Reverse Lymphatic Mapping: A New Technique for Maximizing Safety in Vascularized Lymph Node Transfer

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Background: The authors introduce the technique of reverse lymphatic mapping for vascularized lymph node transfer. This physiologic technique allows one to identify which lymph nodes drain the trunk as opposed to the extremity, to minimize the risk of iatrogenic lymphedema.
Methods: A prospective study of patients undergoing vascularized lymph node transfer using the reverse lymphatic mapping technique was conducted. Patients received technetium injections in the first and second webspaces of the foot and intradermal indocyanine green injections in the lower abdomen. Lymphatic vessels were traced to the lymph nodes draining the lower abdomen that were harvested; a gamma probe was used to localize lymph nodes draining the lower extremity, which were avoided. In cases of vascularized axillary lymph node transfer, technetium was injected into the hand and indocyanine green was injected into the back and lateral chest. Ten-second counts were recorded of the lymph node flap and the sentinel node draining the extremity for comparison.
Results: Thirty-five patients underwent vascularized lymph node transfer (19 groin and 16 axillary lymph node transfers) guided by reverse lymphatic mapping. Follow-up time was 1 to 30 months. Mean 10-second count using the gamma probe for all lymph node flaps was 88.6 (SD, 123; median, 39); mean 10-second count of extremity sentinel nodes was 2462 (SD, 2115; median, 2000). On average, 10-second signal strength of the lymph node flap was 6.0 percent that of the extremity sentinel node.
Conclusion: Reverse lymphatic mapping guides vascularized lymph node flap harvest based on physiologic drainage patterns of the trunk and limb that may minimize the risk of iatrogenic lymphedema. (*Plast. Reconstr. Surg.* 135: 277, 2015.)
CLINICAL QUESTION/LEVEL OF EVIDENCE: Therapeutic, IV.

Breast cancer–related lymphedema is one of the most distressing complications following sentinel lymph node biopsy or axillary lymphadenectomy.[1–3] Vascularized lymph node transfer has become an increasingly popular option for the treatment of lymphedema as successful reports of its use have emerged.[4–14] However, the risk of donor-site lymphedema remains a significant concern. Two relatively recent articles reported impaired lymphatic function at the donor site[15] and iatrogenic lymphedema following vascularized lymph node transfer.[16] In addition, there is very little in the literature regarding specific harvest techniques for vascularized lymph node transfer, which can vary considerably. This underscores the need for a method to differentiate lymph nodes that drain the trunk from those that drain the extremities to carefully negotiate variable lymphatic pathways during flap harvest.[15–18] In addition, lymph node flap design is typically based on static anatomical landmarks, yet lymphatic drainage patterns may vary.[4–6] A well-defined method for lymph node harvest

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based on physiologic lymphatic pathways specific to the patient has not yet been described.

The purpose of this article is to present a safety-oriented approach to vascularized lymph node transfer using a method the authors refer to as reverse lymphatic mapping. This technique is a modification of the axillary reverse mapping technique described by Klimberg and others for sentinel lymph node biopsy and axillary lymphadenectomy in patients with breast cancer.[19–27] In axillary reverse mapping, isosulfan blue dye is injected into the upper extremity and technetium is injected into the breast. Sampling the technetium-labeled nodes that drain the breast while avoiding the blue nodes that drain the arm may minimize the risk of lymphedema in the extremity. We applied this concept to both axillary and groin lymph node transfers and further modified it by using technetium and indocyanine green lymphangiography. The concept of reverse lymphatic mapping involves injecting technetium into the extremity adjacent to the inguinal or axillary donor site. Indocyanine green is then injected into the trunk. A gamma probe is used intraoperatively to localize lymph nodes draining the extremity that are avoided during flap harvest. Using the SPY Elite (LifeCell Corp., Branchburg, N.J.), near-infrared fluorescence lymphangiography is performed simultaneously to identify the lymph nodes draining the trunk, which are targeted for flap harvest. This provides an intraoperative map of lymph node drainage patterns specific to the patient that can safely guide lymph node harvest. The technical details of this method are described, as are the findings of lymphatic drainage patterns in the axillary and inguinal regions.

PATIENTS AND METHODS

A prospective study was conducted on patients undergoing both groin and axillary vascularized lymph node transfers using the reverse lymphatic mapping technique. Informed consent for all patients was obtained, as was institutional review board approval (no. 177-13). A total of 35 consecutive patients were studied from March of 2011 to December of 2013. Nineteen patients underwent groin lymph node transfers based on the superficial circumflex iliac artery, and 16 had axillary lymph node transfers based on the thoracodorsal artery, with four of these flaps supercharging the lateral thoracic system. All patients underwent preoperative imaging using magnetic resonance angiography at both recipient and donor sites to clarify the vascular anatomy of these areas following prior surgery and irradiation. Quality and quantity of donor-site lymph nodes are assessed to determine the best side for lymph node harvest and technetium injection site preoperatively. Magnetic resonance angiography also allowed us to obtain limb volume for use in future outcomes studies that are currently underway. Follow-up time was 1 to 30 months.

Reverse Lymphatic Mapping Technique for Vascularized Groin Lymph Node Transfer

Patients who underwent vascularized groin lymph node transfer had 0.2 ml of filtered technetium sulfur colloid (0.2 mCi/0.2 ml) injected into the first and second webspaces of the foot on the side of the inguinal donor site approximately 2 hours before surgery. Once the patient was prepared in the operating room, a gamma probe was used to localize the lymph nodes with technetium uptake from the lower extremity. This site was marked on the skin and avoided. Subsequently, 0.2 ml of indocyanine green was injected intradermally in 4 locations along a line approximately 5 cm above and parallel to the inguinal ligament. The SPY device was then used to visualize the lower abdominal lymphatic vessels and their collecting lymph nodes that were targeted for harvest (Fig. 1).

As Dayan et al. demonstrated in an anatomical study of superficial inguinal lymph nodes, target lymph nodes for groin lymph node transfer are most likely to be found within a 3-cm radius of a point one-third the distance from the pubic tubercle toward the anterior superior iliac spine and 3 cm perpendicularly below this line.[14] A handheld Doppler probe was used to mark the course of the superficial circumflex iliac artery. The incision was then made directly over the course of the superficial circumflex iliac artery. Dissection was carried down to the Scarpa facia and skin flaps were elevated superficial to the Scarpa fascia. The SPY device was then used again to confirm the location of the lymph nodes of interest. The gamma probe was used throughout harvest to avoid lymph nodes draining the lower extremity. The flap was elevated in a suprafascial plane from lateral to medial, and the superficial circumflex iliac vessels were completely mobilized to their origin (Fig. 2).

Intravenous injection of 4 ml of indocyanine green followed by 10 ml of normal saline and SPY evaluation confirmed adequate perfusion of the lymph node flap. Following lymph node flap harvest, 10-second counts of the highest focus of technetium were taken in the flap and the donor site, respectively. Two consecutive 10-second

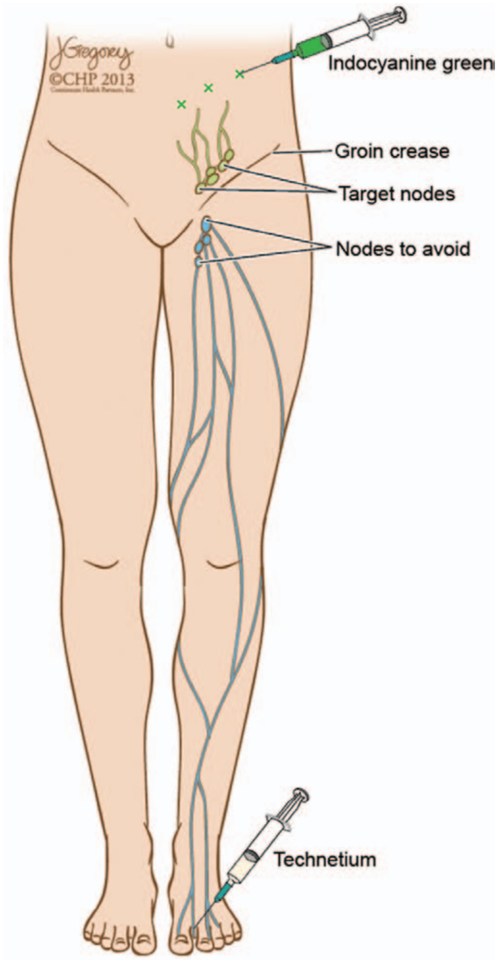


Fig. 1. Filtered technetium is injected into the first and second webspaces of the foot. Indocyanine green is injected intradermally in four areas across the lower abdomen. (Published with permission from © Mount Sinai Health System.)

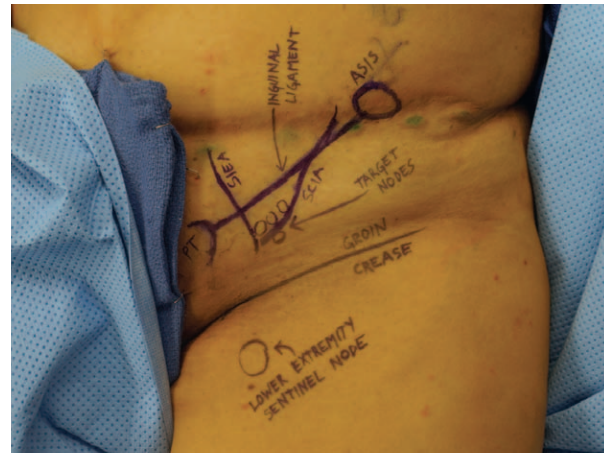
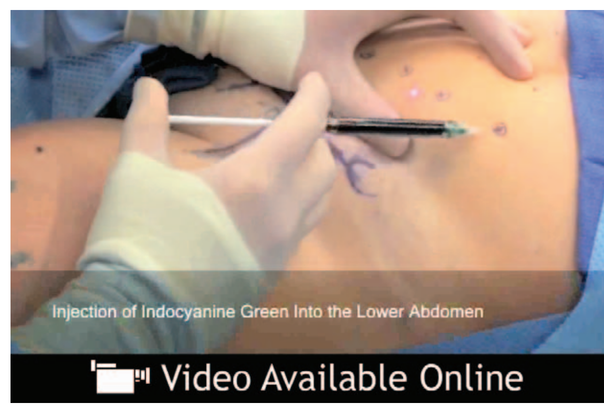


Fig. 2. Marking for a vascularized groin lymph node flap using reverse lymphatic mapping.



Video 1. Supplemental Digital Content 1 demonstrates the reverse lymphatic mapping technique in vascularized groin lymph node transfer, ***http://links.lww.com/PRS/B182.***

counts were performed and the highest value from each site was recorded. (**See Video, Supplemental Digital Content 1**, which demonstrates the reverse lymphatic mapping technique in vascularized groin lymph node transfer, ***http://links.lww.com/PRS/B182***.)

Reverse Lymphatic Mapping Technique for Vascularized Thoracodorsal Artery and Lateral Thoracic Artery–Based Lymph Node Transfer

In patients who underwent a thoracodorsal artery– or lateral thoracic artery–based lymph node transfer, 0.2 ml of filtered technetium sulfur colloid (0.2 mCi/0.2 ml) was injected into the first and second webspaces of the ipsilateral hand approximately 2 hours before surgery. Then, 0.2 ml of indocyanine green was injected intradermally into four areas transversely across the lateral chest and anterior back, approximately 20 cm inferior to the axilla. The gamma probe was used to locate the lymph nodes draining the upper extremity, which were avoided during flap harvest. The SPY device was used to visualize lymphatics leading to the lymph nodes draining the trunk (Fig. 3).

A transverse incision was made in the axilla where the indocyanine green–labeled lymphatics coalesced, indicating the lymph nodes of interest. Subcutaneous flaps were elevated and the SPY device was used again to confirm location of the targeted nodes. The gamma probe then identified lymph nodes draining the upper extremity, and care was taken to restrict dissection inferior to these critical lymph nodes. At this point, a decision is made to harvest lymph nodes based on the thoracodorsal artery or the lateral thoracic artery. For example, if the lateral thoracic artery–based lymph nodes have significant technetium uptake and the thoracodorsal artery–based nodes are silent, the thoracodorsal artery–based lymph nodes are harvested, and vice versa. The

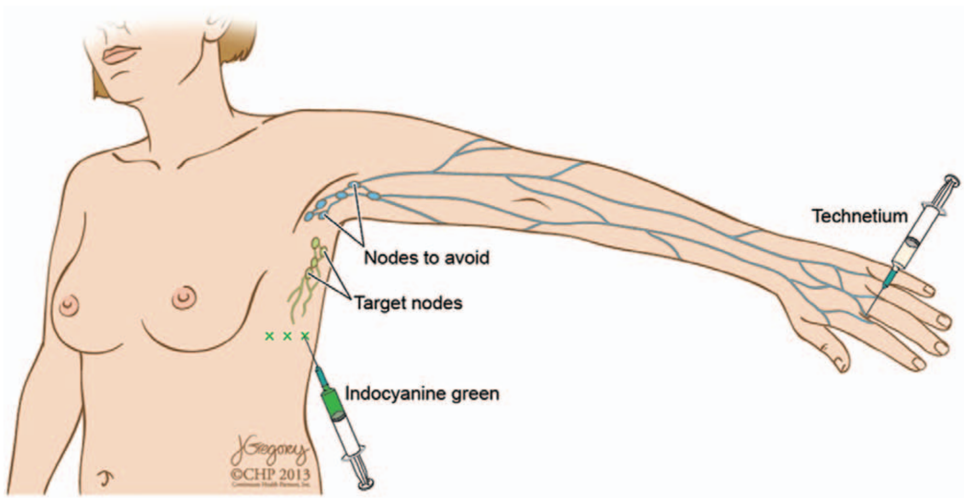


Fig. 3. Filtered technetium is injected into the first and second webspaces of the hand. Indocyanine green is injected intradermally into four areas across the lateral chest wall and back. (Published with permission from © Mount Sinai Health System.)

SPY device and gamma probe are used throughout this procedure to ensure that critical lymph nodes are preserved and the target lymph nodes are more precisely harvested. The thoracodorsal, intercostobrachial, and long thoracic nerves were identified and preserved. If a thoracodorsal or intercostobrachial nerve branch coursed through the lymph nodes being harvested, it was divided and repaired (Fig. 4).

Intravenous indocyanine green injection was performed to confirm satisfactory perfusion of the lymph node flap. A 10-second count at both the donor site and the flap was performed, and the highest number of two counts was recorded. (**See Video, Supplemental Digital Content 2**, which demonstrates the reverse lymphatic mapping technique in vascularized thoracodorsal artery–based lymph node transfer, ***http://links.lww.com/PRS/B183***.)

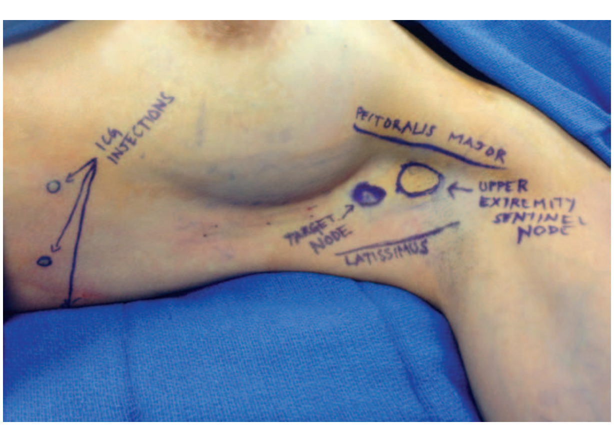


Fig. 4. Markings for axillary lymph node flap using reverse lymphatic mapping.

RESULTS

Groin Lymph Node Harvest

There were a total of 19 vascularized groin lymph node transfers in this study. The sentinel lymph node draining the lower extremity was located inferior to the groin crease and medial, along the superficial femoral vessels in 18 of 19 patients. There was one case where the lymph node with the highest technetium uptake was located above the groin crease and based on the superficial circumflex iliac artery. All lymph nodes based on the superficial circumflex iliac artery were consistently located above the groin crease, but at or slightly below the level of the inguinal ligament. However, in five of 19 patients, significant technetium uptake was found above the groin crease in lymph nodes supplied by the superficial circumflex iliac artery (Fig. 5). In one case subsequent to the completion of this study, groin flap harvest was aborted because the sentinel lymph node draining the lower extremity was based on the superficial circumflex iliac artery and located above the groin crease. A supraclavicular flap was performed in this case. The 10-second count at the highest focus of technetium uptake in the lower extremity averaged 1791 (range, 263 to 4347). The highest 10-second count in the lymph node flap following harvest averaged 141 (range, one to 455). On average, the technetium uptake in the lymph node flap was 8.7 percent that of the uptake of the sentinel node of the lower limb (Table 1). There were no observed cases of donor-site lymphedema in this series to date.

Video 2. Supplemental Digital Content 2 demonstrates the reverse lymphatic mapping technique in vascularized thoracodorsal artery–based lymph node transfer, ***http://links.lww.com/PRS/B183.***

Axillary Lymph Node Harvest

There were a total of 16 axillary lymph node transfers in this study. Axillary lymph node harvest tended to be more challenging in terms of variability of lymphatic drainage pathways compared with the groin. Unlike groin lymph node transfer where there are discrete anatomical landmarks such as the groin crease, axillary lymph node harvest was guided primarily by reverse lymphatic mapping. We found that the sentinel lymph nodes draining the upper limb were often located high in the axilla, and anteriorly, just deep to the pectoralis major muscle. These nodes were found to have a variable blood supply that could originate directly from the axillary artery, lateral thoracic artery, or thoracodorsal artery. In this series, most of our axillary lymph node flaps were thoracodorsal artery based, guided by the reverse lymphatic mapping technique (Fig. 6). Ten axillary lymph node transfers were based solely on the thoracodorsal artery, two were based solely on the lateral thoracic artery, and four were based on both the thoracodorsal and lateral thoracic vessels. The 10-second count at the highest focus of technetium uptake in the upper extremity averaged 3260 (range, 272 to 11,327). The highest 10-second count in the lymph node flap following harvest averaged 27 (range, 0 to 125). The average amount of technetium uptake in the lymph node flap was 2.8 percent that of the extremity sentinel node (Table 2). There were no observed cases of donor-site lymphedema in this series to date.

DISCUSSION

Safety in vascularized lymph node transfer is of paramount importance in the rapidly evolving field of lymphatic surgery.[16] Although there

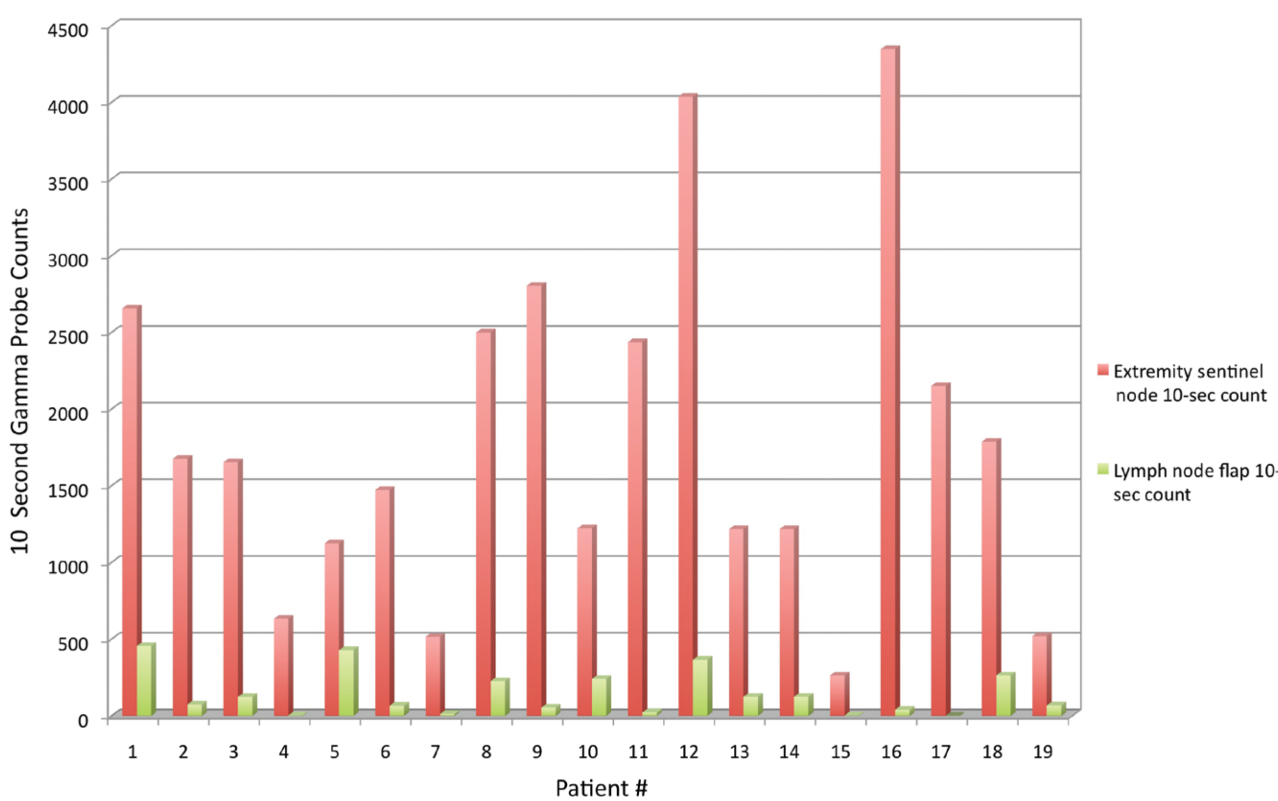


Fig. 5. Vascularized groin lymph node transfers. Lymph node flap versus extremity sentinel node 10-second gamma probe counts.

Table 1. Ten-Second Counts of Technetium Uptake in Groin Lymph Node Flaps Relative to the Donor-Site Sentinel Nodes

Patient	Flap 10-Sec Count	Sentinel Node 10-Sec Count	Flap Count/Sentinel Node Count (%)
1	455	2657	17.1
2	73	1676	4.4
3	123	1653	7.4
4	3	633	0.5
5	428	1124	38.1
6	66	1472	4.5
7	12	515	2.3
8	226	2500	9.0
9	53	2804	1.9
10	240	1222	19.6
11	22	2436	0.9
12	365	4037	9.0
13	108	1012	10.7
14	124	1217	10.2
15	2	263	0.8
16	39	4347	0.9
17	1	2151	0.0
18	263	1787	14.7
19	68	519	13.1
Average	141	1791	8.7
SD	147	1134	
Median	73	1653	

has been a significant improvement in the quality of life of patients undergoing this procedure, there is no doubt that this procedure carries the risk of causing the very problem it aims to treat. During the course of flap dissection, one must make a decision to either harvest or preserve certain lymph nodes, ultimately treading a fine line between the risk of iatrogenic lymphedema and inadequate capture of lymph nodes, leading to an unsatisfactory therapeutic result.

Conventional techniques for lymph node harvest are based largely on anatomical landmarks.[4–6] References to the inguinal ligament and groin crease have been used interchangeably, resulting in confusion about the exact location of the desired nodes. In addition, anatomical landmarks do not necessarily correlate with the physiology of lymphatic drainage pathways that may differ among patients. Reverse lymphatic mapping enables the surgeon to navigate the groin or axillary lymph node basin based on a real-time physiologic assessment of the patient's individual lymphatic anatomy, allowing for safe harvest of lymph nodes that drain the trunk while avoiding those that drain the extremity.[19–26] We have not observed any clinical evidence of donor-site lymphedema to date, with our longest follow-up being 30 months. This is only a clinical impression based on physical examination and patients' subjective reports. A prospective study of the donor site using objective endpoints

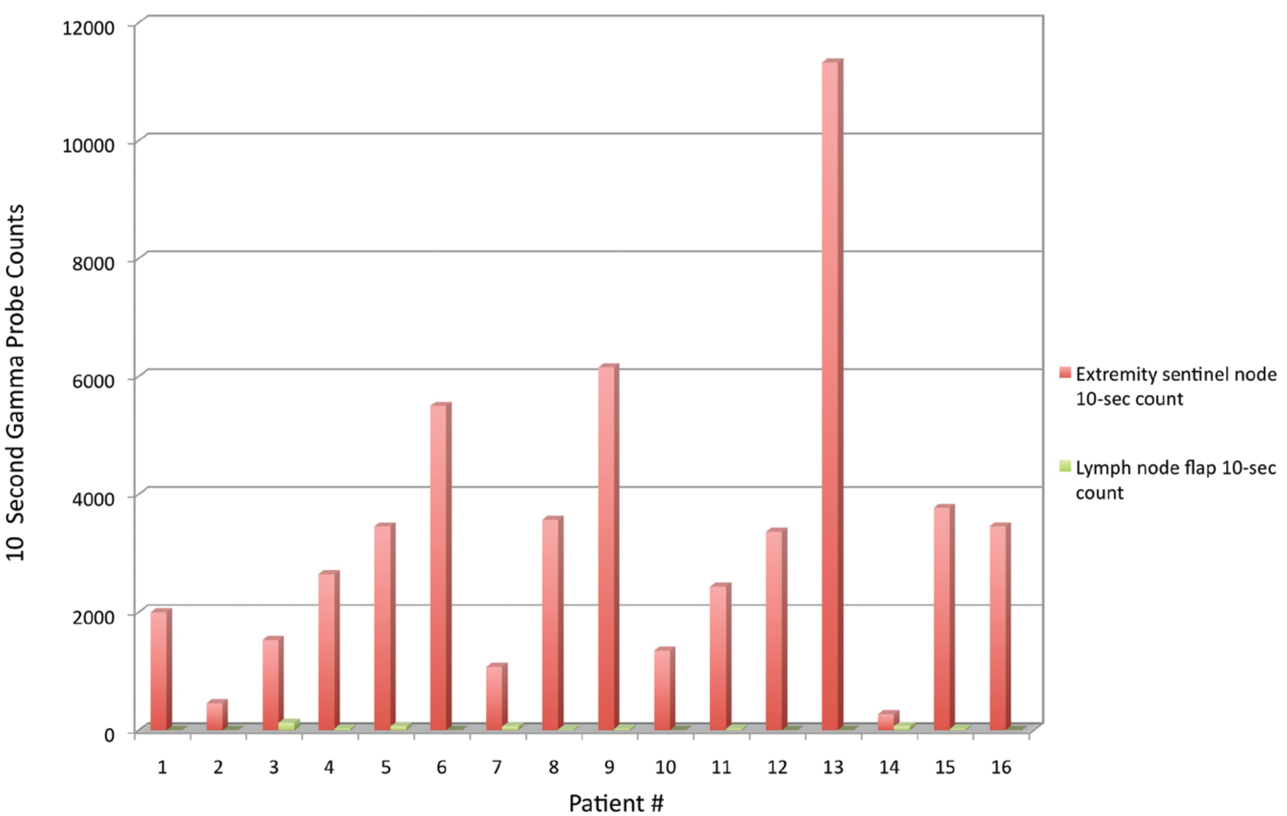


Fig. 6. Vascularized axillary lymph node transfers. Lymph node flap versus extremity sentinel node 10-second gamma probe counts.

Table 2. Ten-Second Counts of Technetium Uptake in Axillary Lymph Node Flaps Relative to the Donor-Site Sentinel Nodes

Patient	Flap 10-Sec Count	Sentinel Node 10-Sec Count	Flap Count/Sentinel Node Count (%)
1	0	2000	0.0
2	0	457	0.0
3	125	1530	8.2
4	27	2644	1.0
5	64	3455	1.9
6	2	5500	0.0
7	62	1073	5.8
8	13	3568	0.4
9	22	6154	0.4
10	3	1349	0.2
11	17	2230	0.8
12	0	3368	0.0
13	3	11,327	0.0
14	68	272	25.0
15	20	3770	0.5
16	3	3457	0.1
Average	27	3260	2.8
SD	35	2710	
Median	15	3006	

including donor-site lymphoscintigraphy and indocyanine green lymphangiography is currently underway to adequately assess the potential for reduced morbidity using this technique. To date, there are six patients beyond the 1-year follow-up mark that have had postoperative lymphoscintigraphy and indocyanine green lymphangiography at the donor site, all of whom had normal studies.

Alternative donor sites for lymph node transfer are available, such as the supraclavicular flap, which has been gaining popularity. However, supraclavicular nodes do contribute to upper extremity drainage. Although this is beyond the scope of this study, we routinely use reverse lymphatic mapping when harvesting supraclavicular nodes to guide dissection, and the risk of upper extremity lymphedema is discussed with the patient during informed consent. When harvesting lymph nodes on the left side, particular care should be taken to avoid injury to the thoracic duct. Injection of indocyanine green and/or blue dye can be helpful in these cases. Other risks include injury to the spinal accessory nerve or phrenic nerves that are encountered in the field.

Reverse lymphatic mapping is a modification of Klimberg's technique of axillary reverse mapping used in sentinel lymph node biopsy and lymphadenectomy in breast cancer.[19–26] In axillary reverse mapping, technetium is injected into the breast and blue dye is injected into the upper arm. Avoiding the "blue" nodes theoretically minimizes the risk of iatrogenic lymphedema. Our initial experience with reverse lymphatic mapping involved the injection of indocyanine green into the chest wall and blue dye into the upper limb. One limitation of this technique is that the blue dye is often not apparent until one is directly on the lymph node.[27] At this point, the lymphatic vessels may have been disrupted or the lymph node may have become inadvertently devascularized. It is preferable to be able to accurately locate these critical lymph nodes from a greater distance to preserve the surrounding lymphatic network and perfusion. We have since abandoned blue dye and now use filtered technetium injection into the extremity, which allows the surgeon to detect critical lymph nodes before they are encountered during dissection. By using the gamma probe, this technique allows one to continuously be guided away from extremity lymph nodes throughout the flap harvest.[27]

Using axillary reverse mapping, Klimberg and others identified lymph nodes that demonstrated uptake of both technetium and blue dye, indicating that there are sentinel lymph nodes that drain both the breast and the upper extremity.[19–29] In this study, we also observed several patients with lymph nodes that had significant uptake of both technetium and indocyanine green. From a vascular standpoint, these nodes may be based on either the thoracodorsal or lateral thoracic artery. Without reverse lymphatic mapping, one cannot confirm whether or not harvest of these lymph nodes will disrupt the drainage from the upper extremity. Lymph nodes located more posteriorly, along the thoracodorsal vessels, consistently drain the back and lateral chest wall, where little to no crossover with the upper extremity drainage exists. Thus, in general, reverse lymphatic mapping has guided us toward selecting the thoracodorsal artery–based lymph nodes as opposed to the lateral thoracic artery–based lymph nodes for transfer. However, lymphatic drainage patterns vary, and in some cases there were lateral thoracic artery–based lymph nodes located more inferiorly that did not drain the upper extremity. Conversely, we have also observed thoracodorsal artery–based lymph nodes that are situated higher in the axilla, near the axillary vein, that have contributed to upper extremity drainage. It appeared that the superior location of the lymph node had more to do with its likelihood of draining the upper limb than the blood vessel that was perfusing it. Preoperative magnetic resonance angiographic imaging was useful in determining a more favorable grouping of lymph nodes (i.e., lymph nodes that were found to be located inferiorly and separate from lymph nodes high in the axilla were generally better candidates for axillary lymph node transfer). This variability underscores the utility of reverse lymphatic mapping.

In the inguinal region, the lower extremity sentinel nodes were typically located below the groin crease—often a few centimeters away from the superficial circumflex iliac artery–based lymph nodes. However, there was one sentinel lymph node based on the superficial circumflex iliac artery located above the groin crease. We did encounter an additional three of 19 patients with greater than 10 percent technetium uptake superior to the groin crease in the superficial circumflex iliac artery territory in this series. This demonstrates that variable lymphatic pathways exist in the inguinal region as well. Using reverse lymphatic mapping, one can selectively preserve a technetium-rich node or consider exploring an alternative donor site.

One limitation of this study is the fact that the technetium may only have reached the sentinel lymph node and not second- or third-echelon nodes.[27] Although it is useful to have identified the sentinel lymph node draining the extremity, ideally one would prefer to identify all lymph nodes that contribute to extremity drainage. There are a number of variables that come into play, including the type of radioisotope being injected and the site, depth, and timing of injection. To minimize these variables, standard injection techniques of 0.2 ml of filtered technetium into the first and second webspaces were used. This was performed approximately 2 hours before surgery. Filtered technetium was used rather than unfiltered technetium, because the filtered variety has a more consistent molecular weight and transit time and exhibits faster uptake into the lymph nodes.[27] With a normal lymphatic system, we have observed that filtered technetium typically reaches the draining lymph node basins of the injected extremity within 30 minutes or less during lymphoscintigraphy. The half-life of technetium is 6 hours, allowing the tracer to be detected well beyond the duration of the case. Unfiltered technetium can be used as well but, because of its slower transit time, should be injected 1 day before surgery. We have used unfiltered technetium on five patients when operating abroad and were able to perform reverse lymphatic mapping. However, these patients were excluded from this study to eliminate potential inconsistencies in the results between filtered and unfiltered technetium. Despite the current limitations of lymphatic mapping, using reverse lymphatic mapping to guide flap harvest has become a useful tool in the authors' practice.

CONCLUSIONS

At this relatively early state in the evolution of lymph node transfer, maintaining high standards of safety is critical in responsibly developing this field. Reverse lymphatic mapping is a logical method that guides flap dissection based on physiologic drainage pathways of the trunk and extremity. This technique may minimize the risk of donor-site lymphedema and facilitates flap harvest, although long-term studies are needed to properly assess outcomes.

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