Axillary Reverse Mapping: Mapping and Preserving Arm Lymphatics May Be Important in Preventing Lymphedema During Sentinel Lymph Node Biopsy

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BACKGROUND: Several recent reports have shown a lymphedema rate of about 7% with sentinel lymph node biopsy (SLNB) only. We hypothesized that this higher than expected rate of lymphedema may be secondary to disruption of arm lymphatics during an SLNB procedure.

STUDY DESIGN: This IRB-approved study, from May 2006 to June 2007, involved patients undergoing SLNB with or without axillary lymph node dissection. After sentinel lymph node (SLN) localization with subareolar technetium was assured, 2 to 5 mL of dermal blue dye was injected in the upper inner arm for localization of lymphatics draining the arm (axillary reverse mapping, ARM). The SLNB was then performed through an incision in the axilla. Data were collected on identification rates of hot versus blue nodes, variations in ARM lymphatic drainage that might impact SLNB, crossover between the hot and the blue lymphatics, and final pathologic nodal diagnosis.

RESULTS: Median age was 57.6 ± 12.5 years. Lymphatics draining the arm were near or in the SLN field in 42.7% (56 of 131) of the patients, placing the patient at risk for disruption if not identified and preserved during an SLNB or axillary lymph node dissection. ARM demonstrated that arm lymphatics do not cross over with the SLN drainage of the breast 96.1% of the time and that none of the ARM lymph nodes removed were positive, even when the SLN was (5 of 12). Seven (5.5%) blue ARM lymphatics were juxtaposed to the hot SLNBs.

CONCLUSIONS: Disruption of the blue ARM node because of proximity to the hot SLN may explain the surprisingly high rate of lymphedema seen after SLNB. Identifying and preserving the ARM blue nodes may translate into a lower incidence of lymphedema with SLNB and axillary lymph node dissection. (J Am Coll Surg 2008;206:1038–1044. © 2008 by the American College of Surgeons)

Even as we approach the molecular age of breast cancer, the status of the axillary lymph nodes remains the most important predictor of outcomes, so it continues to direct therapy. The technique of axillary lymph node dissection (ALND), although supplanted by sentinel lymph node (SLN) for the majority of patients, has changed little since its inception, being purely an anatomic dissection. Axillary lymph node dissection does not distinguish breast from arm lymphatics because the possibility of mapping the drainage from the arm into the axilla has only recently been published.[1,2] Transection of arm lymphatics during an ALND most likely results in lymphedema and is perhaps the most widely published complication of ALND.[3]

Although SLN clearly reflects the status of the axillary lymph node basin and is less morbid, it has not prevented lymphedema. There can be no doubt that lymphedema is minimized with SLN in comparison with ALND, as seen in eight clinical trials comparing the two.[3-10] Rates of lymphedema with SLN were much lower than those with ALND, in the range of 0% to 13%, compared with 7% to 77% for ALND. Several cooperative group trials have shown lymphedema rates in approximately the 7% range with SLN biopsy alone.[11,12] We hypothesized that this higher than expected rate of lymphedema may be secondary to disruption of low-lying arm lymphatics during a

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Abbreviations and Acronyms
ALND = axillary lymph node dissection
ARM = axillary reverse mapping
SLN = sentinel lymph node
SLNB = sentinel lymph node biopsy

sentinel lymph node biopsy (SLNB) procedure. In addition, identification and ultimately, protection of these low-lying arm lymphatics through axillary reverse mapping (ARM) could be a technique to prevent lymphedema.

METHODS

Patients

This prospective IRB-approved database involved 131 patients, newly diagnosed with breast cancer and clinically negative axilla, undergoing SLNB with or without ALND from May 2006 to June 2007. Patients who underwent neoadjuvant chemotherapy before SLNB were excluded from this study.

Sentinel lymph node procedure

Our SLNB technique has been described in detail in previous studies.[13] In summary, we performed a subareolar plexus injection of 1.0 mCi of technetium sulfur colloid diluted to final volume of 4 mL intraoperatively immediately after general anesthesia induction. After routine preparation and drape were completed, a hand-held gamma probe (Neoprobe) was used to localize radioactivity (hot lymph node) before skin incision. If a hot SLN could not be localized (defined by counts > 10% of background), then isosulfan blue dye was also injected in the subareolar complex and the ARM procedure not performed.

Axillary reverse mapping procedure

After SLN localization was assured, 2 to 5 mL of dermal blue dye was injected dermally and then later subcutaneously in the ipsilateral extremity for localization of lymphatics draining the arm (ARM).[1] The first few patients were injected in the dorsum of the hand or posterior arm. We subsequently moved the site of injection to the upper inner arm along the medial intermuscular groove. The SLNB was then performed through an incision in the axilla.

Axillary lymph node dissection

When the SLN was positive and a mastectomy was performed, the ALND was completed through the same incision; otherwise, an axillary incision was made. Standard resection of level I and level II lymph nodes was completed to include blue lymph nodes in the initial patients; otherwise, the blue lymphatics and blue nodes were preserved if not hot or clinically suspicious. All wounds were closed after placing a single drain.

Pathology

Blue or hot lymph nodes > 5 mm in size were sectioned at 3-mm intervals along the long axis. Intraoperative touch preparation cytology was performed, followed by routine hematoxylin and eosin staining.[14] Complete axillary dissection specimens were bisected along the long axis, and one section from each node was submitted for hematoxylin and eosin staining.

Data collection and statistics

In a prospective database in Microsoft Excel, we collected data on identification rates of hot versus blue nodes, variations in ARM lymphatic drainage that may affect SLNB, crossover between the hot and the blue lymphatics, and final pathologic nodal diagnosis. Results were treated with descriptive analysis.

RESULTS

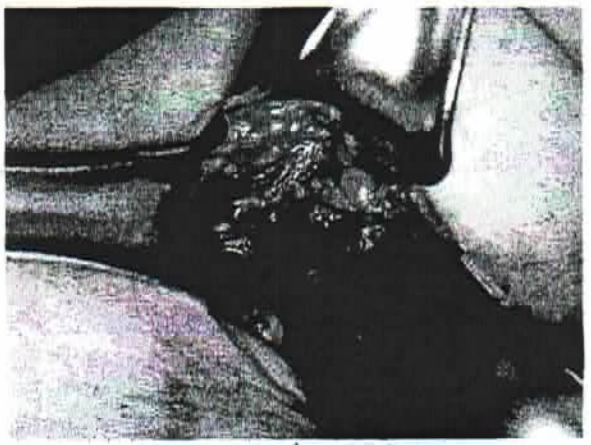
Patients

From May 2006 to June 2007, a total of 131 ARM procedures were performed in 113 patients enrolled in our study (Table 1). Mean age of the study population was 57.6 ± 12.5 years. Eighteen patients had bilateral procedures, with SLN and ARM procedures on both sides. Twenty-six ALNDs were performed in patients who had breast cancer on intraoperative touch preparation of the SLN. Three ALNDs were performed for nonlocalization of the SLN and one for clinically suspicious lymph nodes.

Table 1. Results of Axillary Reverse Mapping Procedure

Procedure	Hot SLN identification rate n,%	Hot SLN positive for malignancy n,%	Blue ARM lymphatics identified near or in SLN field n,%	Crossover rate (hot and blue nodes removed) n,%	Blue ARM node juxtaposed to SLN n,%	Blue ARM nodes ± hot that were positive for malignancy n,%
SLNB (n = 131) and/or	128/131	26/128	56/131	5/128	7/128	0/12
ALND (n = 26)	97.7	20.3	20.3	42.7	3.9	5.5

ALND, axillary lymph node dissection; ARM, axillary reverse mapping; SLN, sentinel lymph node; SLNB, sentinel lymph node biopsy.



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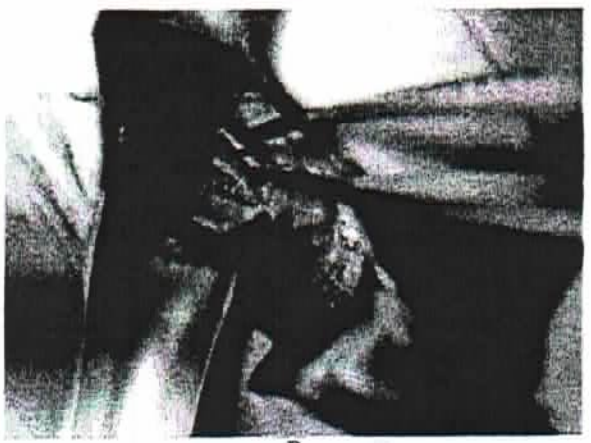

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Figure 1. Juxtaposed hot sentinel lymph node and blue axillary reverse mapping node. Large blue lymphatic under the identified hot node (A) before and (B) after removal of the hot node.

Operations included partial mastectomies (54, 41.2%), mastectomies (75, 57.2%), and wide local excision (1, 0.8%). There was one SLN biopsy alone before neoadjuvant chemotherapy (0.8%).

Sentinel lymph node

A hot SLN was identified in 128 of 131 axillae (97%). Of those axillae, 26 (20.3%) were positive for malignancy. In three patients, no SLN was found, and one had a clinically positive axilla (Table 1).

Axillary reverse mapping

Blue lymphatics draining the arm were visible from the SLN incision, so were located near or in the SLN field in 56 of the 131 patients (42.7% of the patients). The blue nodes on the first seven patients (5.5%) were taken during ALND and were blue but not hot and did not contain metastases. Crossover of the blue ARM lymphatics with the hot SLN was seen in five (3.9%) patients; these lymph nodes were taken and did not contain metastases. Figure 1 demonstrates a large blue lymphatic under the identified hot node before (Fig. 1A) and the nonhot blue node after removal of the hot node (Fig. 1B). All 12 blue lymph nodes resected were negative for malignancy, even in positive axillae.

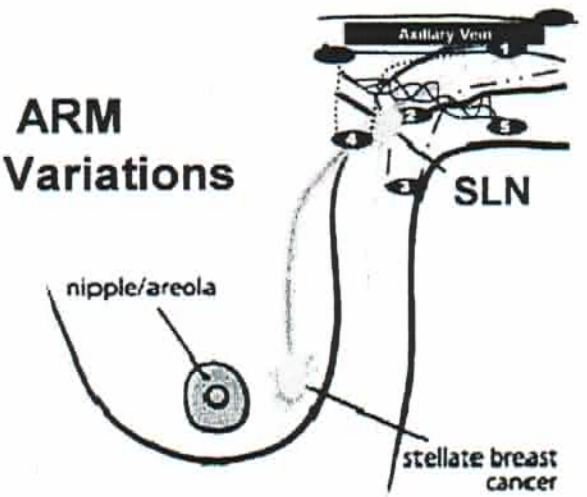

Figure 2. Variations in axillary reverse mapping (ARM)–anatomic variations in ARM drainage. 1, traditional teaching of lymphatics from the arm running juxtaposed to the axillary vein either above or below; 2, sling low in the axilla; 3, lateral apron; 4, medial apron (lateral and medial aprons usual consist of multiple blue nodes); 5, entwined cord of lymphatics. SLN, sentinel lymph node.

Axillary lymph node dissection

ALND was necessary in 30 patients, including all 26 patients with metastatic breast cancers to the axilla, 3 patients in whom SLN was not identified, and 1 with intraoperatively clinically suspicious nodes. We identified multiple variations of the arm lymphatics, with some being as much as 4 cm below the vein (Fig. 2). Variations were also seen as a medial or lateral apron and some as a sling low in the axilla. Another variation involved blue lymphatics just below the vein or even above the vein. Some ARM lymphatics were as large as 6 mm. One variation was a complex of smaller lymphatics entwined as a cord.

Pathology

The average number of lymph nodes removed during the ALND was 11.7 ± 6 nodes. All blue nodes identified and sent separately to pathology were negative. Complete axillary dissection revealed an average of 3.1 ± 4.3 positive lymph nodes.

Complications

There were no systemic allergic reactions. Most patients experienced a temporary blue tattoo at the injection site, which lasted anywhere from a few days to a few months. Two cases of lymphedema developed in the 12 patients in whom the blue lymphatic node or lymphatic was sacrificed. No lymphedema has been reported in short-term followup in patients in whom the blue ARM node was spared, whether an SLN biopsy alone or an ALND was performed.

DISCUSSION

Pathologic status of the axillary lymph nodes is the single most important prognostic factor for outcomes in the treatment of breast cancer. The growing recognition of ALND morbidity (lymphedema and sensory deficits) and increased capability to detect small cancers have originated SLNB as a staging procedure for potentially node negative patients.[1-5] Even though SLNB carries a lower morbidity than ALND does, the rate of postoperative lymphedema range ranges from 0% to 13%, with SLNB alone, even in experienced hands, averaging approximately 7% in two large cooperative group trials.[11,12] The need for a better understanding of the lymphatic drainage from the upper extremity in relation to the breast lymphatic drainage led us to develop the ARM procedure,[1,2] wherein the arm and breast lymphatic drainage can be identified separately, allowing safe removal of only the lymphatics of interest (SLN or ALND) and protection of the lymphatic channels draining the upper extremity. Others have confirmed our initial results on ALND.[16]

Traditional teaching tells that if one could avoid skeletonizing the vein, then the lymphatics that reside juxtaposed to the vein could be avoided and the risk of lymphedema minimized. In our study, severe lymphatics with positioning hugging the axillary vein were rarely seen. Figure 2 demonstrates the multiple variations that we did identify during ALND and SLN biopsy. Of note is that 42.7% of axillae had blue ARM lymphatics close or juxtaposed (5.5%) to the SLN, placing them in harms way during an SLN biopsy.

While we developed the ARM technique, anywhere in the arm seemed to work well, but injection of 2.5 mL to 5.0 mL of isosulfan blue dye in the upper inner arm drained very quickly and was hidden from obvious view of the patient. Because the richest lymphatic supply is subcutaneous, these injections worked well and blue skin staining was minimized. In our initial report, ARM was performed in 18 patients in whom ALND was done, and we identified blue dye within the axilla proper in 61%.[1] With more experience using this technique and knowledge of the variations in lymphatics, we can now identify the blue arm drainage in nearly all patients. We have identified multiple variations of the arm lymphatics, with some above the vein, and others being 3 or 4 cm below the vein (Fig. 2). Variations can be seen as a medial or lateral apron, a distinct sling low in the axilla, or a cord of entwined lymphatics. Some individual ARM lymphatics have been as large as 6 mm and can be easily confused with the intercostalbrachial nerve.

Not all patients will benefit from the ARM procedure. Only 42.7% of the patients had lymphatic channels from the arm in the SLNB field, posing them at particular risk of disruption. Of those, 3.9% had common channels draining the arm and the breast, although none of these lymph nodes had metastases. These patients would have some disruption of the arm lymphatics no matter what technique is used to stage the axillae. But the remaining 38.9% of patients at risk can avoid arm lymphatic injury using the ARM procedure. This is of particular benefit in 5.5% of the cases, where the arm lymphatics juxtaposed to the SLN will be resected in virtually all patients when not clearly delineated.

A clear downside of the ARM approach is the fact that at present, about one-third of SLN mapping is still done with blue dye alone. To use ARM, these surgeons would have to use radioactivity in the breast to use the blue dye in the arm.

The extent of lymphatic channel disruption required to cause clinically significant lymphedema is unknown. The reported rate of lymphedema after SLN biopsy is very similar to our finding of 9.4% of patients expected to sustain some degree of arm lymphatic drainage disruption, that is, those with cross over and those with juxtaposed lymphatics. This suggests that identification and preservation are essential in decreasing postoperative lymphedema rates.

Our study is limited by the small number of patients and relative inexperience with the procedure inherent to a newly devised technique. An ongoing trial is quantifying arm measurements after ARM and SLNB, ALND, or both. With short-term followup only, lymphedema has not occurred in any patients undergoing successful preservation of their lymphatics with ARM. Lymphedema developed in two of 12 patients in whom the blue ARM node or lymphatic was knowingly resected. So the success of this procedure at reducing lymphedema is yet to be determined, but at least it gets us closer to our goal. Larger multicenter trials of safety and efficacy are being planned.

Even though all patients in whom a blue node was resected were negative for malignancy, future studies with a larger number of patients and longterm followup will allow us to test our initial results and also to elucidate the risk of missing a positive axilla when preserving blue nodes.

In summary, a substantial number of patients are susceptible to arm lymphatic injury during an SLNB because of the ARM node anatomic location. An injury to these arm lymphatic channels can be prevented by identification with the ARM procedure. Nonconcordance of arm and breast lymphatic drainage, even in diseased axillae, allows its use for SLNB and for ALND. Current data suggest that blue lymph nodes can be safely preserved. Because many and varied procedures have failed to fix lymphedema, it is our opinion that prevention is the key to avoiding lymphedema. Axillary reverse mapping may help us optimize the technique of axillary staging when performing SLNB.

Author Contributions

Study conception and design: Boneti, Korourian, Adkins, Henry-Tillman, Klimberg
Acquisition of data: Boneti, Henry-Tillman, Klimberg
Analysis and interpretation of data: Korourian, Adkins, Klimberg
Drafting of manuscript: Boneti, Bland, Cox, Henry-Tillman, Klimberg
Critical revision: Boneti, Korourian, Adkins, Klimberg

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Discussion

DR KIRBY I BLAND (Birmingham, AL): President Burns, Secretary Britt, Fellows and Guests of the Association, it is a pleasure to discuss this excellent addition to the Breast Oncology literature by Drs. Boneti, Klimberg, and associates of the University of Arkansas. These authors have made major contributions to the literature and have presented virtually annually at this Association.

As indicated by the authors, axillary lymph node status remains the strongest prognostic variable for prediction of outcomes in breast carcinoma despite the application of various risk parameters in the molecular age of staging. Many studies currently exist in the literature which state that sentinel lymph node biopsy (SLNB) has an accuracy exceeding 95%; and currently, sentinel lymph node biopsy has supplanted the axillary lymph node dissection (ALND) as the initial procedure utilized in the management of the clinically node-negative breast cancer patient. Further, as indicated by the authors, the transection of arm lymphatics with an axillary lymph node dissection enhances the probability of chronic lymphedema and remains the most widely feared and published complication of node dissection. Rates of lymphedema with SLNB remain considerably lower than that of axillary node dissection with ranges of 0-13% compared with some series for axillary node dissection that include three-quarters of patients with Levels I-III Patey dissections. Moreover, the addition of radiation therapy combined with comprehensive node dissection will increase the lymphedema rate some 8-10 fold. Therefore, in this paper the authors hypothesize that a higher rate of lymphedema than would be expected with this simple procedure is related to disruption of low-lying arm lymphatics during the SLNB procedure. Thus, the

authors have championed the axillary reverse mapping (ARM) as a technique to decrease or prevent lymphedema related to SLNB.

The classical node distribution that we are principally concerned with are Levels I and II, e Level II, overlies the axillary vein and the four groups in Level I: external mammary, Rotters' nodes (inner pectoral group), subscapular, and lateral nodal groups. In the technique the authors have used the dermal blue dye that is injected in the ipsilateral upper extremity to localize lymphatics that drain the arm. As one can predict from the cutaneous distribution of the upper extremity, as well as the breast, localization of blue lymphatics that drain the arm are visible from the SLN incision and locate near or within the SLN field in 43% of the cases. Importantly, crossover of blue arm lymphatics with the hot SLN was seen in only 4% of patients. As emphasized by the authors, it is this 43% of axillary nodes with blue arm lymphatics near or juxtaposed to the 6% of axillary nodes that place them in harms way for sentinel lymph node biopsy. Almost certainly, this is the inciting genesis for the increasing lymphedema seen with the sentinel lymph node biopsy. However, not all of these patients will benefit from the procedure as described by the authors, as only 43% of all patients had lymphatics from the arm in the SLN field, thus increasing their risk for disruption with lymph node dissection. The authors have determined that approximately 39% of all patients at risk can have avoidance of harm to the lymphatics using the ARM procedure. I, therefore, have some questions for the authors.

Please give us some estimate, in view of your significant experience with the ARM procedure, of the learning curve for ARM. Is it as extensive as that many of us have gone through for the SLNB, requiring some 25-40 patients to have consistent replication of our results in SLNB?

I think it is probably unclear to many of us what is the underlying extent of lymphatic channel disruption, as a consequence of dissection, that will lead to clinically significant lymphedema. With your rate of approximately 9% for lymphedema post-SLNB, are there measures that you have utilized to enhance preservation of nodes in the apron you describe? You have proposed in your manuscript an ongoing trial to measure lymphedema with ARM after SLND and/or ALND. What is the success rate thus far of the trial that you are accruing patients to study and can you give us any preliminary thoughts, concepts or techniques that may further enhance preservation of lymphatics with the ARM procedure?

I enjoyed this important contribution to the literature. I congratulate the authors and I thank the membership for the privilege of the floor.

DR HARRY D BEAR (Richmond, VA): This is a very nice paper and a nice description of anatomy of the lymphatics. I have a couple of comments and two questions.

The comment is that at least in the very limited incision that most of us make to do a sentinel node biopsy, I wonder how many of us would actually identify the lymphatics that you have shown at least in the illustrations you presented here. And more importantly, most of us still use both blue dye and radioisotope to map and identify the sentinel lymph nodes draining the breast, and all of us, I think, have had the experience of finding blue nodes that are not hot and hot nodes that are not blue, either of which may be the only positive sentinel node. So I for one and others I have talked to are loathe to give up using the blue dye to help with the sentinel mapping procedure.

So that leads to two questions. One, do you have any evidence that this does not alter the accuracy of the sentinel lymph node biopsy procedure by doing this using the blue dye to identify the ARM lymphatics? Secondly, is there any work on finding a dye of a second color that would actually make it possible to use blue dye in the breast and a second dye to map the ARM lymphatics so that we didn't have to give up the colored dye for the sentinel nodes?

DR R PHILLIP BURNS (Chattanooga, TN): I have a couple of questions as well. Now that we have heard this, a very simple question, should we all be doing it to avoid the potential for lymphedema? And the other one is that at least at our institution we now cannot get the isosulfan blue, and I know there are reports, I think, of a higher incidence of anaphylactic reactions with methylene blue. Do you do anything to protect the patient? Is methylene blue what you use, or is there any other dye potentially out there that we might be able to use?

DR V SUZANNE KLIMBERG (Little Rock, AR): First, basically I called this the ARM procedure because I wanted to be able to explain to patients that it is for the arm. And then I tried to figure out an acrostic that would work for that. And I called it reverse because it is the opposite of the breast, because we tried to map the breast sentinel lymph node to take it and here we are mapping it to leave it behind.

The learning curve, I think, is about the same as with the sentinel lymph node, at least in my 25 hand cases or so, because we reported our earlier experience, and we are about 85% in axillary lymph node dissections in identifying these lymphatics. I think surgeons who do sentinel lymph node for melanoma probably would not need much of a learning curve at all because they are already looking at some of these lymphatics.

I am not sure about your second question, Dr Bland, about the axillary lymph node dissection and the underlying extent. I didn't quite get what you meant by that.

I think we really don't know the anatomy. This is really the first paper to describe it, because we have always we have always looked at the axilla and said it is an apical node, it is a lateral node, et cetera. But that doesn't really tell you that much about where it drains from. If you look at the Foley and the lymphology of data, they really look at more where it drains from from the specific arm as the diagram I showed you.

Our ongoing trial we are trying to get NIH to fund because I think this is an important thing. But what we are doing is just training anybody who wants to start doing this.

I think with the blue dye. We have trouble getting blue dye, too. So what we have done, and it is something anybody can do, we went to a compounding pharmacy in our town — and Little Rock is not that big — and they can make it for us. So we send the patients with a prescription. And it is really not that hard.

I do not use blue dye. They did make a mistake when we were doing a plastic surgery procedure and handed me the plastic surgeon's methylene blue and injected it. And as you know, people have reported necrosis, et cetera. You can use steroid in that area if that should happen. I don't recommend it. I think it doesn't identify the lymphatics as well, so I wouldn't do that. And you can get a compounding pharmacy to do any of that.

A second color would be difficult, because if you think about it, if it is green it is too close to blue, if it is yellow it is too close to fat, if it is red it is bloody. So it is a very difficult problem to find a different color. You could use fluorescents. You could use a number of things.

I think that the people using two different colors, lymphatic or radioactivity and blue dye together only helps you in your initial learning curve, and after awhile if you are good at either one of them, you can use either one of them successfully with a high localization rate, as I showed you 98%. And that is as good as most studies.

Should we all be doing it? Well, I think so. You are cutting through things you can't see. This allows to you see what is really there. And I think Dr Bear mentioned, this is 40% I can see from a limited sentinel lymph node site. The work I showed you as far as the whole anatomy and these different variations we got from actual lymph node dissections and just cataloging them. And this is just the beginning of it. But you can see there are lots of variations. They are low on the axilla. They are not where we thought they were. The studies that have been done are just not there. So I think it allows to you see more, and why wouldn't you do it. About two-thirds of people are using radioactivity, a third of people are using blue dye alone. But that is going to change as we have shortages, et cetera. But I think you can use this from a compounding sense. You could use any color, green dye or whatever, but this seems to have the most data for being able to see lymphatics.