Axillary reverse mapping: Five-year experience

Daniela Ochoa, MD,[a] Soheila Korourian, MD,[b] Cristiano Boneti, MD,[a] Laura Adkins, MS,[a] Brian Badgwell, MD, MPH,[c] *and* **V. Suzanne Klimberg, MD,[a,b]** *Little Rock, AR, and Houston, TX*

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 involved 360 patients undergoing sentinel lymph node biopsy (SLNB) and/or axillary lymph node dissection (ALND) from May 2006 to October 2011. 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, 348 of whom underwent a SLNB. Of those, 237 (68.1%) had a SLNB only, and 111 (31.9%) went on to an ALND owing to a positive axilla. An additional 12 of 360 (3.3%) axilla had ALND owing to a clinically positive axilla/preoperative core needle biopsy. In 96% of patients with SLNB (334/348), breast SLNs were hot but not blue; crossover (SLN hot and blue) was seen in 14 of 348 patients (4%). Blue lymphatics were identified in 80 of 237 SLN incisions (33.7%) and in 93 of 123 ALND (75.4%). Average follow-up was 12 months (range, 3–48) and resulted in a SLNB lymphedema rate of 1.7% (4/237) and ALND of 2.4% (3/123).*

Conclusion. *ARM identified substantial 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 lesser rates of lymphedema. (Surgery 2014;156:1261-8.)*

From the Departments of Surgery[a] and Pathology,[b] University of Arkansas for Medical Sciences and the Winthrop P. Rockefeller Institute, Little Rock, AR; and the Department of Surgical Oncology,[c] MD Anderson Cancer Center, Houston, TX

Lymphedema remains the most published complication of axillary lymph node dissection (ALND).[1-23] The technique of ALND is an anatomic dissection and has changed little over the decades.[24] The procedure itself, however, does not take into account the anatomic 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.[25-28] Yet, lymphedema likely results from transection of lymph vessels from the arm coursing through the axilla and is among the most distressing complications resulting from ALND.[29,30] The morbidity of lymphedema especially from an ALND is such that some surgeons have advocated sentinel lymph node biopsy (SLNB) as the only treatment for patients with 1–2 positive nodes when undergoing breast conservation surgery, with whole breast radiation (XRT), because the local regional recurrence (LRR) and overall survival (OS) are unchanged in the group with complete ALND over SLNB. There are no similar data for partial breast irradiation or mastectomy patients.[31] Indeed, this treatment approach has only limited experience and follow-up. Its application is also

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Reprint requests: V. Suzanne Klimberg, MD, Rockefeller Cancer Institute, UAMS, Slot 725, Little Rock, AR 72212. E-mail: klimbergsuzanne@uams.edu.

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limited to specific subgroups of patients, namely, those with small, hormone-sensitive neoplasms who are clinically node negative undergoing breast conservation surgery with whole breast XRT, excluding patients who undergo partial breast XRT or mastectomy. We propose alternatively that trying to identify and spare the lymphatics draining the upper extremities may be a better approach to decreasing the morbidity from lymphadenectomy.[32-34] 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 administration of 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 involving patients undergoing SLNB and/or ALND. Technetium sulfur colloid (~4 mL) was injected in the subareolar plexus, and ~5 mL of isosulfan blue dye was injected subcutaneously 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 fourth publication on this cohort, which began in May 2006.[35]

Sentinel lymph node 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 administered intraoperatively, 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.

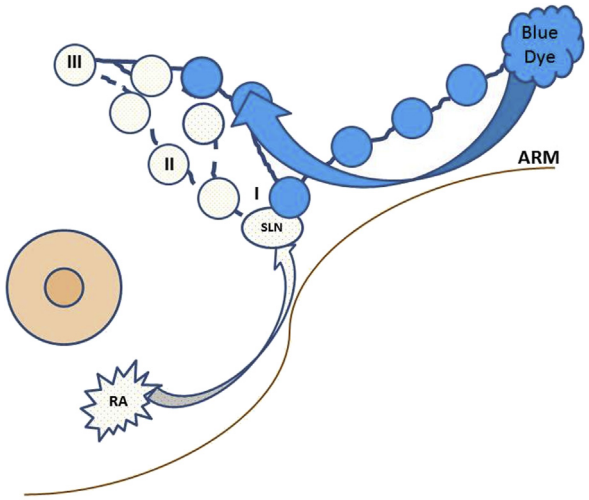

Fig 1. Confluence of breast and axillary reverse mapping (ARM) lymphatics typically seen at level III, but variations may place ARM lymphatics within operative field of dissection (level I or II) or in juxtaposition to SLN. *RA*, Radioactive.

ARM procedure. As described previously, 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 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] 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, 1 from the breast and 1 from the arm, determines the presence of crossover between the breast and arm drainage (Figs 1 and 2). Initially when there was crossover, that is, when the ARM node was also the sentinel lymph node (SLN), the ARM node was taken. Later in the study, when ARM nodes were removed, there was a conscious effort made to "reanastomose" the remaining afferent and efferent lymphatics. Their "reanastomosis" is not a lumen-to-lumen anastomosis, but rather a reapproximation of the transected ends of the lymphatic channel.

ALND. When the SLN was positive and a mastectomy was performed, the ALND was

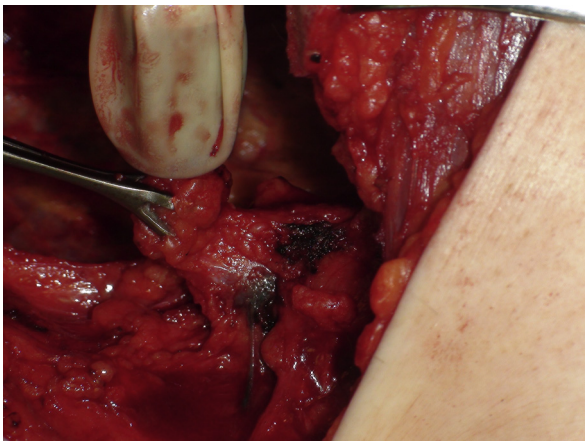

Fig 2. Blue node seen juxtaposed to radioactive sentinel lymph node (SLN; identified by gamma probe and in Babcock) without crossover and able to be spared. Afferent blue lymphatic seen connecting to blue node as well.

completed through the same incision; otherwise, a separate axillary incision was made. An anatomic resection of level I and 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 ultrasonography), 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 7.0–9.0 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 <5 mm, in which case they were bisected. Intraoperative touch-prep cytology was performed followed by permanent section and routine hematoxylin and eosin staining.[9,42] Lymph nodes from the completion ALND were bisected along the long axis, and 1 section from each node was submitted for hematoxylin and eosin staining.

Lymphedema assessment. The measurements of arm volume were obtained by water volume displacement as described previously 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 measured similarly 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 [(affected current volume − affected baseline volume)/(affected baseline volume) × 100] − [(contralateral current volume − contralateral baseline volume)/(contralateral baseline volume) × 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% 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 underwent standard operative treatment for the primary breast cancer (ie, lumpectomy or mastectomy) and axillary staging, including SLNB alone, SLNB followed by ALND, and ALND only. Their average age was 56 years. Of 336 invasive cancers, 67% (225/336) were T1 lesions, 24.4% (80/336) T2, and 6.5% (22/336) T3. In 9 cases (2.7%), the size of the tumor could not be assessed accurately. Patients with metastatic axillary disease had N1 disease in 76.1% (83/109), N2 disease in 15.5% (17/109), and N3 disease in 8.2% (9/109).

The mean ± standard deviation follow-up was 12.0 ± 13.6 months for all 360 patients. Only 9 patients (2.5%) were lost to follow-up; 11 died during the study. A total of 122 patients had the operative procedure done recently, and no follow-up information is available. The remaining 238 patients had an average follow-up of 18 months (range, 3–48) and were used in the analyses for lymphedema outcome. The 20 patients lost to follow-up or deceased were included only in the analyses regarding the anatomy and blue nodes involved by malignancy.

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

Anatomy. Blue lymphatics were identified in 80 of 237 SLN incisions (33.7%) and 93 of 123 ALND incisions (75.4%). In 96% of patients with SLNB

(334/348), breast SLNs were hot but not blue. Crossover (SLN hot and blue) was seen in 15/348 SLN procedures (4.3%). Blue nodes were found to be juxtaposed yet separate in 36 of 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 of 80 (35%). Anatomic 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 1 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 of 15 (14.3%) contained malignancy. Of the blue-only nodes resected, 3 of 12 (25%) were positive. Of the total 96% nonconcordant axilla, 3 of 345 blue nodes (0.9%) were involved by malignancy, all in heavily positive axilla. Of the transected ARM lymphatics, the lymphatics were anastomosed in 3 patients. One lymphatic was partially avulsed during dissection. The other 2 were clinically positive/not hot, blue nodes (N1; 3 of 8 and 4 of 26).

Lymphedema. Overall, 20 of 238 patients (8.4%) 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 of 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 3 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 difference in objective volume or did not meet the threshold for 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 whom 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 whom an identified blue lymphatic was transected, there was a 4.5% rate of lymphedema (1/22). That patient has since improved with treatment. In the patients in whom there were no blue lymphatics identified in the surgical field, the incidence of lymphedema was 2.1% (2/94). The use of the 20% volume change was based on an effort to report our data in a manner that would allow comparison with 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 lymphedema, 5% were grade 3, 35% grade 2, and 60% grade 1. Of the ALND patients, 5% were grade 3, 50% grade 2, and 45% 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 whom blue lymphatics were preserved and lymphedema was found, the SLN case demonstrated lymphedema at 18 months, whereas the ALNDs cases demonstrated lymphedema at 6 and 12 months (×2). Of the 3 patients in whom the blue lymphatics were reanastomosed, there were no cases of lymphedema.

Recurrence. Blue lymphatics were identified in 173 patients; these lymphatics were able to be preserved in 137 of 173 cases (79.2%) in which they were identified. In this group there were 11 distant recurrences among 173 patients (6.4%) and 2 local recurrences (1.2%). There was 1 axillary recurrence over an average follow-up of 12 months, which was found at 17 months of follow-up in a patient in whom blue dye was not identified and therefore no blue nodes were 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 anatomic variations that were well below (caudal to) the axillary vein, the traditional superior border of an ALND.[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 dorsi muscle, followed by the sling, the apron, and those surrounding the axillary vein. The apron required the most tedious dissection to separate and spare uninvolved ARM lymphatics. This cohort of patients experienced an overall lymphedema rate of 8.4% (20/238), including both

Table. Summary of ARM publications

Study	*No. of patients*	*SLNB*	*ALND*	*Blue lymphatics or nodes ID*	*No. of nodes resected*	*ARM nodes removed*	*ARM nodes +*	*Crossover*
Thompson et al[34]	40	36	18	61% (11/18) with ALND	12.5	7	0	0
Nos et al[52]	23	—	23	91% (21/23)	10.7	1.6 (21 cases)	14% (3/21) all in ≥9; radioactivity to ID ARM + blue dye in node	—
Kang et al[46]	129	124	48	71.6% (58/81) SLN field 89.5% (43/48) ALND	—	1.5 (96 SLNB and 5 ALND)	36% (7/19) when there is crossover; 1.3% (1/77) in nonconcordant axilla	18.9% (19/96)
Casabona et al[53]	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	—
Boneti et al[33]	220	214	40	40.6% (87/214) in the SLN field	12.7	15	0	2.8% (6/214)
Ponzone et al[54]	49	6/49	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 LN)	—
Noguchi et al[55]	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 LN), no isotope	14% (2/14)
Bedrosian et al[56]	30	—	30	70% (21/30) lymphatic; 50% (15/30) nodes	26	1 av	18% (2/11 with metastases); no isotope used to detect crossover	—
Ochoa, present study	360	237	123	80/237 (33.7%) SLN; 93/123 (75.4%) ALND	—	27 cases	5/27 (18.5%)	4.3% (15/348)

ALND, Axillary lymph node dissection; *ARM*, axillary reverse mapping; *ID*, identify; *LN*, lymph node; *SLN*, sentinel lymph node; *SLNB*, sentinel lymph node biopsy.

objective findings of lymphedema as well as subjective symptoms. Objective findings of volume difference were seen in 7 of 238 (2.9%), and another 13 patients experienced subjective symptoms but 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 do not understand what is really meant by lymphedema. In addition, of the 3 patients in whom the lymphatics were transected and reanastomosed, there were no cases of objective or subjective lymphedema.

In our original study,[34] blue nodes were removed routinely; the contrast with this study is that we only removed them if they had crossover or appeared abnormal. Others have shown rates of metastatic involvement of blue nodes between 14 and 43% and almost exclusively in patients with N2 or N3 disease (Table). 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). Notably, Kang et al[46] used our described dual mapping technique and had similar results demonstrating that nodes with blue dye alone are rarely positive. Kang et al reported a 36% rate of malignancy in the blue nodes with crossover and only 1.3% in nonconcordant axilla. In our study, 5 of 27 resected ARM nodes (18.5%) contained tumor. Two of these ARM nodes were in cases of crossover with N1 and N2 disease. The other 3 cases were nonconcordant in palpable or entrapped nodes in a heavily positive axilla (N2 or N3) without crossover. We therefore found a 14.3% rate of malignancy (2/15) in the concordant cases and only 0.9% (3/334) in nonconcordant but

heavily positive axilla. Currently, all of these nodes would be resected and reanastomosed.

Furthermore, only 1 axillary recurrence was seen, and occurred in a patient in whom blue dye was not identified; therefore, no blue nodes were specifically left behind. This recurrence was found 17 months after modified radical mastectomy for yT2 (4 cm) N1 (3/7) disease. When found, the patient had metastatic disease present within her liver. The finding that when blue lymphatics were spared in this fairly large trial with an average of 12 months of follow-up is a surrogate for the safety of ARM despite leaving blue, nonradioactive nodes lymph nodes in the axilla. This is important because patients with ≥4 positive nodes receive XRT.

There are ~240,000 cases of breast cancer per year and an extant total of 3–5 million cases of lymphedema in the United States, making this among the most clinically important postoperative problems.[47,48] Reports on the incidence of lymphedema vary with measurement technique, duration of follow-up, time to measurement, use of XRT, and extent of operation.[48] Symptoms of lymphedema may present within days or ≤30 years later; although 80% present within 3 years of operation, with the remainder at a rate of 1% per year.[13,49] Volume displacement is the gold standard for measurement, because subjective symptoms of pain or discomfort are often mistaken for lymphedema. 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 5–8% with SLN biopsy alone.[43] In the American College of Surgeons Oncology Group Z0010 prospective observational study,[18] lymphedema defined as a change in arm circumference of >2 cm 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 less morbidity and lymphedema rates for SLNB when compared with ALND. Lymphedema in ALND groups ranged from 13 to 77%, varying with how closely lymphedema was monitored, duration of follow-up,[19-23] questionably the number of positive lymph nodes,[50] postoperative irradiation,[12] extent of operation, body habitus, and a number of other patient characteristics.[43,51] Although the rate of lymphedema was much less with the SLNB, it remained clinically significant (range, 0–13%) and NSABP B-32 found lymphedema with SLNB to be ~8%.[43] Thus, SLNB has improved but not abolished the problem of lymphedema. Our group placed 97 patients on the B-32 protocol. Our rate of lymphedema 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 with and improved over our B-32 rates.

Surprisingly, just as many women get lymphedema from a negative SLNB as all those who undergo 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 3-fold that of ALND. In the present study, a blue lymphatic was seen in 80 of 237 SLNB-only procedures. In 7 of these SLNB-only (small incision) procedures, crossover was identified; therefore, in 73 of the 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. 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. Surgeons do not need necessarily to stop doing ALNDs for positive lymph nodes, but rather to 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 able to further minimize the morbidity of these procedures, while not compromising our oncologic resection.

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