UpToDate<sup>®</sup> Official reprint from UpToDate<sup>®</sup> www.uptodate.com © 2023 UpToDate, Inc. and/or its affiliates. All Rights Reserved.



# Sentinel lymph node biopsy in breast cancer: Techniques

**AUTHOR:** Seth P Harlow, MD **SECTION EDITOR:** Anees B Chagpar, MD, MSc, MA, MPH, MBA, FACS, FRCS(C) **DEPUTY EDITOR:** Wenliang Chen, MD, PhD

All topics are updated as new evidence becomes available and our peer review process is complete.

Literature review current through: **Oct 2023.** This topic last updated: **Jul 19, 2023.** 

#### INTRODUCTION

According to the sentinel lymph node hypothesis, tumor cells migrating from a primary tumor metastasize to one or a few lymph nodes before involving others. Evidence suggests that the entire breast drains to the same few sentinel lymph nodes regardless of the injection site [1]. These few lymph nodes are called "sentinel" lymph nodes, the status of which would accurately predict the status of the remaining lymph nodes.

Sentinel lymph node biopsy (SLNB) was first introduced as a technique of axillary nodal staging for breast cancer by Giuliano and Krag in 1993 and 1994 [2,3]. It has since become the standard of care for axillary staging in clinically node-negative breast cancer [4]. A properly performed SLNB identifies patients who need further axillary treatment, while sparing others a potentially morbid axillary lymph node dissection (ALND) [5].

The techniques of SLNB in breast cancer will be reviewed here. The indications, contraindications, and outcomes of SLNB as well as the management of patients after an SLNB are discussed separately. (See "Overview of sentinel lymph node biopsy in breast cancer" and "Overview of management of the regional lymph nodes in breast cancer".)

#### **TECHNIQUES**

Proper surgical technique in SLNB minimizes the risk of understaging and undertreating patients, which in turn influences outcomes.

SLNB typically begins with injection of one or two tracers into breast skin or parenchyma either in the vicinity of the tumor or under the areolar plexus. These tracers enter lymphatic channels and passively flow to the draining lymph nodes. Sentinel lymph nodes are then identified as those first receiving drainage from the tumor by the presence of tracer and removed. Although sentinel nodes draining the breast can be variably located, they are usually found within the lower axilla (level I) [6].

Clinical practices vary regarding the tracer(s) and injection technique for SLNB. Each surgeon needs to find the method that works best for their practice. The sections below describe best practices for each tracer agent as suggested by the experts in the field [7].

**Blue dye** — The surgeon injects 3 to 5 mL of blue dye (1% isosulfan blue or diluted methylene blue) around the tumor periphery, at the palpable edge of the biopsy cavity or into the subareolar plexus. It is important not to inject the dye into the tumor itself (because the lymphatics can be occluded by tumor) or into the seroma cavity following breast biopsy (as the seroma itself does not contain lymphatic channels). These errors in technique are likely to lead to a failure of mapping.

The use of isosulfan blue dye for SLNB is associated with severe anaphylactic reactions requiring resuscitation in 0.16 to 1.1 percent of cases [6,8-11]. However, routine prophylaxis is not standard practice, due to the low reported rate of anaphylaxis [7]. In high-risk cases, prophylactic treatment with 100 mg of hydrocortisone (or 20 mg of methylprednisolone or 4 mg of dexamethasone), 50 mg of diphenhydramine, and 20 mg of famotidine intravenously just before or at the induction of anesthesia appears to decrease the severity but not the incidence of dye reactions [8].

Methylene blue is an alternative to isosulfan blue dye with a lower rate of anaphylactic reactions (0.0006 percent) [11-14]. Methylene blue also has side effects [15,16]. Intradermal injection of methylene blue can lead to skin necrosis; intraparenchymal injection can cause induration and erythema with associated pain [16]. Pulmonary edema and serotonin syndrome in patients who take serotonergic medications have also been reported [17] (see "Serotonin syndrome (serotonin toxicity)"). Side effects can potentially be minimized by diluting the methylene blue with normal saline (practices vary from 1:1 to 1:7 dilution) [18].

Following tracer injection, the breast should be massaged for five minutes to dilate breast lymphatics [19,20]. The axillary fascia is then entered through an axillary incision. If blue dye is used as the sole tracer, the surgeon cannot rely on a gamma probe signal to identify the location of the sentinel node. In that situation, the incision should be placed inferiorly, rather than centered within the axilla [7]. Some surgeons make the incision at the inferior edge of the

#### Sentinel lymph node biopsy in breast cancer: Techniques - UpToDate

axillary hair, extending medially to the border of the pectoralis major muscle. Any incision for SLNB should be made in a way that can be incorporated into the incision for a subsequent completion axillary lymph node dissection (ALND) if necessary.

A careful and systematic search is then made for blue lymphatic channels. Once identified, these fragile blue lymphatic channels should be followed with gentle, ideally bloodless dissection, until they lead to blue-stained lymph nodes ( picture 1). All blue lymph nodes and any lymph nodes at the end of a blue lymphatic channel are removed and designated as sentinel nodes. Care must be taken to identify the bluest node and the blue node most proximal to the tumor in the axilla, because the dye transit time is rapid and blue staining of distal, nonsentinel axillary lymph nodes is not uncommon. Failure to consider the node at the end of a blue lymphatic channel as a sentinel node, whether or not the node itself appears blue, and failure to remove the most proximal blue node are two common technical errors. Suspicious palpable nodes should also be removed for evaluation, as a lymph node replaced with tumor is likely not to take up the tracer dye.

**Radioactive colloid** — The radioactive material may be injected peritumorally, intradermally, or into the subareolar plexus. There is ongoing debate about the best site for injection. Intradermal injection of radiocolloid appears to be superior to subdermal injection [21-23]. Injections into the dermis and subareolar area are associated with a lower potential for internal mammary node visualization [24-27].

In the United States, both filtered and unfiltered technetium sulfur colloid agents are normally used; others use technetium-labeled human serum albumin. When available, unfiltered radioactive colloid is better for SLNB because the larger particles in the unfiltered solution are trapped better by the sentinel lymph nodes. Filtered colloid is more suitable for lymphoscintigraphy by quickly identifying the sentinel nodes before passing onto second and third echelon nodes in the axilla.

A newer approved radiolabeled agent for identifying sentinel lymph nodes is <sup>99m</sup>Tc-tilmanocept (Tc-TM). This agent has a theoretical advantage of faster clearance from the injection site and higher uptake and retention within sentinel lymph nodes than many of the other injected agents. Studies comparing this agent with other approved agents indicate superiority of the Tc-TM compared with vital blue dyes, albumin colloids, and equivalency to sulfur colloid [28-30].

The amount of radioactive colloid injected varies based on the time of injection; the half-life of technetium sulfur colloid is six hours. Typically, 0.5 mCi is injected on the day of surgery, or 2.5 mCi is injected the day before surgery. Following breast massage, a handheld gamma probe is used to identify the maximum radioactivity in the axilla.

When a hot spot cannot be located with a gamma probe before incision, 10 to 40 mL of saline or local anesthetic can be injected into the site of previous radioactive colloid injection followed by repeat breast massage to increase the interstitial pressure and force more tracer into lymphatic channels. In patients who have had prior breast or axillary surgery, the normal lymphatic channels may be blocked, causing alternate drainage pathways to be formed. In such patients, the risk of failing to localize sentinel lymph nodes with a gamma probe is higher than usual, and a preoperative lymphoscintigraphy and/or the use of dual tracers may help better localize the sentinel nodes ( picture 2). (See 'Single versus dual technique' below.)

An axillary skin incision is made over the "hot spot." Again, any incision for SLNB should be made in a way that can be incorporated into the incision for a subsequent completion ALND if necessary. The lymph node with the most radioactivity as determined by the gamma probe is first removed, and an ex vivo count is obtained. Removal of subsequent lymph nodes follows the "10 percent rule" (ie, all lymph nodes with counts >10 percent of ex vivo count of the most radioactive node should be removed) [31]. On average, two to three sentinel lymph nodes are removed [32]. Once four or five sentinel lymph nodes have been removed, the value of additional nodes is extremely low [33,34]. If the residual axillary bed count is still >10 percent of the most radioactive node, but uniform, some surgeons do not remove any additional nodes that are not suspicious by palpation, although this issue is controversial (see 'Optimum number of sentinel lymph nodes' below). Any suspicious palpable nodes should be removed, regardless of whether they are radioactive, since tumor-laden nodes may not take up much tracer. (See 'Decreasing the false negative rate of SLNB' below.)

In patients with tumors in the upper outer quadrant or axillary tail of the breast, the gamma probe may fail to isolate the sentinel lymph nodes due to overlapping signals from the injection site and the axilla (ie, "shine-through"). Attaching a collimator to the gamma probe, making it more directional, may circumvent the problem. Other solutions include injecting radioactive colloid subareolarly, as opposed to peritumorally, or injecting a smaller volume of radioactive colloid. If the problem is discovered after injection, the surgeon should proceed with tumor resection, which eliminates the interference from the injection site when reevaluating the axilla afterwards.

**Investigational techniques** — Other techniques for localizing sentinel lymph nodes have been reported utilizing novel tracers such as indocyanine green (ICG), superparamagnetic iron oxide (SPIO), and microbubble contrast agent. However, these newer techniques have wide variability in results between studies, small patient numbers, and short patient follow-up [35]. At this time, these techniques should be considered investigational until there is conclusive evidence that they can reliably identify sentinel lymph nodes, and with a low false negative rate.

- ICG ICG has been approved by the FDA for lymphatic mapping of breast cancer. The tracer agent, ICG, is injected directly into the breast (most studies use subareolar or intradermal sites). The sentinel nodes are then localized using a fluorescent imaging system [36-38]. In a study of early breast cancer patients, each of whom serves as their own control, ICG-fluorescence showed a higher sentinel lymph node detection rate than Tc-TM-nanocoilloid, and equal detection rate for pathological lymph nodes [39]. In a meta-analysis of 12 nonrandomized comparative studies, ICG was equal to or better than radioactive colloid in localizing sentinel lymph nodes and tumor-positive sentinel nodes [40]. In a subsequent trial, ICG plus radioisotope performed as well as blue dye plus radioisotope in sentinel node biopsy [41].
- SPIO The magnetic tracer agent, SPIO, is injected into the breast at a subareolar or intradermal location. The sentinel nodes are then localized using a handheld magnetometer [42-44]. In a meta-analysis of seven studies in which both SPIO and standard tracers were used in each patient, the SPIO technique was not inferior to the standard technique in identification rate (97.1 versus 96.8 percent), total lymph nodes retrieved (1.9 versus 1.8 nodes per patient), and false negative rate (8.4 versus 10.9 percent). The mean discordance rate between the two techniques was 3.9 percent (range 1.7 to 6.9 percent) [45].
- Microbubble contrast The microbubble contrast agent based on the use of dispersion with sulfur hexafluoride gas is injected intradermally around the areola. Breast lymphatics are then visualized by contrast-enhanced ultrasound and followed to identify and biopsy axillary sentinel lymph nodes [46]. In a meta-analysis of five studies, this technique identified sentinel lymph nodes in 9.3 to 55.2 percent of patients with a sensitivity of 61 to 89 percent and a false negative rate of 6.6 to 39 percent [47]. Comparative studies with a standard technique are required to validate this technique.

#### **CONTROVERSIAL ISSUES**

**Single versus dual technique** — SLNB can be performed with the blue dye, the radioactive colloid, or both tracers; the choice is determined by surgeon and institutional preference.

Although excellent results are reported in single-institution series using either radioactive colloid or blue dye [20,48-50], combined use of both tracers appears to be complementary, minimizing the false negative rate in most [6,51-54], but not all, studies [55]:

- In a systematic review of the data supporting the use of SLNB conducted by an expert panel convened by American Society of Clinical Oncology, the use of both blue dye and radiocolloid was associated with an almost significant trend toward fewer false negative results (7 versus 9.9 percent, p = 0.07) [24].
- In an early report of NSABP B-32, a randomized trial of SLNB versus conventional axillary lymph node dissection (ALND) in patients with clinically node-negative breast cancer, both blue dye and radiocolloid injection were used to detect sentinel nodes intraoperatively [6]. Most of the sentinel nodes were both hot and blue (65 percent), while 24 percent were hot only, 5 percent were blue only, and 3.9 percent were neither hot nor blue, but palpably abnormal.

Besides surgeon preference, the use of dual tracers may be warranted in the following situations where the sentinel node identification rate is expected to be low and the false negative rate high [7]:

- The surgeon has limited experience with SLNB. (See 'Decreasing the false negative rate of SLNB' below.)
- The patient has undergone neoadjuvant therapy prior to SLNB. In the ACOSOG Z1071 trial, the sentinel node identification rate was 78.6 percent with blue dye alone, 91.4 percent with radioactive colloid alone, and 93.8 percent with dual agents [56].
- The patient has had prior breast or axillary surgery. In such patients, the normal lymphatic channels may be blocked, causing alternate drainage pathways to be formed. As a result, the risk of failing to localize with one agent is higher, and the use of dual tracers and/or a preoperative lymphoscintigraphy may help. (See 'Lymphoscintigraphy' below.)
- The patient is obese.
- The use of blue dye or radioactive colloid alone fails to produce a signal in the axilla (eg, blue nodes or radioactivity hot spot). In such cases, the use of a second tracer may facilitate identification of the sentinel nodes.

**Lymphoscintigraphy** — Lymphoscintigraphy is performed using a gamma camera to identify areas of increased radioactivity ("hot spots") and to mark the skin in such areas [57]. Unlike in melanoma, where lymphoscintigraphy is standard as these patients often have variable drainage patterns, the use of lymphoscintigraphy is more controversial in breast cancer.

In general, lymphoscintigraphy is not needed before SLNB, as a sensitive handheld gamma probe is used to systematically survey all potential regional node sites to identify the hot spots

[58]. In the operating room, a small skin incision is made over the hot spot and the handheld gamma probe is used to guide the surgeon to the labeled lymph nodes. Because this technique is easy to learn, proficiency using radioactive tracer (along with blue dye) is attained sooner than with blue dye alone [59].

Routine preoperative lymphoscintigraphy before SLNB can add cost and create scheduling conflicts unnecessarily [58]. Selective preoperative lymphoscintigraphy, however, is advocated before repeat SLNB in patients who have had a previous SLNB or axillary node dissection on the same side, where there is a high likelihood of an abnormal drainage pattern [60]. (See "Overview of sentinel lymph node biopsy in breast cancer", section on 'Recurrent breast cancer and previous axillary procedures'.)

**Optimum number of sentinel lymph nodes** — Successful sentinel lymph node identification by blue dye is defined as the identification of any blue node or any nonblue node with a blue afferent lymphatic. For SLNB with radioactivity, the "10 percent rule" has been proposed as a guideline, which refers to removal of all nodes with counts greater than 10 percent of the most radioactive node [31]. In most cases, more than one sentinel node is identified [32,61]; the maximum number of sentinel nodes that should be removed, however, is debated.

Some authors argued that the procedure can be terminated after three sentinel nodes have been removed, because the only positive sentinel node is rarely identified in the fourth or higher number node (2 percent in >1000 patients) [62]. In another large study of over 144,000 patients, the adjusted disease-specific survival was better for patients with two or three sentinel nodes than for those with only one sentinel node, and best for patients with three nodes [63].

Others advocated removal of all nodes that fit the criteria detailed above. In one study, more than three sentinel nodes were removed in 18 percent of patients; limiting SLNB to the first three nodes would have increased the false negative rate from 7.7 to 10.3 percent [64]. However, literature suggests that the marginal yield of removing more than four or five sentinel nodes is extremely low [33,34].

**Intraoperative evaluation of sentinel lymph nodes** — Approximately one-quarter of patients with a positive sentinel node will be found to have residual disease in the axilla [65], and a completion ALND may be required in some cases. Intraoperative evaluation of sentinel nodes allows immediate ALND, which obviates the need for a second operation in certain patients, such as those who are undergoing mastectomy (and therefore will not receive postoperative radiation) and those who have received neoadjuvant therapy. For patients undergoing breast-conserving surgery, some surgeons perform intraoperative evaluation in all patients, while others defer to permanent pathology and perform a completion ALND as a second operation if

necessary. Given that the criteria for completion ALND are not completely resolved, each surgeon must decide what would lead them to do a completion ALND and perform intraoperative evaluation of the sentinel lymph nodes accordingly. (See "Overview of sentinel lymph node biopsy in breast cancer", section on 'Management after sentinel lymph node biopsy'.)

Intraoperative evaluation of sentinel nodes adds time and cost to the SLNB procedure and is associated with a significant false negative rate. It should be omitted if the information gained will not impact surgical decision making (eg, surgeon does not plan to proceed with ALND regardless of result). Additionally, ALND may be avoided in select patients who meet the American College of Surgeons Oncology Group Z0011 criteria, if they only have one or two positive sentinel nodes. Following Z0011, the use of intraoperative sentinel node evaluation has decreased significantly [66,67]. The management of patients with positive sentinel nodes is discussed in detail elsewhere. (See "Overview of sentinel lymph node biopsy in breast cancer", section on 'Management after sentinel lymph node biopsy'.)

Although several intraoperative techniques can be used to identify a positive sentinel node (inspection of the cut faces of the node, cytology of node imprints [68], cell smears, cytokeratin staining [69], and/or frozen sections [70,71]), none of these methods will identify all patients with positive nodes intraoperatively because of sampling limitations. Evaluation is more accurate on the basis of permanent (paraffin) sections.

Although the average false negative rate of intraoperative sentinel lymph node evaluation is 25 percent [9,24,70], the range is wide. Additional refinements of intraoperative evaluation may improve the identification rate of nodal metastases. For example, the combination of frozen section and rapid cytokeratin immunostaining decreased the false negative rate of intraoperative analysis in a small prospective trial of 100 patients [69]. Caution should be used, however, as cytokeratin immunostaining can be falsely positive, leading to unnecessary completion axillary lymph node dissection.

Identifying tiny metastases intraoperatively may not be clinically helpful; caution should be exercised to ensure that pathologists are certain of their diagnosis of a true macrometastasis prior to completion of axillary dissection. Indeed, in a prospective study of intraoperative evaluation of sentinel nodes with frozen section and touch prep analysis, there were 2 percent false positives [70]; most studies, however, have found the false positive rate to be 0. Although many patients would want to avoid a second operation if possible, there is no evidence that immediate completion ALND is associated with more favorable outcomes than a delayed procedure [72].

Molecular methods using reverse transcriptase polymerase chain reaction (RT-PCR) have been used to identify tumor-specific RNA from occult malignant cells in axillary lymph nodes [73]. Concerns about the RT-PCR approach include the fact that measurement of the size of the metastatic tumor and morphologic correlation is not possible and destructive processing of the sample is required. There is also the significant limitation of false positive results, caused by benign epithelial inclusions, which could lead to erroneous upstaging [74].

Permanent sections remain the gold standard, and patients must be informed as to the possibility that a second operation may be necessary for completion of the ALND. (See "Overview of sentinel lymph node biopsy in breast cancer", section on 'Management after sentinel lymph node biopsy'.)

## DECREASING THE FALSE NEGATIVE RATE OF SLNB

For a set of patients undergoing SLNB, the false negative rate is calculated as the number of false negative cases divided by the number of cases with any axillary nodal metastasis (ie, true positive cases plus false negative cases). The false negative rate of SLNB is an important measure of procedural accuracy in the surgical management of breast cancer. Potential adverse outcomes from missing node metastases include understaging the patient and an increased risk of cancer recurrence [75]. Thus, every effort is made to reduce the false negative rate.

A systematic review of 69 trials of SLNB, including 8059 patients, showed that sentinel lymph nodes could be identified in 95 percent of patients with a false negative rate of 7.3 percent (range 0 to 29 percent) [76]. The false negative rate of SLNB is influenced by multiple surgeon and patient factors, including:

• When performed by experienced surgeons, SLNB is a safe procedure with few complications. However, a significant amount of experience is necessary to master the procedure. Proper performance requires significant training, and results vary according to a surgeon's skill and experience.

The importance of experience to the accuracy of the SLNB technique was illustrated in a multicenter trial in which all patients underwent SLNB followed by completion axillary lymph node dissection (ALND) [77]. Although the false negative rate varied between 0 and 29 percent among the participating surgeons, proficiency improved with increasing number of cases. After five training cases, the success rates for individual surgeons identifying a sentinel lymph node ranged from 79 to 98 percent. In another study, the false

negative rate was more than halved when performed by surgeons who had performed ≥20 cases of SLNB previously [78].

- The success of the sentinel node biopsy is dependent on lymphatic drainage. A previous excisional biopsy has the potential to increase the false negative rate compared with prior percutaneous biopsy. Because of this, open surgical biopsies should be avoided if diagnosis with core biopsy is possible. If open surgical biopsy has already been performed, care should be taken to avoid injecting the blue dye or the radioactive tracer directly into the seroma cavity. Patients with prior breast or axillary surgery may benefit from preoperative lymphoscintigraphy and/or the dual tracer technique. (See 'Single versus dual technique' above and 'Lymphoscintigraphy' above.)
- The false negative rate is directly related to the number of sentinel nodes removed [79]. In the NSABP B-32 study, removal of two sentinel nodes rather than one almost halved the false negative rate [6]. All nodes that qualify as sentinel nodes should be removed, not just the bluest or hottest nodes. (See 'Optimum number of sentinel lymph nodes' above.)
- Gentle palpation of the axilla through the incision should also be done to identify any firm suspicious nodes. In the B-32 trial, 4 percent of all sentinel nodes were identified by palpation, and almost one-quarter of these contained metastases. Other series also note that approximately one-half of patients in whom the identified sentinel node proves to be falsely negative will have clinically suspicious nodes palpable at surgery. This is thought to be because gross tumor involvement interferes with the uptake of both radiocolloid and blue dye, and lymph flow is diverted to a node other than the true sentinel node [22,80]. Therefore, not only should blue and hot lymph nodes be removed, but palpably suspicious lymph nodes should also be considered sentinel nodes.
- The false negative rates are similar for all standard techniques of SLNB and are dictated by anatomy. Cadaver studies suggest that lymphatic watersheds exist in the breast and that direct drainage may occur to multiple nodes in the axilla and other nodal regions, rather than an orderly and predictable pattern of lymphatic drainage [81].

#### SOCIETY GUIDELINE LINKS

Links to society and government-sponsored guidelines from selected countries and regions around the world are provided separately. (See "Society guideline links: Breast surgery".)

## **INFORMATION FOR PATIENTS**

UpToDate offers two types of patient education materials, "The Basics" and "Beyond the Basics." The Basics patient education pieces are written in plain language, at the 5<sup>th</sup> to 6<sup>th</sup> grade reading level, and they answer the four or five key questions a patient might have about a given condition. These articles are best for patients who want a general overview and who prefer short, easy-to-read materials. Beyond the Basics patient education pieces are longer, more sophisticated, and more detailed. These articles are written at the 10<sup>th</sup> to 12<sup>th</sup> grade reading level and are best for patients who want in-depth information and are comfortable with some medical jargon.

Here are the patient education articles that are relevant to this topic. We encourage you to print or e-mail these topics to your patients. (You can also locate patient education articles on a variety of subjects by searching on "patient info" and the keyword(s) of interest.)

• Basics topic (see "Patient education: Sentinel lymph node biopsy for breast cancer (The Basics)")

#### SUMMARY AND RECOMMENDATIONS

- Purpose of sentinel lymph node biopsy for breast cancer The status of the axillary lymph nodes remains one of the most important prognostic factors in women with earlystage breast cancer. Histologic examination of excised lymph nodes is the most accurate method for assessing spread of disease to these nodes. Sentinel lymph node biopsy (SLNB) is the standard of care for axillary staging in clinically node-negative breast cancer.
  (See "Overview of sentinel lymph node biopsy in breast cancer" and 'Introduction' above.)
- **Techniques** A standard SLNB can be performed with blue dye and/or radioactive colloid. Besides surgeon preference, the use of dual tracers may be warranted in situations including surgeon inexperience, a history of prior breast or axillary surgery, neoadjuvant chemotherapy, obesity, or failure to localize with a single tracer agent. (See 'Techniques' above and 'Single versus dual technique' above.)
- Lymphoscintigraphy Routine lymphoscintigraphy before SLNB is not required. Preoperative lymphoscintigraphy should be performed before repeat SLNB in patients who have had a previous SLNB or axillary node dissection on the same side because of a high likelihood of an abnormal drainage pattern. (See 'Lymphoscintigraphy' above.)
- **Optimum number of sentinel lymph nodes** Successful sentinel lymph node identification by blue dye is defined as the identification of any blue node or any nonblue node with a blue afferent lymphatic. For SLNB with radioactivity, the "10 percent rule" has

been proposed as a guideline, which refers to removal of all nodes with counts greater than 10 percent of the most radioactive node. On average, two or three sentinel nodes are identified. While some authors stop the procedure after removing three sentinel lymph nodes, others continue until all lymph nodes meeting the criteria have been removed. (See 'Techniques' above and 'Optimum number of sentinel lymph nodes' above.)

- Intraoperative pathologic evaluation Intraoperative evaluation of the sentinel lymph nodes will not identify all patients with positive nodes, because of sampling limitations, and may also yield a false positive result. Permanent section is the most accurate method of assessment. Additionally, patients who meet certain criteria may not require completion ALND despite having only one or two positive sentinel nodes. Given that the criteria for completion ALND are not completely resolved, each surgeon must decide what would lead them to do a completion ALND and perform intraoperative evaluation of the sentinel lymph nodes accordingly. (See 'Intraoperative evaluation of sentinel lymph nodes' above and "Overview of sentinel lymph node biopsy in breast cancer", section on 'Management after sentinel lymph node biopsy'.)
- Minimizing false negative rate The false negative rate is an important measure of procedural accuracy of SLNB and can be minimized by percutaneous (core biopsy, fine needle aspiration) rather than surgical biopsy of the primary breast lesion, use of dual tracer, removal of any firm suspicious nodes noted at the time of surgery, and removal of more than one sentinel node. Surgeon experience is also an important factor. (See 'Decreasing the false negative rate of SLNB' above.)

## ACKNOWLEDGMENT

The UpToDate editorial staff acknowledges Donald L Weaver, MD, who contributed to an earlier version of this topic review.

Use of UpToDate is subject to the Terms of Use.

#### REFERENCES

- 1. Chagpar A, Martin RC 3rd, Chao C, et al. Validation of subareolar and periareolar injection techniques for breast sentinel lymph node biopsy. Arch Surg 2004; 139:614.
- 2. Giuliano AE, Kirgan DM, Guenther JM, Morton DL. Lymphatic mapping and sentinel lymphadenectomy for breast cancer. Ann Surg 1994; 220:391.

- 3. Krag DN, Weaver DL, Alex JC, Fairbank JT. Surgical resection and radiolocalization of the sentinel lymph node in breast cancer using a gamma probe. Surg Oncol 1993; 2:335.
- 4. Lyman GH, Somerfield MR, Bosserman LD, et al. Sentinel Lymph Node Biopsy for Patients With Early-Stage Breast Cancer: American Society of Clinical Oncology Clinical Practice Guideline Update. J Clin Oncol 2016; :JCO2016710947.
- 5. Rao R, Euhus D, Mayo HG, Balch C. Axillary node interventions in breast cancer: a systematic review. JAMA 2013; 310:1385.
- 6. Krag DN, Anderson SJ, Julian TB, et al. Technical outcomes of sentinel-lymph-node resection and conventional axillary-lymph-node dissection in patients with clinically node-negative breast cancer: results from the NSABP B-32 randomised phase III trial. Lancet Oncol 2007; 8:881.
- 7. James TA, Coffman AR, Chagpar AB, et al. Troubleshooting Sentinel Lymph Node Biopsy in Breast Cancer Surgery. Ann Surg Oncol 2016; 23:3459.
- Raut CP, Hunt KK, Akins JS, et al. Incidence of anaphylactoid reactions to isosulfan blue dye during breast carcinoma lymphatic mapping in patients treated with preoperative prophylaxis: results of a surgical prospective clinical practice protocol. Cancer 2005; 104:692.
- 9. Julian TB, Krag D, Brown A, et al. Preliminary technical results of NSABP B-32, a randomized phase III clinical trial to compare sentinel node resection to conventional axillary dissection in clinically node-negative breast cancer patients (abstract). Presented at the 27th Annual S an Antonio Breast Cancer Symposium, San Antonio, Texas, December 9, 2004 (abstract 14).
- 10. Wilke LG, McCall LM, Posther KE, et al. Surgical complications associated with sentinel lymph node biopsy: results from a prospective international cooperative group trial. Ann Surg Oncol 2006; 13:491.
- Perenyei M, Barber ZE, Gibson J, et al. Anaphylactic Reaction Rates to Blue Dyes Used for Sentinel Lymph Node Mapping: Systematic Review and Meta-analysis. Ann Surg 2021; 273:1087.
- 12. Brahma B, Putri RI, Karsono R, et al. The predictive value of methylene blue dye as a single technique in breast cancer sentinel node biopsy: a study from Dharmais Cancer Hospital. World J Surg Oncol 2017; 15:41.
- 13. Zhang GC, Liao N, Guo ZB, et al. Accuracy and axilla sparing potentials of sentinel lymph node biopsy with methylene blue alone performed before versus after neoadjuvant chemotherapy in breast cancer: a single institution experience. Clin Transl Oncol 2013; 15:79.

- 14. Somashekhar SP, Zaveri Shabber S, Udupa Venkatesh K, et al. Sentinel lymphnode biopsy in early breast cancer using methylene blue dye and radioactive sulphur colloid - a single institution Indian experience. Indian J Surg 2008; 70:111.
- 15. Thevarajah S, Huston TL, Simmons RM. A comparison of the adverse reactions associated with isosulfan blue versus methylene blue dye in sentinel lymph node biopsy for breast cancer. Am J Surg 2005; 189:236.
- Bleicher RJ, Kloth DD, Robinson D, Axelrod P. Inflammatory cutaneous adverse effects of methylene blue dye injection for lymphatic mapping/sentinel lymphadenectomy. J Surg Oncol 2009; 99:356.
- 17. Teknos D, Ramcharan A, Oluwole SF. Pulmonary edema associated with methylene blue dye administration during sentinel lymph node biopsy. J Natl Med Assoc 2008; 100:1483.
- 18. Zakaria S, Hoskin TL, Degnim AC. Safety and technical success of methylene blue dye for lymphatic mapping in breast cancer. Am J Surg 2008; 196:228.
- 19. Schwartz GF, Giuliano AE, Veronesi U, Consensus Conference Committee. Proceedings of the consensus conference on the role of sentinel lymph node biopsy in carcinoma of the breast, April 19-22, 2001, Philadelphia, Pennsylvania. Cancer 2002; 94:2542.
- 20. Giuliano AE, Jones RC, Brennan M, Statman R. Sentinel lymphadenectomy in breast cancer. J Clin Oncol 1997; 15:2345.
- 21. McMasters KM, Wong SL, Martin RC 2nd, et al. Dermal injection of radioactive colloid is superior to peritumoral injection for breast cancer sentinel lymph node biopsy: results of a multiinstitutional study. Ann Surg 2001; 233:676.
- 22. Povoski SP, Olsen JO, Young DC, et al. Prospective randomized clinical trial comparing intradermal, intraparenchymal, and subareolar injection routes for sentinel lymph node mapping and biopsy in breast cancer. Ann Surg Oncol 2006; 13:1412.
- 23. Motomura K, Komoike Y, Hasegawa Y, et al. Intradermal radioisotope injection is superior to subdermal injection for the identification of the sentinel node in breast cancer patients. J Surg Oncol 2003; 82:91.
- 24. Lyman GH, Giuliano AE, Somerfield MR, et al. American Society of Clinical Oncology guideline recommendations for sentinel lymph node biopsy in early-stage breast cancer. J Clin Oncol 2005; 23:7703.
- 25. Shimazu K, Tamaki Y, Taguchi T, et al. Lymphoscintigraphic visualization of internal mammary nodes with subtumoral injection of radiocolloid in patients with breast cancer. Ann Surg 2003; 237:390.

- 26. Tanis PJ, Deurloo EE, Valdés Olmos RA, et al. Single intralesional tracer dose for radioguided excision of clinically occult breast cancer and sentinel node. Ann Surg Oncol 2001; 8:850.
- 27. Doting MH, Jansen L, Nieweg OE, et al. Lymphatic mapping with intralesional tracer administration in breast carcinoma patients. Cancer 2000; 88:2546.
- 28. Wallace AM, Han LK, Povoski SP, et al. Comparative evaluation of [(99m)tc]tilmanocept for sentinel lymph node mapping in breast cancer patients: results of two phase 3 trials. Ann Surg Oncol 2013; 20:2590.
- 29. Tokin CA, Cope FO, Metz WL, et al. The efficacy of Tilmanocept in sentinel lymph mode mapping and identification in breast cancer patients: a comparative review and metaanalysis of the <sup>99</sup>mTc-labeled nanocolloid human serum albumin standard of care. Clin Exp Metastasis 2012; 29:681.
- 30. Unkart JT, Hosseini A, Wallace AM. Tc-99m tilmanocept versus Tc-99m sulfur colloid in breast cancer sentinel lymph node identification: Results from a randomized, blinded clinical trial. J Surg Oncol 2017; 116:819.
- 31. Martin RC 2nd, Edwards MJ, Wong SL, et al. Practical guidelines for optimal gamma probe detection of sentinel lymph nodes in breast cancer: results of a multi-institutional study. For the University of Louisville Breast Cancer Study Group. Surgery 2000; 128:139.
- 32. Chung A, Yu J, Stempel M, et al. Is the "10% rule" equally valid for all subsets of sentinelnode-positive breast cancer patients? Ann Surg Oncol 2008; 15:2728.
- 33. Ban EJ, Lee JS, Koo JS, et al. How many sentinel lymph nodes are enough for accurate axillary staging in t1-2 breast cancer? J Breast Cancer 2011; 14:296.
- 34. Yi M, Meric-Bernstam F, Ross MI, et al. How many sentinel lymph nodes are enough during sentinel lymph node dissection for breast cancer? Cancer 2008; 113:30.
- 35. Ahmed M, Purushotham AD, Douek M. Novel techniques for sentinel lymph node biopsy in breast cancer: a systematic review. Lancet Oncol 2014; 15:e351.
- 36. Xiong L, Gazyakan E, Yang W, et al. Indocyanine green fluorescence-guided sentinel node biopsy: a meta-analysis on detection rate and diagnostic performance. Eur J Surg Oncol 2014; 40:843.
- 37. Samorani D, Fogacci T, Panzini I, et al. The use of indocyanine green to detect sentinel nodes in breast cancer: a prospective study. Eur J Surg Oncol 2015; 41:64.
- 38. Pitsinis V, Provenzano E, Kaklamanis L, et al. Indocyanine green fluorescence mapping for sentinel lymph node biopsy in early breast cancer. Surg Oncol 2015; 24:375.

- 39. Bargon CA, Huibers A, Young-Afat DA, et al. Sentinel Lymph Node Mapping in Breast Cancer Patients Through Fluorescent Imaging Using Indocyanine Green: The INFLUENCE Trial. Ann Surg 2022; 276:913.
- 40. Sugie T, Ikeda T, Kawaguchi A, et al. Sentinel lymph node biopsy using indocyanine green fluorescence in early-stage breast cancer: a meta-analysis. Int J Clin Oncol 2017; 22:11.
- 41. Nguyen CL, Zhou M, Easwaralingam N, et al. Novel Dual Tracer Indocyanine Green and Radioisotope Versus Gold Standard Sentinel Lymph Node Biopsy in Breast Cancer: The GREENORBLUE Trial. Ann Surg Oncol 2023; 30:6520.
- 42. Rubio IT, Diaz-Botero S, Esgueva A, et al. The superparamagnetic iron oxide is equivalent to the Tc99 radiotracer method for identifying the sentinel lymph node in breast cancer. Eur J Surg Oncol 2015; 41:46.
- **43.** Douek M, Klaase J, Monypenny I, et al. Sentinel node biopsy using a magnetic tracer versus standard technique: the SentiMAG Multicentre Trial. Ann Surg Oncol 2014; 21:1237.
- 44. Thill M, Kurylcio A, Welter R, et al. The Central-European SentiMag study: sentinel lymph node biopsy with superparamagnetic iron oxide (SPIO) vs. radioisotope. Breast 2014; 23:175.
- 45. Zada A, Peek MC, Ahmed M, et al. Meta-analysis of sentinel lymph node biopsy in breast cancer using the magnetic technique. Br J Surg 2016; 103:1409.
- 46. Cox K, Sever A, Jones S, et al. Validation of a technique using microbubbles and contrast enhanced ultrasound (CEUS) to biopsy sentinel lymph nodes (SLN) in pre-operative breast cancer patients with a normal grey-scale axillary ultrasound. Eur J Surg Oncol 2013; 39:760.
- 47. Gkegkes ID, Iavazzo C. Contrast Enhanced Ultrasound (CEU) Using Microbubbles for Sentinel Lymph Node Biopsy in Breast Cancer: a Systematic Review. Acta Chir Belg 2015; 115:212.
- **48.** Veronesi U, Paganelli G, Galimberti V, et al. Sentinel-node biopsy to avoid axillary dissection in breast cancer with clinically negative lymph-nodes. Lancet 1997; 349:1864.
- 49. Crossin JA, Johnson AC, Stewart PB, Turner WW Jr. Gamma-probe-guided resection of the sentinel lymph node in breast cancer. Am Surg 1998; 64:666.
- **50.** Morrow M, Rademaker AW, Bethke KP, et al. Learning sentinel node biopsy: results of a prospective randomized trial of two techniques. Surgery 1999; 126:714.
- 51. Albertini JJ, Lyman GH, Cox C, et al. Lymphatic mapping and sentinel node biopsy in the patient with breast cancer. JAMA 1996; 276:1818.
- 52. McMasters KM, Tuttle TM, Carlson DJ, et al. Sentinel lymph node biopsy for breast cancer: a suitable alternative to routine axillary dissection in multi-institutional practice when

optimal technique is used. J Clin Oncol 2000; 18:2560.

- 53. Cody HS 3rd, Fey J, Akhurst T, et al. Complementarity of blue dye and isotope in sentinel node localization for breast cancer: univariate and multivariate analysis of 966 procedures. Ann Surg Oncol 2001; 8:13.
- 54. Chagpar AB, Martin RC, Scoggins CR, et al. Factors predicting failure to identify a sentinel lymph node in breast cancer. Surgery 2005; 138:56.
- 55. He PS, Li F, Li GH, et al. The combination of blue dye and radioisotope versus radioisotope alone during sentinel lymph node biopsy for breast cancer: a systematic review. BMC Cancer 2016; 16:107.
- 56. Boughey JC, Suman VJ, Mittendorf EA, et al. Factors affecting sentinel lymph node identification rate after neoadjuvant chemotherapy for breast cancer patients enrolled in ACOSOG Z1071 (Alliance). Ann Surg 2015; 261:547.
- 57. Uren RF, Howman-Giles R, Chung D, Thompson JF. Nuclear medicine aspects of melanoma and breast lymphatic mapping. Semin Oncol 2004; 31:338.
- 58. McMasters KM, Wong SL, Tuttle TM, et al. Preoperative lymphoscintigraphy for breast cancer does not improve the ability to identify axillary sentinel lymph nodes. Ann Surg 2000; 231:724.
- 59. Derossis AM, Fey J, Yeung H, et al. A trend analysis of the relative value of blue dye and isotope localization in 2,000 consecutive cases of sentinel node biopsy for breast cancer. J Am Coll Surg 2001; 193:473.
- 60. Ahmed M, Baker R, Rubio IT. Meta-analysis of aberrant lymphatic drainage in recurrent breast cancer. Br J Surg 2016; 103:1579.
- 61. Liu LC, Lang JE, Jenkins T, et al. Is it necessary to harvest additional lymph nodes after resection of the most radioactive sentinel lymph node in breast cancer? J Am Coll Surg 2008; 207:853.
- 62. Zakaria S, Degnim AC, Kleer CG, et al. Sentinel lymph node biopsy for breast cancer: how many nodes are enough? J Surg Oncol 2007; 96:554.
- 63. Bonneau C, Bendifallah S, Reyal F, et al. Association of the number of sentinel lymph nodes harvested with survival in breast cancer. Eur J Surg Oncol 2015; 41:52.
- 64. Chagpar AB, Scoggins CR, Martin RC 2nd, et al. Are 3 sentinel nodes sufficient? Arch Surg 2007; 142:456.
- 65. Giuliano AE, Hunt KK, Ballman KV, et al. Axillary dissection vs no axillary dissection in women with invasive breast cancer and sentinel node metastasis: a randomized clinical trial. JAMA 2011; 305:569.

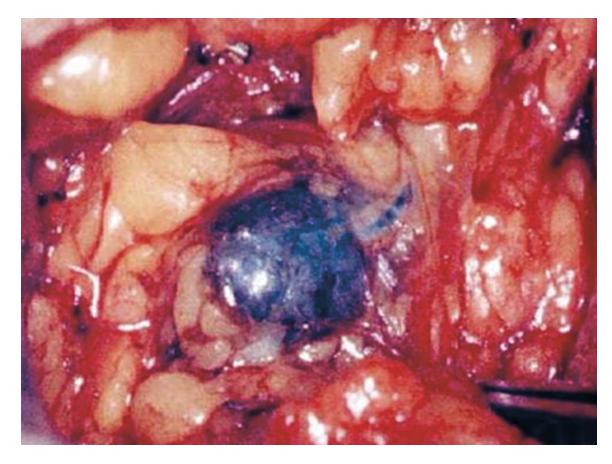
- 66. Bishop JA, Sun J, Ajkay N, Sanders MA. Decline in Frozen Section Diagnosis for Axillary Sentinel Lymph Nodes as a Result of the American College of Surgeons Oncology Group Z0011 Trial. Arch Pathol Lab Med 2016; 140:830.
- 67. Jorns JM, Kidwell KM. Sentinel Lymph Node Frozen-Section Utilization Declines After Publication of American College of Surgeons Oncology Group Z0011 Trial Results With No Change in Subsequent Surgery for Axillary Lymph Node Dissection. Am J Clin Pathol 2016; 146:57.
- 68. Motomura K, Nagumo S, Komoike Y, et al. Accuracy of imprint cytology for intraoperative diagnosis of sentinel node metastases in breast cancer. Ann Surg 2008; 247:839.
- 69. Krishnamurthy S, Meric-Bernstam F, Lucci A, et al. A prospective study comparing touch imprint cytology, frozen section analysis, and rapid cytokeratin immunostain for intraoperative evaluation of axillary sentinel lymph nodes in breast cancer. Cancer 2009; 115:1555.
- 70. Vanderveen KA, Ramsamooj R, Bold RJ. A prospective, blinded trial of touch prep analysis versus frozen section for intraoperative evaluation of sentinel lymph nodes in breast cancer. Ann Surg Oncol 2008; 15:2006.
- 71. Langer I, Guller U, Berclaz G, et al. Accuracy of frozen section of sentinel lymph nodes: a prospective analysis of 659 breast cancer patients of the Swiss multicenter study. Breast Cancer Res Treat 2009; 113:129.
- 72. Olson JA Jr, McCall LM, Beitsch P, et al. Impact of immediate versus delayed axillary node dissection on surgical outcomes in breast cancer patients with positive sentinel nodes: results from American College of Surgeons Oncology Group Trials Z0010 and Z0011. J Clin Oncol 2008; 26:3530.
- 73. Viale G, Dell'Orto P, Biasi MO, et al. Comparative evaluation of an extensive histopathologic examination and a real-time reverse-transcription-polymerase chain reaction assay for mammaglobin and cytokeratin 19 on axillary sentinel lymph nodes of breast carcinoma patients. Ann Surg 2008; 247:136.
- 74. Patani N, Mokbel K. The clinical significance of sentinel lymph node micrometastasis in breast cancer. Breast Cancer Res Treat 2009; 114:393.
- **75.** Pesek S, Ashikaga T, Krag LE, Krag D. The false-negative rate of sentinel node biopsy in patients with breast cancer: a meta-analysis. World J Surg 2012; 36:2239.
- 76. Kim T, Giuliano AE, Lyman GH. Lymphatic mapping and sentinel lymph node biopsy in early-stage breast carcinoma: a metaanalysis. Cancer 2006; 106:4.

- 77. Krag D, Weaver D, Ashikaga T, et al. The sentinel node in breast cancer--a multicenter validation study. N Engl J Med 1998; 339:941.
- 78. Hutchinson JR, Chagpar AB, Scoggins CR, et al. Surgeon and community factors affecting breast cancer sentinel lymph node biopsy. Am J Surg 2005; 190:903.
- 79. Wong SL, Edwards MJ, Chao C, et al. Sentinel lymph node biopsy for breast cancer: impact of the number of sentinel nodes removed on the false-negative rate. J Am Coll Surg 2001; 192:684.
- 80. Hill AD, Tran KN, Akhurst T, et al. Lessons learned from 500 cases of lymphatic mapping for breast cancer. Ann Surg 1999; 229:528.
- 81. Suami H, Pan WR, Mann GB, Taylor GI. The lymphatic anatomy of the breast and its implications for sentinel lymph node biopsy: a human cadaver study. Ann Surg Oncol 2008; 15:863.

Topic 805 Version 22.0

#### **GRAPHICS**

# Blue sentinel lymph node



Blue sentinel lymph node at the end of a blue lymphatic channel.

*From: Chagpar AB. Sentinel lymph node biopsy for breast cancer. In: Operative Techniques in Surgery, Mulholland MW, Albo D, Dalman A, et al. (Eds), Wolters Kluwer Health, Philadelphia 2015. Copyright* © 2015. *Reproduced with permission from Wolters Kluwer Health. Unauthorized reproduction of this material is prohibited.* 

Graphic 113023 Version 3.0

# Lymphoscintigraphy of early breast cancer

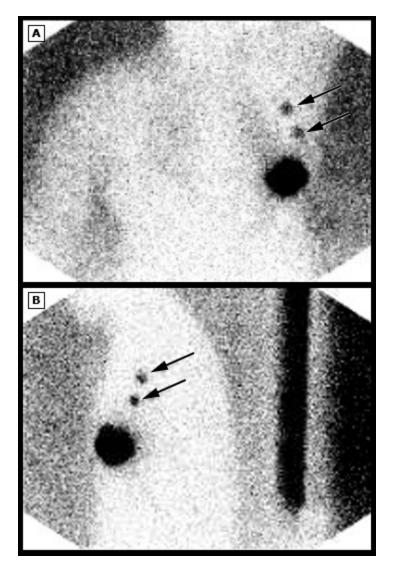


Figure A (anterior projection) and B (lateral projection): Lymphoscintigraphy using technetium sulfur colloid demonstrates two foci of posterior and superior migration of the radiopharmaceutical into the axilla.

Courtesy of Pierre J Sasson, MD.

Graphic 61541 Version 6.0

#### **Contributor Disclosures**

**Seth P Harlow, MD** No relevant financial relationship(s) with ineligible companies to disclose. **Anees B Chagpar, MD, MSc, MA, MPH, MBA, FACS, FRCS(C)** Consultant/Advisory Boards: Guardant Health [Breast cancer]; Merck [Breast cancer]; Novartis [Breast cancer]; Protean BioDiagnostics [Breast cancer]; Sanofi-Aventis [Breast cancer]. Speaker's Bureau: Merck [Breast cancer]. All of the relevant financial relationships listed have been mitigated. **Wenliang Chen, MD, PhD** No relevant financial relationship(s) with ineligible companies to disclose.

Contributor disclosures are reviewed for conflicts of interest by the editorial group. When found, these are addressed by vetting through a multi-level review process, and through requirements for references to be provided to support the content. Appropriately referenced content is required of all authors and must conform to UpToDate standards of evidence.

Conflict of interest policy