top, indicated by arrows), and frozen specimen showing lymphoid tissue (bottom). The scale bar is 5.0 mm in length. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

within the specimen was recorded. The specimen was then harvested, labeled individually with cadaver identification number and side, and bagged. Fresh specimens were refrigerated overnight and sent to the Pathology Department at the University of Pennsylvania. There, specimens were weighed and examined for grossly identifiable nodes. Identified nodes were embedded and prepared as frozen sections. Specimens in which nodes were not identified were also embedded in their entirety. Specimens were stained using hematoxylin and eosin. Conventional microscopy was used to examine the frozen sections and perform lymph node counts. After analysis, all labeled specimens were returned to the cadavers from which they had been removed.

Means and standard deviations were calculated for internal mammary and serratus branch vessel diameters. Comparison between internal mammary and serratus branch vessel diameters was made using a *t* test. Kappa statistic examined the correlation between surgeon-reported and pathologist-reported lymph node counts.

RESULTS

The internal mammary lymph node packets averaged 70 mm by 10 mm by 8 mm in size and weighed 1.69 g $\pm$ 0.60 g. Pathologic gross examination and frozen section showed that 60% of specimens contained between 1 and 3 lymph nodes (mean 2.0 lymph nodes when lymph nodes were present). When present, palpable lymph nodes were clustered within the interspace between the second and third ribs (Fig. 2).

Surgeon-reported lymph node counts had moderate correlation with number of nodes identified by gross pathologic analysis (kappa 0.57). Two specimens had both macro- and microscopic nodes present. Surgeon-reported gross lymph node counts were less well correlated with microscopic node counts (kappa 0.46). On the three occasions in which surgeons identified zero lymph nodes in the specimen, no specimen had gross nodes on pathology. Surgeons incorrectly predicted that one lymph node was present when there were actually none in two cases (Table 1).

The serratus branch artery and vein were similar in size to the internal mammary artery and vein at the proximal portion of the flap. Artery diameters for the internal mammary artery and the serratus branch artery were not significantly different (2.67 mm $\pm$ 0.25 mm vs. 2.42 mm $\pm$ 0.37 mm, $P = 0.20$). Vein diameters for the internal mammary vein and the serratus branch vein were not significantly different (2.83 mm $\pm$ 0.51 mm vs. 2.42 mm $\pm$ 0.37, $P = 0.29$).

DISCUSSION

The internal mammary lymph node flap is a small flap in size and weight. When present, a mean of two lymph nodes were routinely identified in the interspace

Table 1. Gross and Frozen Node Counts Stratified by Specimen Number and Side

Specimen ID	Weight (g)	Gross nodes—surgeon	Gross nodes—pathologist	Frozen section macro and microscopic nodes
S141143-R	1.48	2	2	2
S141153-L	1.14	1	0	0
S141191-R	1.54	0	0	3
S141191-L	1.0	1	1	1
S141181-R	1.04	1	1	1
S141181-L	1.81	2	2	2
C140745-R	1.71	0	0	0
C140745-L	2.90	1	2	3
L140681-R	1.87	1	0	0
L140681-L	2.39	0	0	0

between the second and third ribs. We did not routinely identify nodes within the interspace between the third and fourth or fourth and fifth ribs. We found that surgeons can readily identify lymph nodes when present and, importantly, can identify when lymph nodes are not present as well. In 80% of specimens, surgeons correctly predicted the presence or absence of lymph nodes.

The definitive mechanism of VLNT for lymphedema remains unknown. However, shunting of lymphatic fluid into the venous system by the transplanted nodes is a possible mechanism.[13,14] The optimal donor site for VLNT similarly remains unknown. Prior studies have utilized lymph nodes vascularized by the superficial circumflex iliac and superficial inferior epigastric vessels,[7–10,15] the transverse cervical vessels,[11,16] or the facial vessels.[12,14,16] A theoretic risk of donor site lymphedema exists when nodes are harvested from an unaffected axilla or groin, although careful preoperative planning and a "reverse sentinel node technique" can minimize this risk.[12,15] Patients whose flaps are harvested from the groin may develop abnormalities in lymph flow in the donor extremity, although patients do not develop clinically significant lymphedema.[17] Use of a transverse cervical artery-based flap has a visible neck scar and carries a risk of injury to the thoracic duct, so a right sided neck flap is typically used.[11,16] Facial artery-based flaps put the marginal mandibular nerve at risk.[12,14,16]

Lymphovenous bypass techniques may be more effective than VLNT for chronic or long-standing lymphedema.[18] The goal of lymphovenous bypass is to augment lymphatic drainage, ideally using a side-to-end technique, without disruption of existing drainage patterns.[18] End-stage lymphedema can be treated with the Charles procedure.[19] More recent studies have shown that combining the Charles procedure with a VLNT may prevent residual foot lymphedema.[20]

The internal mammary nodal chain has previously been studied.[21,22] Stibbe published an outstanding gross anatomic description of the internal mammary nodes in 1918, based on dissection in 60 cadavers.[22] His findings showed that, on average, four to five internal mammary nodes were present along the internal mammary artery and vein. One or two nodes were found medial to the vessels in the interspace between ribs one and two in 96% of cases and above the first rib in 91% of cases. These interspaces are too high to be easily dissected during the standard approach to recipient vessels during free flap breast reconstruction. However, 78% of specimens had one or two nodes lateral to the vessels in the space between ribs two and three. Inferior to that space, the next node was typically found in the vessel bifurcation near ribs five and six. Stibbe's study approached the entirety of the internal mammary nodal chain from a posterior approach, after the rib cage was removed. Our study builds on Stibbe's gross anatomic description by simulating a surgical approach to the nodes using a limited, one or two-rib resection.

Anatomic knowledge from Stibbe's study, coupled with the results of our dissection study, demonstrate that the most likely location for internal mammary lymph nodes to be found is in the interspace between ribs two and three. Fortunately, the third rib is the rib most commonly removed to access the internal mammary vessels during free flap breast reconstruction. Third rib removal gives access to the internal mammary vessels between the inferior edge of the second rib and the superior edge of the fourth rib. Our findings, as well as Stibbe's dissection study, demonstrate that, when present, nodes are found within the interspace between the second and third ribs. Thus, surgeons can identify and harvest lymph nodes during a standard recipient vessel exposure without needing to remove the fourth rib as we did in our anatomic study.

Previous reports have used multirow-detector CT angiogram[23] and MR angiogram[15] to perform preoperative examinations of the number and location of lymph nodes in a superficial circumflex iliac artery (SCIA)-based groin lymph node flap. A small case–control study has used both CT and MRI to identify internal mammary node size after tissue expander placement.[24] Pre-operative imaging using either CT or MRI could likely quantify the number and location of lymph nodes along the internal mammary chain prior to internal mammary lymph node flap harvest, and would also detect possibly pathologic nodes prior to lymph node transfer. This information would be a useful adjunct to surgeon inspection and palpation in the operating room.

Breast cancer most commonly spreads to the ipsilateral axilla. Internal mammary involvement is most common in patients with medial tumors and positive axillary nodes. Among patients whose sentinel node(s) map to the internal mammary chain, only 8–27% are malignant.[25] In a series of 113 breast cancer patients, 19% had extra-axillary sentinel lymph nodes. Ipsilateral internal mammary nodes were most common, followed distantly by ipsilateral intramammary, supraclavicular, and interpectoral. No contralateral sentinel lymph nodes were seen.[26] Contralateral internal mammary nodal drainage is rare enough that it is not discussed in recent systematic reviews.[25] As this drainage pattern has been shown to occur rarely and is published in case reports,[27] we believe that individual discussion with the patient's breast oncologist is mandatory prior to utilization of contralateral (prophylactic, non-cancer) internal mammary lymph node flap. We do not recommend harvesting an internal mammary lymph node flap from the ipsilateral (cancer) side.

The internal mammary lymph node flap could be used as a prophylactic option for lymphedema prevention in the setting of immediate bilateral breast reconstruction after modified radical mastectomy with contralateral prophylactic mastectomy. Similar prophylactic procedures have been performed simultaneously with modified radical mastectomy using axillary lympho-venous bypass.[28,29] The flap could also be harvested in cases of bilateral delayed breast reconstruction and transplanted from the prophylactic side to the cancer-side axilla. In cases of bilateral breast reconstruction, the internal mammary lymph node donor site is a "freebie"—there is no additional skin incision, rib removal, or additional transection of named vessels. When lymph nodes are identified, surgeons can harvest the flap while leaving an adequate length of vessel for free flap anastomosis. If lymph nodes are not present, the surgeon would need a secondary option for lymph node donor site. Pre-operative imaging may help to identify these patients in advance. The mean pedicle length obtained by harvesting the 3rd and 4th ribs was 6.5 cm. Although we did not explicitly measure this distance, pedicle length with removal of the 3rd rib only would be approximately 4 cm. Palpation and inspection can identify nodes within the flap, and the flap could be oriented antegrade or retrograde based on the lymph node position. To preserve the latissimus dorsi option for breast reconstruction, surgeons should consider using the serratus anterior branch for inflow and outflow. We believe that this technique requires removal of a rib to increase pedicle length. This technique would not be feasible using a "rib-sparing" approach.

Multiple reports on endoscopic internal mammary lymph node dissections with and without harvest of adjacent vessels have been published[30–34]; this may represent a minimally invasive approach to VLNT donor sites. The entire dissection can be completed in 70 min via three trocar sites in the lateral chest wall.[21,24] One study of complete unilateral internal mammary nodal chain dissection demonstrated that an average of 4.6 nodes can be removed.[24] Of note, lymph nodes harvested using this technique were destined for pathology, not VLNT, and the ability to preserve adjacent vessels using an endoscopic approach remains unknown. Further feasibility research would be necessary prior to attempting this minimally invasive approach.

The internal mammary lymph node flap is a small flap with an average weight of 1.69 g. By comparison, the transverse cervical artery-based flap, which is known to have clinical effectiveness, has an average weight of 12.9 g (Gerety PA, et al. A cadaveric assessment of the supraclavicular and thoracodorsal-based axillary flaps for VLNT. Unpublished data.). The bloodflow requirements of this small flap are likely greatly exceeded by the inflow provided by the re-anastomosed internal mammary artery. We are concerned that the volume of venous blood produced by the flap will be small, resulting in a relative stasis within the internal mammary vein that may predispose to venous clot. The physiology of this small flap requires further investigation.

Use of the internal mammary nodes would require a case-by-case consultation with the patient's surgical oncologist to confirm there was no cancer risk in the contralateral internal mammary nodes. Existing imaging modalities, such as CT or MRI studies, may be helpful prior to this discussion.[15,23] Further research will also need to quantify the number of lymph nodes required in a VLNT in order to obtain a clinical response. Anatomic dissection studies performed by our group have shown that the transverse cervical artery-based flaps contain, on average, 3.0 nodes, and thoracodorsal artery-based flaps contain, on average, 2.4 nodes (Gerety PA, et al. A cadaveric assessment of the supraclavicular and thoracodorsal-based axillary flaps for VLNT. Unpublished data.). Clinical success has been achieved using these flaps. Interestingly, up to 3% of women can have lymphedema after sentinel lymph node biopsy, which generally removes one or two lymph nodes.[1] Perhaps, then, replacement of one to two lymph nodes using a VLNT technique will be sufficient.

CONCLUSIONS

Inspection and palpation can correctly predict the presence or absence of lymph nodes in 80% of internal mammary lymph node specimens. Nodes were present in 60% of internal mammary-based flaps, and one to three lymph nodes can be transferred. The internal mammary vessels have adequate caliber for microvascular anastomoses and the donor site morbidity from this surgery is minimal. When the internal mammary flap is harvested from the non-cancer side, we recommend that cases be individually discussed with the patient's surgical oncologist; of note, breast cancer metastases to the contralateral internal mammary nodal basin are exceptionally rare. Further research is necessary to identify the minimum number of lymph nodes necessary for transfer to ensure successful lymphedema prevention or treatment.

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