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Axillary Reverse Mapping: Five Year Experience

Daniela Ochoa, M.D.^{1,*}, Soheila Korourian, M.D.², Cristiano Boneti, M.D.¹, Laura Adkins, MS.¹, Brian Badgwell, M.D., MPH³, and V. Suzanne Klimberg, M.D.^{1,2,**}

¹Department of Surgery, University of Arkansas for Medical Sciences and the Winthrop P. Rockefeller Institute, Little Rock, Arkansas

²Department of Pathology, University of Arkansas for Medical Sciences and the Winthrop P. Rockefeller Institute, Little Rock, Arkansas

³Department of Surgical Oncology, M.D. Anderson Cancer Center

Abstract

BACKGROUND—We hypothesize that mapping the lymphatic drainage of the arm with blue dye (axillary reverse mapping, ARM) during axillary lymphadenectomy decreases the likelihood of disruption of lymphatics and subsequent lymphedema.

METHODS—This institutional review board-approved study from May 2006 to October 2011 involved 360 patients undergoing SLNB and/or ALND. Technetium sulfur colloid (4 mL) was injected subareolarly and 5 mL of blue dye was injected subcutaneously in the volar surface ipsilateral upper extremity (ARM). Data were collected on variations in lymphatic drainage, successful identification and protection of arm lymphatics, crossover, and occurrence of lymphedema.

RESULTS—A group of 360 patients underwent SLNB and/or ALND. A total of 348 patients underwent a SLNB. Of those, 237/348(68.1%) had a SLNB only and 111/348(31.9%) went on to an ALND due to a positive axilla. An additional 12/360(3.3%) axilla had ALND due to a clinically positive axilla/preoperative core needle biopsy. In 96%(334/348) of patients with SLNB, breast SLNs were hot but not blue; crossover (SLN hot and blue) was seen in 14/348(4%). Blue lymphatics were identified in 80/237(33.7%) of SLN incisions and in 93/123(75.4%) ALND. Average follow-up was 12 months (range 3 to 48 months) and resulted in a SLNB lymphedema rate of 1.7%(4/237) and ALND of 2.4%(3/123).

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Address for correspondence: V. Suzanne Klimberg, MD, Rockefeller Cancer Institute, UAMS, Slot 725, Little Rock, Arkansas 72212, klimbergsuzanne@uams.edu.

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CONCLUSIONS—ARM identified significant lymphatic variations draining the upper extremities and facilitated preservation. Metastases in ARM-identified lymph nodes were acceptably low indicating that ARM is safe. ARM added to present-day ALND and SLNB may be useful to lower lymphedema rates.

Keywords

breast; breast cancer; lymphadenectomy; sentinel; axillary reverse mapping

Introduction

Lymphedema remains the most published complication of axillary lymph node dissection (ALND).^{1,2,3,4,5,6,7,8,9,10,11,12,13,14,15,16,17,18,19,20,21,22,23} The technique of ALND is a purely anatomical dissection and has changed little over the decades.²⁴ However, the procedure itself does not take into account the anatomical drainage from the breast versus that of the arm because drainage from the arm into the axilla has only recently been published by our group.^{25,26,27,28} Yet, lymphedema likely results from transection of lymph vessels from the arm coursing through the axilla and is one of the most distressing complications resulting from ALND.^{29,30} The morbidity of lymphedema especially from an ALND is such that some have advocated sentinel lymph node biopsy as the only treatment for patients with one to two positive nodes when undergoing breast conservation surgery (BCS) with whole breast radiation (XRT) because the LRR and OS are unchanged in the group with CALND over SLNB. However, there is not similar data for partial breast irradiation or mastectomy patients.³¹ This treatment approach has only limited experience and follow-up. Its application is also limited to specific subgroups of patients i.e. those with small hormone sensitive tumors who are clinically node negative undergoing BCS with whole breast XRT, excluding patients who undergo partial breast radiation or mastectomy. We alternatively propose that trying to identify and spare the lymphatics draining the upper extremities may be a better approach to decreasing the morbidity from lymphadenectomy.^{32,33,34} We hypothesized that mapping the lymphatic drainage of the arm with blue dye (axillary reverse mapping, ARM) to delineate and preserve the lymphatics draining the arm during lymphadenectomy added to intraoperative technetium to map the drainage of the breast may decrease the likelihood of disruption of lymphatics and subsequent lymphedema. To this end we present the short-term follow-up of a Phase II single institution prospectively accrued cohort of patients undergoing ARM.

Methods

This institutional review board and Radiation Safety and Monitoring Committee approved this study that involved patients undergoing sentinel lymph node biopsy (SLNB) and/or ALND. Technetium sulfur colloid (~4 mL) was injected in the subareolar plexus, and ~5 mL of isosulfan blue dye was subcutaneously injected in the ipsilateral volar surface of the upper extremity (ARM). Data were collected on variations in lymphatic drainage that impacted SLNB or ALND, successful identification and protection of the arm lymphatics, any crossover between a radioactive breast node and a blue ARM node, and occurrence of lymphedema.

Patients

Patients undergoing SLNB and/or ALND were enrolled in a prospective, single-arm trial at the Winthrop P. Rockefeller Cancer Institute. The study was approved by the University of Arkansas for Medical Sciences Institutional Review Board. All patients requiring a SLNB or ALND were invited to participate in the study. This is an extension of our ongoing series and 4th publication on this cohort which began in May 2006.³⁵

SLN procedure

The SLNB technique has been described in detail in previous studies.^{36,37} In brief, a subareolar plexus injection of 1.0 mCi of unfiltered technetium sulfur colloid diluted to a final volume of 4 mL was intraoperatively administered immediately after induction of general anesthesia. After routine prep and drape, a handheld gamma probe (Neoprobe Corporation, Dublin, OH) was used to localize radioactivity (hot lymph node) before skin incision.

ARM procedure

As previously described, most lymphatics from the distal arm enter the axilla along the volar surface of the upper arm.³⁸ There can be alternate anatomy, for example a branch that courses in the deltopectoral groove and thus can completely bypass the axilla.³⁹ ARM was performed by injecting 5 mL of blue dye deep subcutaneously in the ipsilateral upper inner arm for localization of lymphatics draining the arm.^{33,34,40,41} The SLNB was then performed through the mastectomy incision or an incision in the axilla. The ARM procedure always included both radioactivity in the breast as well as blue dye in the arm because in a small fraction of patients, the ARM node will also be the SLN from the breast.^{34,35,38} Also in patients with a heavily positive axilla, the tumor can cause obstruction of the lymphatic drainage and theoretically lead the tumor to flow retrograde into the nodes primarily draining the arm. Dual mapping, one from the breast and one from the arm determines the presence of crossover between the breast and arm drainage.(Figure 1 and 2). Initially when there was cross-over, ie the ARM node was also the SLN, the ARM node was taken. Later in the study, when ARM nodes were removed there was a significant effort made to reanastomose the remaining afferent and efferent lymphatics.

ALND

When the SLN was positive and a mastectomy was performed, the ALND was completed through the same incision; otherwise, a separate axillary incision was made. An anatomical resection of level I and level II lymph nodes was completed taking care to identify and preserve blue lymphatics.⁴⁰ If the radioactive sentinel node was also a blue node, or was suspicious (palpable or via ultrasound), the ALND included the blue nodes and lymphatics; otherwise, the blue lymphatics and blue nodes were preserved. When possible after removing blue ARM nodes the remaining afferent and efferent lymphatics were anastomosed using 7.0 to 9.0 prolene.⁴¹ This was documented intraoperatively.

Pathology

Lymph nodes were sectioned at 3-mm intervals in the long axis unless the lymph node itself was smaller than 5 mm in which case they were bisected. Intraoperative touch prep cytology was performed followed by permanent section and routine hematoxylin and eosin (H&E) staining.^{9,42} Lymph nodes from the completion ALND were bisected along the long axis, and one section from each node was submitted for H&E staining.

Lymphedema Assessment

The arm volume measurements were obtained by water volume displacement as previously described in our initial series.^{34,40} Briefly, a mark was placed 10 cm proximal from the lateral epicondyle. The arm was then inserted into a cylinder filled with water up to the mark on the arm. The water displacement was recorded at baseline and every 6 months over a 4-year follow-up period. The arm volume of the contralateral arm was similarly measured as a control for weight gain or loss. The arm volume increase was obtained by subtracting the volume change on the contralateral side from the volume change on the affected side using the formula $[(\text{affected current volume} - \text{affected baseline volume}) / (\text{affected baseline volume}) \times 100] - [(\text{contralateral current volume} - \text{contralateral baseline volume}) / (\text{contralateral baseline volume}) \times 100]$. This protocol is based on the same protocol used for the NSABP B 32 Protocol for arm volume measurements.⁴³ Based on the consensus document of the International Society of Lymphology, an arm volume increase of the affected side over the opposite side of 20% or more was considered lymphedema.⁴⁴

Statistics and Data

Data were collected in a prospective database in Microsoft Excel (Microsoft Corporation, Redmond, WA) on identification rate, variations in lymphatic drainage, ARM lymphatics preservation rate, nodal status, and lymphedema rate at 6 month intervals. Results were examined with descriptive analysis utilizing SigmaPlot (Systat Software Inc, San Jose, CA).

Results

Study Population

The 360 patients included in the study received standard surgical treatment for the primary breast cancer (i.e. Lumpectomy or mastectomy) and axillary staging including SLNB alone, SLNB followed by ALND, and ALND only. Their average age was 56+/- years old. Of 336 invasive cancers, 67% (225/336) were T1 lesions, 24.4% (80/336) were T2, and 6.5% (22/336) patients had T3 lesions. In 9 (2.7%) cases the tumor size could not be accurately assessed. Patients with metastatic axillary disease had N1 disease in 76.1% (83/109) of the cases, N2 disease in 15.5% (17/109) and N3 disease in 8.2% (9/109).

Average follow-up was 12 months \pm 13.6, SD for all 360 patients. Only nine patients (2.5%) were lost to follow-up. Eleven patients died during the study. A total of 122 patients had the surgical procedure recently done and no follow-up information is available yet. The remaining 238 patients had an average follow-up of 18 months (range 3 to 48 months), and were used in the analyses for lymphedema outcome. The 20 patients who were lost to

follow-up or are deceased were included only in the analyses regarding the anatomy and blue nodes involved by malignancy.

Surgical Procedure

A total of 348 patients underwent a SLNB. Of those, 237/348(68.1%) had a SLNB only and 111/348(31.9%) went on to an ALND due to a positive axilla. An additional 12/360(3.3%) axilla had ALND due to a clinically positive axilla/preoperative core needle biopsy.

Anatomy

Blue lymphatics were identified in 80/237(33.7%) of SLN incisions and in 93/123(75.4%) of ALND. In 96%(334/348) of patients with SLNB, breast SLNs were hot but not blue. Crossover (SLN hot and blue) was seen in 15/348(4.3%) SLN procedures. Blue nodes were found to be juxtaposed yet separate in 36/360(10%) overall which would place them at risk of injury. When blue lymphatics were seen within the SLN bed, the blue ARM node was juxtaposed to the SLN in 28/80(35%). Anatomical variations seen included: above or below the axillary vein, slings, and aprons. Even in patients in whom a blue node was resected, there were cases where additional blue lymphatics visualized within the wound were able to be spared.

Pathology

Of the resected ARM nodes, 5 of 27 (18.5%) contained tumor. Two of these ARM nodes were in cases of crossover with one each being yN1 and N2 disease. The other 3 cases were palpable or entrapped nodes in heavily positive axilla (N2 or N3) without crossover.

Of the 4% of cases where crossover (concordant with SLN) was identified and nodes resected, 2/15(14.3%) contained malignancy. Of the blue only nodes resected, 3/12(25%) were positive. Of the total 96% non-concordant axilla, 3/345(0.9%) blue nodes were involved by malignancy, all in heavily positive axilla.

Of the transected ARM lymphatics, the lymphatics were anastomosed in three patients. One lymphatic was partially avulsed during dissection. The other two were clinically positive/not hot, blue nodes (N1: 3/8 & 4/26).

Lymphedema

Overall 20/238(8.4%) patients undergoing SLNB and/or ALND either experienced an objective finding of lymphedema or were treated for lymphedema based on subjective symptoms. Objective findings of volume difference were seen in 7/238(2.9%). Two patients had an objective volume difference measured earlier in follow-up that has since improved, although they never experienced any symptoms subjectively. Another 5 patients had objective findings at their last follow-up, but only three of them experienced symptoms and sought treatment. A total of 13 patients experienced subjective symptoms of lymphedema for which they were treated, but they either showed no objective volume difference or did not meet the threshold volume increase for what was considered lymphedema.⁴⁴ Of those patients with objective findings of lymphedema, we found a SLNB lymphedema rate of 2.5%(4/158) and ALND of 3.7%(3/80). Specifically looking at the group of patients in

which blue lymphatics were able to be identified and preserved, we found a SLNB lymphedema rate of 1.7%(1/58) and ALND of 4.8%(3/62). In those patients in which an identified blue lymphatic was transected, there was a 1/22(4.5%) lymphedema rate. That patient has since improved with treatment. In the cases in which there were no blue lymphatics identified in the surgical field, the incidence was 2/94(2.1%). The use of the 20% volume change was based on an effort to report our data in a manner which would allow comparison to other groups/studies. When we apply the Cancer Therapy Evaluation Program, Common Terminology Criteria for Adverse Events (CTEP) grading system to evaluate those patients with smaller volumetric differences and differentiate how many of our patients experienced greater degrees of severity as a percentile of the lymphedema group, we note that of the SLN patients who developed LE, 5% were Grade 3, 35% Grade 2, and 60% were Grade 1. Of the ALND patients, 5% were Grade 3, 50% were Grade 2, and 45% were Grade 1. Using ARM, we had only 3 patients who experienced Grade 3 lymphedema which underscores the utility of the technique.⁴⁵

Of those patients in which blue lymphatics were preserved and lymphedema was found, the SLN case demonstrated lymphedema at 18 months and the ALNDs cases demonstrated lymphedema at 6, and 12 months (x2). Of the 3 patients in which the blue lymphatics were reanastomosed, there were no cases of lymphedema.

Recurrence

Blue lymphatics were identified in a total of 173 patients; they were able to be preserved in 137/173(79.2%) cases in which they were identified. In this group there were 11/173(6.4%) distant recurrences and 2/173(1.2%) local recurrences. There was one axillary recurrence over an average follow-up of 12 months. This was found at 17 months of follow-up and was in a patient in which blue dye was not identified and therefore no blue nodes were specifically preserved.

Discussion

This Phase II study represents the largest series reported to date on ARM and the only one demonstrating the effectiveness of the ARM procedure in preventing lymphedema. We showed many anatomical variations including that were well below the axillary vein, the traditional superior border of an axillary lymph node dissection.²⁴ The most consistent drainage was to the lymph node just below the vein and just on or lateral to the tendon of the Latissimus, followed by the sling, the apron and those surrounding the axillary vein. The apron required the most tedious dissection in order to separate and spare uninvolved ARM lymphatics. This cohort of patients experienced an overall lymphedema rate of 20/238(8.4%) including both objective findings of lymphedema, as well as subjective symptoms. Objective findings of volume difference were seen in 7/238(2.9%), while another 13 patients experienced subjective symptoms but either showed no objective volume difference or did not meet the threshold volume increase for what was considered lymphedema.⁴⁴ Some of these complaints of “lymphedema” resolved with treatment of pain issues indicating that patients have heard of lymphedema but don’t really know what it is. In

addition, of the three patients in which the lymphatics were transected and reanastomosed, there were no cases of objective or subjective lymphedema.

In our original study³⁴ the blue nodes were taken as a routine; the contrast with this study is that we only took them if they had crossover or appeared abnormal. Others have shown rates of metastatic involvement of blue nodes between 14 and 43%, almost exclusively in patients with N2 or N3 disease. (Table 1) Of note, these investigators did not use our described technique of dual mapping where radioactivity is used to map the breast and blue dye to map the arm. (Table 1) Notably Kang and colleagues did use our described dual mapping technique and had similar results demonstrating that nodes with blue dye alone are rarely positive.⁵³ Kang reported a 36% rate of malignancy in the blue nodes with crossover and only 1.3% in non-concordant axilla. In our study, 5/27(18.5%) of the resected ARM nodes contained tumor. Two of these ARM nodes were in cases of crossover with N1 and N2 disease. The other 3 cases were non-concordant in palpable or entrapped nodes in heavily positive axilla (N2 or N3) without crossover. We therefore found a 2/15(14.3%) rate of malignancy in the concordant cases and only 3/334(0.9%) in nonconcordant but heavily positive axilla. Today all of these would be resected and reanastomosed.

Furthermore, only one axillary recurrence was seen, and this was in a patient in which blue dye was not identified and therefore no blue nodes were specifically left behind. This recurrence was found 17 months after modified radical mastectomy for yT2(4cm)N1(3/7) disease. When found, the patient was as well noted to have distant metastatic disease present within her liver. The finding that when blue lymphatics were spared in this fairly large trial with 12 month average follow-up and as long as 48 month follow-up is a surrogate for the safety of ARM despite leaving blue non-radioactive nodes lymph nodes in the axilla. This is particular true as patients with four or more positive nodes receive radiation.

There are ~240,000 breast cancer cases per year and an extant total of between three and five million cases of lymphedema in the US, making this one of the most significant post-operative problems.^{46,47} Reports on the incidence of lymphedema vary with measurement technique, length of follow-up, time to measurement, use of XRT and extent of surgery.⁴⁷ Symptoms of lymphedema may present within days or up to 30 years later; although 80% present within 3 years of surgery with the remainder at a rate of 1% per year.^{13,48} Volume displacement is the gold standard for measurement as subjective symptoms of pain or discomfort are often mistaken for lymphedema. Sentinel lymph node biopsy (SLNB) was developed in an effort to prevent the high morbidity seen with ALND; however, cooperative group trials have still shown lymphedema rates of approximately five to eight percent with SLN biopsy alone.⁴³ In the American College of Surgeons Oncology Group Z0010 prospective observational study,⁴⁹ lymphedema, defined as a change in arm circumference of >2 cm when compared with the contralateral or control arm and with baseline measurements, occurred at a rate of nearly 7%. Multiple comparison studies, several of which were randomized, have confirmed lower morbidity and lymphedema rates for SLNB when compared to ALND. Lymphedema in ALND groups ranges from 13 to 77%, varying with how closely lymphedema was monitored, length of follow-up,¹⁹⁻²³ questionably the number of positive lymph nodes,⁵⁰ post-operative irradiation,¹² extent of surgery, body habitus and a number of other patient characteristics.^{43,51} Although the lymphedema rate

was much lower with the SLNB, it was still clinically significant with a range of 0 to 13% and NSABP B-32 found lymphedema with SLNB to be ~8%.⁴³ Thus, sentinel lymph node biopsy has improved but not taken away the problem of lymphedema. Our group placed 97 patients on the B-32 protocol. Our groups' lymphedema rate was 8% for SLNB and 23% for ALND on B-32. The exact lymphedema measurement schedule and protocol was used for the present study and lymphedema rates with ARM are sequentially comparable to and improved over our B-32 rates.

Surprisingly, just as many women get lymphedema from a negative SLNB as ALND. Even though the rate of lymphedema from SLNB is only about one-third of that with ALND, the number of SLNBs performed is approximately three-fold that of ALND. In the present study, a blue lymphatic was seen in 80/237 SLNB only procedures. In 7 of these SLNB-only (small incision) procedures crossover was identified; therefore in 73/237(30.8%) a blue lymphatic was identified that would otherwise have been in harm's way in a negative axilla. These are the cases in which we consider it to be most useful, so that patients who do not even have axillary disease are not placed at an unnecessary risk. So there is need for an improved method of SLNB as well as ALND. The technique of ALND is variable in practice but the basic anatomic principles have not changed in decades. So surgeons don't necessarily need to stop doing ALNDs for positive lymph nodes but change the principles and technique of how to perform them. Therefore we hypothesized that we could decrease the rate of lymphedema for both SLNB and ALND using the technique of ARM. ARM allows us to identify lymphatics that are in the surgical field but primarily drain the upper extremity. By identifying and avoiding transection of these lymphatics, we are thus able to further minimize the morbidity of these procedures while not compromising our oncologic resection.

Conclusions

This study demonstrates that ARM identified significant lymphatic variations draining the upper extremities and facilitated preservation. Metastases in ARM-identified lymph nodes were acceptably low indicating that ARM is safe. ARM added to present-day ALND and SLNB may be useful to lower lymphedema rates. ARM represents a way to improve surgery rather than perform less surgery.

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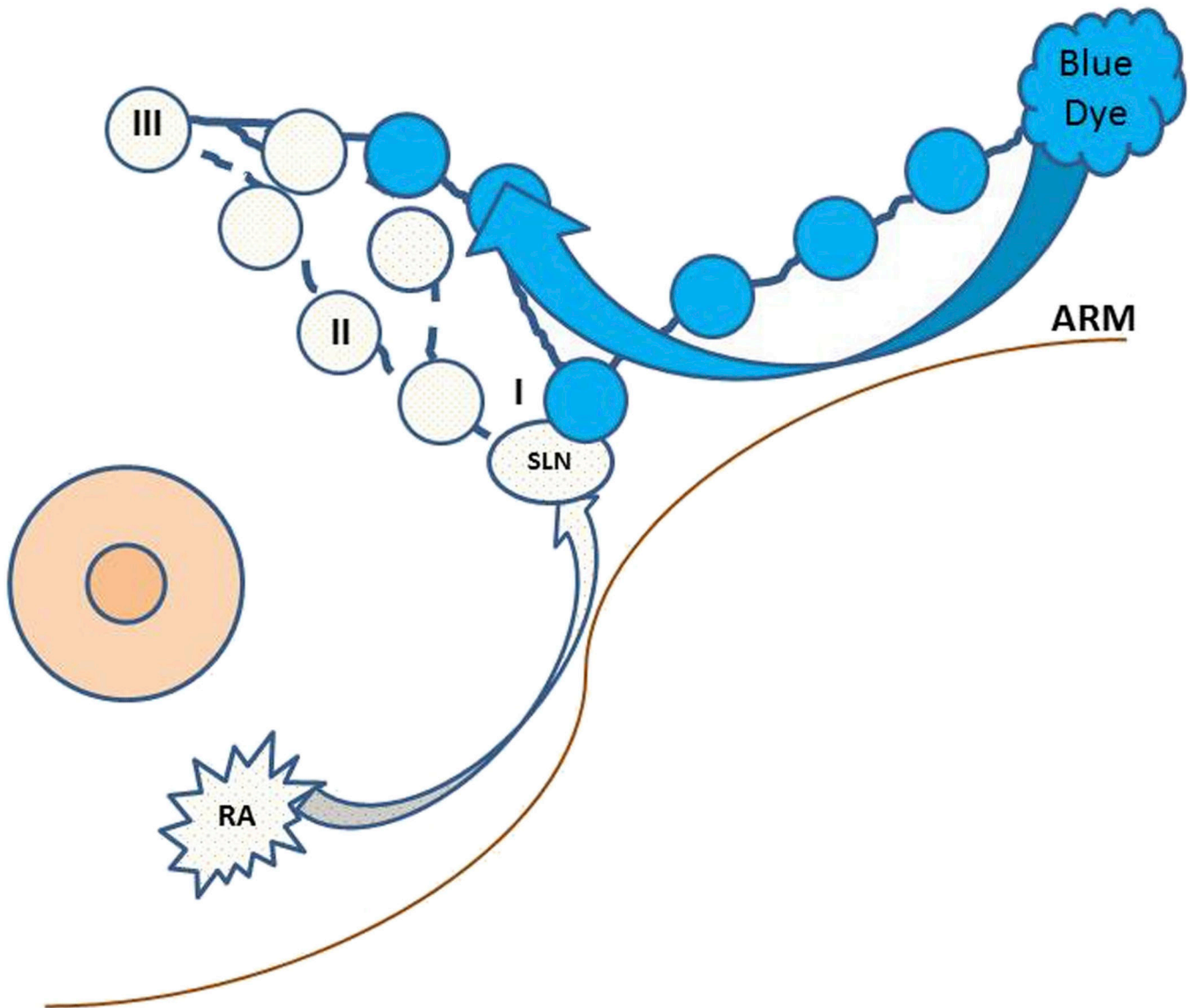


Figure 1. Confluence of breast and ARM lymphatics typically seen at level III, but variations may place ARM lymphatics within operative field of dissection (Level I or II) or in juxtaposition to SLN. RA=radioactive.

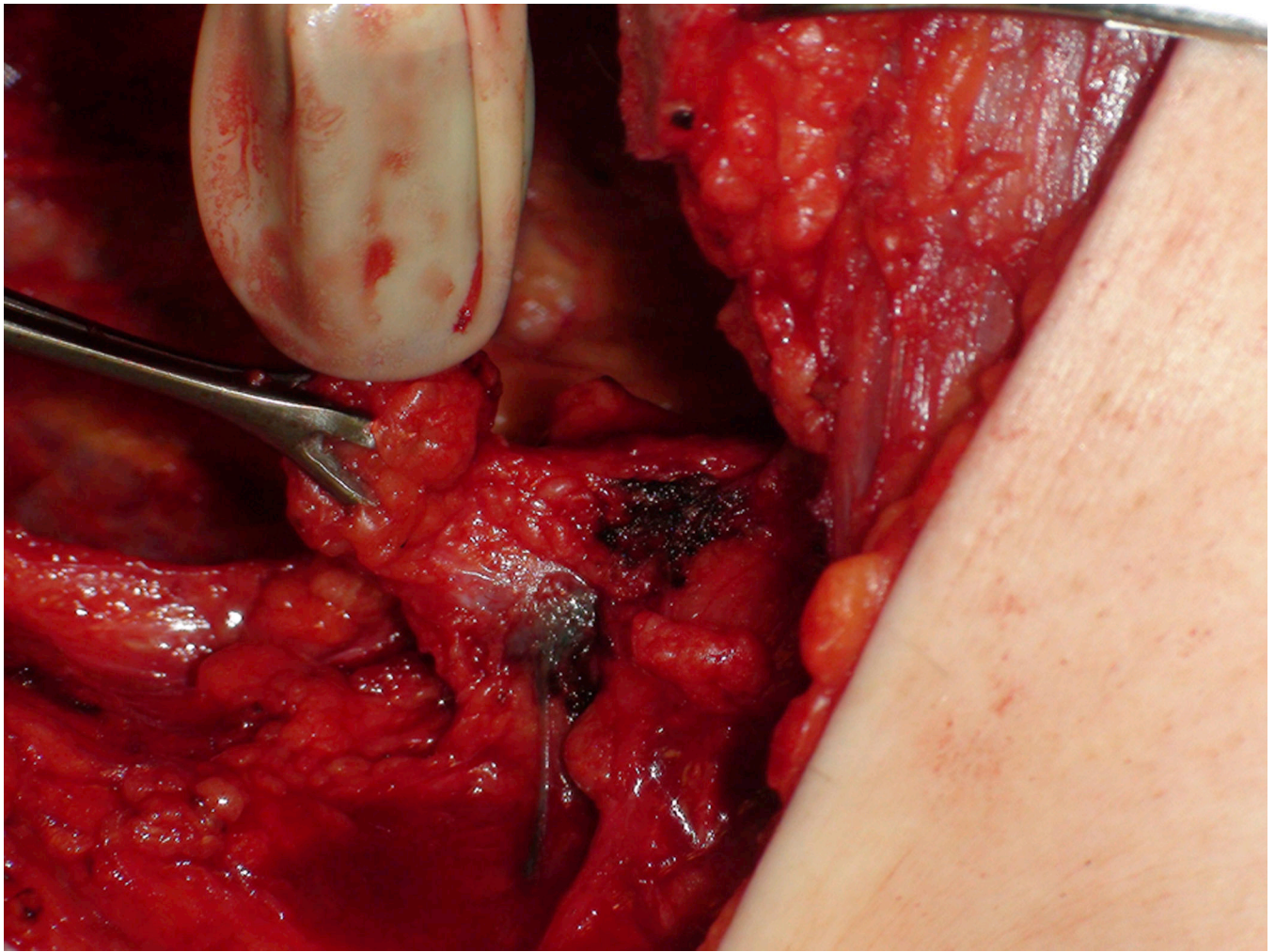


Figure 2.
Blue node seen juxtaposed to radioactive SLN (identified by gamma probe and in Babcock) without crossover and able to be spared. Afferent blue lymphatic seen connecting to blue node as well.

Table

Summary Comparison of ARM publications.

	N of pts	SLNB	ALND	Blue lymphatics or nodes ID	N nodes resected	ARM nodes removed	ARM nodes +	Crossover
Thompson Jun 2007 ³⁴	40	36	18	61% (11/18) with ALND	12.5	7 nodes	0	0
Nos Sep 2008 ³⁴	23	-	23	91% (21/23)	10.7	1.6(21 cases)	14% (3/21) all in N=>9; +Blue dye in node	-
Kang Dec 2008 ³³	129	124	48	71.6% (58/81) SLN field 89.5% (43/48) ALND	-	1.5 (96 SLNB cases and 5 ALND cases)	36% (7/19) when there is crossover 1.3% (1/77) in nonconcordant axilla	18.9% (19/96)
Casabona Jun 2009 ³⁵	72	72	9	37.5% (27/72) in the SLN field 88.9% (8/9) in ALND	SLNB 1.3 ALND 16	3 nodes	0	-
Bonetti Oct 2009 ³³	220	214	40	40.6% (87/214) in the SLN field	12.7	15	0	2.8% (6/214)
Ponzzone Nov 2009 ³⁶	49	6 of 49	49 43 Ø Tc	73.5% (34/49) ID blue Lymphatics 55.1% (27/49) ID blue nodes	-	27 cases	3 cases (18, 18 and 7 + LNs, respectively)	-
Noguchi Mar 2010 ³⁷	20	12	8	ALND 88% (7/8) SLNB 75% (9/12)	23	All cases average 2.7	None in the SLN group; 43% of ALND (3/8) (3, 13, 14+LNs) No Isotope	14% (2/14)
Bedrosian Jun 2010 ³⁸	30	-	30	70% (21/30) lymphatic 50% (15/30)nodes	26	1 av	18% (2/11 with mets) No isotope used to detect crossover	-
Ochoa 2012	360	237	123	80/237(33.7%) SLN; 93/123 (75.4%) ALND	-	27 cases	5/27(18.5%)	4.3% (15/348)