Current Technical Overviews of Sentinel Lymph Node Biopsy for Breast Cancer

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Sentinel lymph node biopsy (SLNB) is based on the hypothesis that the sentinel lymph node (SLN) reflects the lymph-node status and a negative SLN might allow complete axillary lymph node dissection (ALND) to be avoided. Although the survival outcome is still unknown, this technique has already become a standard of care for breast cancer patients. However, it is still important to discuss current techniques and some controversies. This article reviews these issues for a variety of SLNB techniques.

Introduction

Sentinel lymph node biopsy (SLNB) is based on the hypothesis that lymphatic drainage from a tumor reaches the sentinel lymph node (SLN) first and that it can be identified accurately and removed. If SLN exactly reflects the lymph-node status, a negative SLN for metastasis might allow complete axillary lymph node dissection (ALND) to be avoided. SLNs can be identified by using blue dye, radioisotope-labeled colloid (radiocolloid), or both. Krag et al. initially reported SLN mapping using radiocolloid in 1993, Giuliano et al. used blue dye in 1994, and Cox et al. reported a combination technique using these two agents. After those initial reports, SLNB has been tested by many studies with success and evolution of the techniques.

On the other hand, the survival outcome associated with SLNB and omission of ALND compared with ALND is still unknown, and several clinical trials examining these issues are ongoing. However, SLN is thought to be an accurate method for assessing the lymph-node status, and SLNB is a less invasive procedure than ALND. Given these facts, despite the lack of long-term results from controlled randomized studies, SLNB has already become a standard of care for early-stage breast cancer patients.

To perform SLNB, radiocolloid, blue dye, or both are injected in the breast, and a gamma probe detects the SLN containing the radioactive lymph nodes or the surgeon looks for the nodes stained with dye. Once the SLN is located, it is removed through a small incision. Each method seems to be very simple, but it is still important to address some of the ongoing controversies about technical issues.

First, it is critical to evaluate whether blue dye alone, radiocolloid alone, or both are the most useful. However, the success of the procedure depends on several other factors, including the surgeon's experience, patient and tumor characteristics, etc. Moreover, other specific techniques of SLNB including the type of tracer, the volume of injection of each agent, the timing of the injections, and the location of the injections could also influence the success of SLNB. Therefore, it is very difficult to compare the different methods of SLNB directly.

This article focuses on the development of SLNB techniques and reviewed current issues across a variety of techniques for which a significant amount of evidence has been accumulated.

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Abbreviations:
SLNB, sentinel lymph node biopsy; ALND, axillary lymph node dissection; SLN, sentinel lymph node; 99mTc, 99m-technetium; MRI, magnetic resonance imaging; PET, positron emission tomography
Overviews of SLNB Methodologies

There were marked variations in SLNB technique between institutions and surgeons, because these methods depended on the institutions, their surgical fellowship training program, and the surgeons’ preferences.

Previously, a survey of randomly selected fellows of the American College of Surgeons has been reported the current practice of SLNB for breast cancer in the United States in 2001; 77% performed SLNB without ALND, 90% used a combination of blue dye and radiolabeled colloid, and 60% routinely ordered lymphoscintigraphy. When SLN examinations showed drainage to the internal mammary lymph nodes, 28% removed these nodes. Recently, another report of a national trial which had no restrictions on SLNB techniques, showed that both blue dye and radiocolloid were used in 79.4% of the cases, blue dye alone in 14.8%, and radiocolloid alone in 5.7%.

1. SLNB Using Blue Dyes

After the introduction of blue dye technique by Giuliano et al., isosulfan blue dye (Lymphazurin; Zenith Parenterals, Rosemont, Ill) has been traditionally used and is the only dye approved by the Food and Drug Administration for use in SLNB in the United States. The isosulfan blue dye, which is the 2,5-disulfonated isomer of patent blue dye, has been usually used not only in clinical trials but also in clinical practice in the world.

A small prospective randomized study showed that surgeons learning to perform SLNB achieved equivalent results with blue dye alone compared with blue dye and radiocolloid. Use of the radiisotope adds extra cost and there are potential radiation hazards. SLNB using blue dye only could facilitate quick identification of SLNB in centers without nuclear medicine facilities with experiences. Therefore, in Japan, SLNB using the dye method alone has been reported to be performed in about one-third of patients.

However, its use was associated with a significant number of allergic reactions, some of which were life threatening. Allergic reactions to the dye occur in no more than 2% of patients who have SLNB; most of these reactions are hives. True anaphylactic reactions are rare but sometimes life-threatening, occurring in approximately 0.25% to 0.5% of patients. In a recent review of patients undergoing SLNB for breast cancer, adverse reactions to isosulfan blue dye occurred in 39 (1.6%) of 2392 patients. Most reactions (69%) produced urticaria, blue hives, a generalized rash, or pruritus. Hypotensive reactions requiring pressor support occurred in nine patients (0.4%).

To avoid this adverse event, another dye material should be considered. Methylene blue dye had been reported to be equally effective and posed fewer severe allergic and hypersensitivity reactions. However, adverse skin reactions to methylene blue dye, skin eruptions and rashes, and subcutaneous tissue necrosis and abscess formation have also been reported in association with the injection of this dye. Patent blue dye has been reported to cause minor local complications in the form of long-term discoloration of the skin at the site of injection. Although no cases of severe local tissue necrosis has been reported in association with patent blue dye, anaphylactic shock has been observed following its injection for SLNB.

According to the studies evaluating the safety of the blue dye injection, the risk of allergic reactions can be reduced by using corticosteroids and antihistamines. On the other hand, the volume of blue dye as it relates to SLN identification rates and patient safety has been evaluated. This study examined whether the volume of isosulfan blue dye is related to the rate of SLN identification or to the incidence of allergic reactions in SLNB for breast cancer. Although there were no significant differences in the dye-only successes, there was a trend toward fewer allergic reactions with smaller volume.

In Japan, SLNB itself has not been approved by the government for reimbursement but is performed at many institutions. Interestingly, several types of dye beside isosulfan blue have been used, such as indocyanine green, patent blue, and indigo carmine, and, to our knowledge, few allergic reactions to these dyes during SLNB for breast cancer have been reported.

2. SNB Using Radiocolloids

Krag et al. conducted the first multicenter validation study of SLNB with ALND using radiocolloid alone. Eleven surgeons achieved an overall success rate of 93%, sensitivity of 89%, and specificity of 100%. From the point of view of safety, radiation exposure to the patient, surgeon, staff, and pathologist appears to be small. An injected