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Review of Novel Sentinel Lymph Node Biopsy Techniques in Breast Cancer Patients Treated With Neoadjuvant Chemotherapy

Yeliz Emine Ersoy,[1] Huseyin Kadioglu[2]

Abstract

Breast cancer patients who present with nodal metastasis receive neoadjuvant chemotherapy (NAC) with increasing frequency and can have complete pathologic response after treatment. In this clinical scenario, sentinel node mapping and biopsy are gaining acceptance instead of axillary dissection to avoid morbidity. Biopsy proven positive lymph nodes must be reliably excised and examined after NAC to further decrease the false negativity rate of sentinel lymph node (SLN) surgery. The standard method for axillary staging in breast cancer patients even after NAC is SLN biopsy (SLNB) with a radioisotope, blue dye, or both (dual technique). Currently, preoperative axillary staging with ultrasound and biopsy, along with placement of an image-detectable marker to be removed at the time of definitive surgery is recommended. In this study, we evaluated some methods of SLNB for patients treated with NAC like indocyanine green fluorescence, superparamagnetic iron oxide nanoparticles, indigocarmine blue dye, contrast-enhanced ultrasound using microbubbles, and tattooing. Some methods are also needed to ensure that the initially biopsy proven positive node is removed at the time of surgery to be carefully evaluated for residual disease after chemotherapy like clip placement to the suspected or involved nodes before NAC, and removing the clipped node with the guidance of 125I-labeled radioactive seed or guide wires.

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Introduction

Axillary lymph node metastasis helps us to decide about locoregional and systemic treatment in breast cancer.[1] Recently, the patients who present with nodal metastasis mostly receive neoadjuvant chemotherapy (NAC), and 40% to 75% of them can have complete pathologic response.[2-9] In these patients, axillary lymph node dissection (ALND) has no clear benefit, and because it has important morbidities such as lymphedema, pain, numbness, and decreased arm mobility, it should better be avoided.[1,10-12]

Although a less invasive method, sentinel lymph node (SLN) surgery after NAC has been reported to have higher false negative rate (FNRs).[13] The tumor burden and fibrotic changes of the lymphatic channels after chemotherapy, and the nonuniform pattern of tumor regression in the axilla, might result as a difficulty in the detection of the SLN.[14,15]

A few meta-analyses about SLN biopsy (SLNB) after NAC showed detection rates (DRs) of 63% to 100% and FNR of 0 to 39%.[16-18] For patients with clinically negative (cN0) and positive (cN+) lymph node status before NAC, Classe et al[19] reported DRs of 94.6% and 81.5%, and FNRs of 9.4% and 15%, respectively. The SENTINA (SENTInel NeoAdjuvant) study[14] showed a DR of 99.1% in patients having SLNB before NAC. In patients who were initially cN+, but ycN0 after NAC, the DR and FNR were 80.1% and 14.2%, respectively.

Currently, the best surgical approach in the axilla for the patients with initially cN+ who are ycN0 after NAC is unclear.[2,5,14,20]

Novel Techniques of SLNB After NAC

The standard method for axillary lymph node staging in breast cancer patients, even after NAC, is still SLNB with a radioisotope (lymphoscintigraphy with a technetium-labeled colloid), blue dye, or both (dual technique). However, blue dye as well as radioisotope have some disadvantages. For example, blue dye might cause some allergic reactions, skin necrosis, tattoo effect, and technetium 99m has a short half-life causing scheduling of surgery and limiting its

[1]Department of General Surgery, Bezmialem Vakif University School of Medicine, Istanbul, Turkey
[2]Bahcelievler Medicana Hospital, General Surgery Department, Istanbul, Turkey

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Address for correspondence: Yeliz Emine Ersoy, MD, Department of General Surgery, Bezmialem Vakif University Medical Faculty, Adnan Menderes Bulvari, Vatan Caddesi, 34093 Fatih, Istanbul, Turkey
E-mail contact: yersoy@bezmialem.edu.tr

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availability to distant health centers, and radioisotopes cause some problems in handling and disposal of isotopes, training of staff, legislative requirements, and anxiety of some patients related to the radiation.[21,22]

Disadvantages of the existing SLNB techniques have led to the development of alternative methods like indocyanine green fluorescence (fICG), superparamagnetic iron oxide nanoparticles (SPIO), indigocarmine blue dye,[23] intraoperative ultrasound (IOUS),[24] contrast-enhanced ultrasound (CEUS) using microbubbles,[21] and tattooing with a sterile black carbon suspension (Spot; Endoscopic Marker, GI Supply, Inc., Camp Hill, PA).[25] Microbubbles and tattooing were assessed in some studies for SLNB without NAC, but the other 4 methods were studied in SLNBs after NAC also. Thanks to the studies showing feasibility of SLNB after NAC, some methods were also needed to ensure the removal of initially biopsy-proven positive nodes,[13] like clip placement to the suspected or involved nodes before NAC, and removing the clipped node with the guidance of 125I-labeled radioactive seed or guide wires.[26-28]

Clip Placement

At the time of first diagnosis, abnormal axillary lymph nodes with eccentric cortical thickening, hilar compression, displacement, or effacement, and irregular margins are identified, and ultrasound-guided fine needle aspiration is done, and a clip marker is placed within the sampled node.[1]

Clips can be placed during the first percutaneous lymph node biopsy or after learning the pathologic result of it. If they are placed at the time of first biopsy, they can be placed in negative nodes. However, if it is done after biopsy results positive for metastatic disease, it means a second percutaneous procedure for clip placement is required. During SLNB, specimen radiograph of the SLNs or the axillary dissection specimen can show the clip inside, or the pathologist can identify it in the node.[13]

Nathanson et al[29] reported that, in 78% of the patients, there is a correlation between the lymph node identified using percutaneous biopsy and the lymph node(s) resected at the time of SLNB. In most of the cases, resected nodes at SLNB include the node that is identified on initial axillary ultrasound, but sometimes they do not.

In the American College of Surgeons Oncology Group (ACOSOG) Z1071 trial, the patients who had clinical T0 to T4, N1 to N2 disease had NAC followed by SLNB and ALND to determine the accuracy of SLNB after NAC.[13] Here, FNR of 12.6% exceeded the prespecified threshold of 10%, but subgroup analysis showed a lower FNR with immunohistochemistry and if a clip was placed in the biopsy confirmed metastatic node to help removal of it as an SLN.[5,13,26] In their study, Boughey et al[13] had a FNR of 6.8%, and it was related with the other nodes in the axilla having residual disease, or the positivity in nonclipped node or nodes.

Placement of a clip also causes a challenge when the SLN does not contain it, that necessitates alternative strategies to ensure resection of the clipped node. These include preoperative localization of the clipped node with a wire, needle, radioactive seed, or IOUS, and also tattooing the lymph node at the time of biopsy and visualizing it at surgery.[13,25,26,30]

Clip Placement and 125I-Labeled Radioactive Seed Localization

Diego et al[27] stated that, 1 to 5 days before the definitive surgery after NAC, they localized the clipped node with a 125I-labeled radioactive 4.5 × 0.8-mm titanium seed under ultrasound or mammogram guidance. A hand-held gamma probe was used to detect the 125I seed. Excision of the targeted node, including the radiopaque clip and the 125I seed was documented by intraoperative specimen radiograph[1] and when the 125I-localized lymph node was negative, there were no other pathologically positive lymph nodes.[27]

The study of Caudle et al[31] showed that evaluation of the clipped node was a valuable tool in assessing nodal response after systemic therapy and was associated with an FNR of 4.2%, and specifically localizing and removing the clipped node in addition to removal of SLNs resulted in an FNR of 2.0%.

Advantages of using I125 seed included patient comfort, increased ease of surgical scheduling with a half-life of 60 days, decreased risk of displacement, and potential for decreased risk of injury to surrounding vascular structures in the time of surgery.[1,32,33] Several institutions reported I125 seeds to be a safe and oncologically successful method.[34-36]

Because I125 has a gamma emission at 35 keV compared with 140 keV seen with technetium, I125 seed in the lymph node did not have an effect on preoperative lymphoscintigraphy.[32,33]

Clip Placement and Guide Wire Localization

The clipped lymph node could not always be removed even after axillary dissection, and the missed clips were seen on planning for radiation therapy.[28] Missing a positive node could lead to undertreatment of the axilla resulting with regional recurrence. Also, the patient with a positive node might not get further systemic treatment, so it is important for systemic recurrence as well. Because of this, some authors started using wire localization of the preoperatively biopsied positive node to ensure its removal.[26,28] With ultrasound-guided wire localization, the clipped node was removed in 97.3% of the patients, a rate significantly higher than 79.4% of the 34 patients who did not have wire localization.[28]

In the ACOSOG Z1071 trial, the rate for missing the biopsy proven clipped lymph node was 17% for patients who underwent ALND, and when the clipped lymph node was removed during SLNB, the false negative rate fell to 6.6%.[13] However, as a disadvantage, the clip could be dislocated from a node, and might be removed with irrigation and suction.[28] Furthermore, sometimes radiologists are not be able to see the clip in the node using ultrasound guidance for guide wire localization after NAC.

Indocyanine Green Fluorescence

Indocyanine green (ICG) is a widely used green dye for assessing liver function and cardiac output.[37] By binding to plasma proteins in the vascular components, this near infrared imaging can visualize the lymphatic channels through the skin and guide the surgeon to the SLN in the axillary basin with fluorescence imaging systems.[38-40] The fICG method was shown to be safe and can achieve high SLN detection comparable with the radioisotope method.[21,41-43] The use of ICG in SLNB has some advantages compared with isotope like lower cost, fewer adverse effects, and

quick transcutaneous real-time visualization (within several minutes), facilitating the localization of the incision and the detection of SLNs during the surgery.[44] With their fluorescence image-guided resection equipment, He et al[45] identified 276 SLNs in 98 subjects (DR, 99%), whereas the blue dye method only identified 202 in 91 subjects (DR, 91.92%).

The ICG was injected either retroareolarly or periareolarly (subdermal or intradermal) and, SLN identification ranged between 93.1% and 100% of patients, and a mean number of 1.5 to 5.4 SLNs were excised.[39-43,46-50] Tsuyuki et al[51] stated that SLNs were detected in all clinically node-negative cases, whereas in clinically node-positive cases the identification rates (IRs) were 93.8%. Regardless of the node metastasis, the sentinel lymphatic pathways were detected without the influence of NAC in all cases. ICG did not reveal any systemic or even local side effects and the method was significantly less expensive than the scintigraphy method. The only limiting factor was stated to be the body mass index >40.[52]

Superparamagnetic Iron Oxide

With the median diameter of 60 nm, including the organic cover, SPIO allows the SLN to selectively filter those particles. After the injection of the Sienna+ (Endomagnetics Ltd, Cambridge, United Kingdom) intravenously or interstitially by the surgeon, the particles drain through the lymphatic pathways and concentrate on the SLNs. The SLN traced using SPIO can be detected using a hand-held magnetometer (Sentimag; Endomagnetics Ltd).[53]

Superparamagnetic iron oxide has a long half-life of several years, does not need special handling procedures and scheduling with a nuclear medicine department, and has no problems with toxicity in clinical use or safe waste disposal.[21]

After induction of anesthesia, the patient is injected subareolarly with 5 mL consisting of 2 mL of SPIO (Sienna+; Endomagnetics Ltd) diluted in 3 mL of normal saline. After a 5-minute breast massage, the magnetic field is detected using Sentimag (Endomagnetics Ltd). After 20 minutes, an incision on the axilla is performed and the SLNs that have the Sienna+ uptake displaying a black/brownish color are excised guided by Sentimag (Endomagnetics Ltd) until the counts were < 10% of the highest count.[53]

Shiozawa and colleagues[54] recorded the IR of SLNs in 90%, 77%, and 80% of the cases for the combined, SPIO, and blue dye alone techniques, respectively. In the SentiMAG multicenter trial,[55] Douek and colleagues identified SLNs in 95% of patients with the standard and 94,4% with the magnetic technique.[55] Of 25 patients with at least 1 macrometastasis, 23 of 25 were identified with the magnetic, and 24 of 25 with the standard technique. As a result, the magnetic technique was concluded to be noninferior to the standard approach. However, the FNR of the magnetic technique (8%) was twice that of the standard technique (4%).

Rubio et al[53] evaluated the outcome of SLN after NAC using a dual tracer (SPIO-Tc99), and the DR using Tc-99 was successful in 28 patients (93.3%) and SPIO in 30 patients (100%). And they concluded that detection of SLNs with SPIO allows for easy identification of axillary nodes and can be used to reliably identify SLNs.

Indigocarmine Blue Dye

In the modified combination of 4-node axillary sampling (4NAS) and blue dye methods, the "4NAS/dye" technique, SLNB using indigocarmine blue dye (Daiichi Sankyo Co, Ltd, Tokyo, Japan) is first performed by the subareolar injection of approximately 3 to 5 mL of 0.4% indigocarmine dye and then depending on cases, several palpable lymph nodes around, not necessarily 4, are removed as sentinel nodes (SNs).[23] In 2005, Ishikawa et al[56] reported the feasibility of the 4NAS/dye method without NAC and later in 2010, Nauri et al[57] reported an axial recurrence in only 1 of 234 patients without metastases in SNs. Because the use of radioisotopes is restricted to authorized institutions in Japan, Kida et al[23] have used this technique after NAC. The IR on SLNB was 94%; the accuracy 94.7%; and the FNR 13.5%. In 34 patients with clinically negative nodes before NAC, the IR was 97.1%; the accuracy 97.0%; and FNR 0%. With those results, it was concluded that, after NAC, the modified indigocarmine blue dye method was comparable with methods that use other tracers.

Intraoperative Ultrasound

After the SNs were excised, Yu et al[24] explored the entire axilla using IOUS during the processing of SN frozen sections. Sonographic features for suspected malignant lymph nodes are defined by size, morphology, and internal echogenicity (including the cortex and medulla of the visualized node), as well as previously published sonographic criteria like presence of eccentric or uneven cortical thickening (which might be associated with outwardly bulging to perinodal fat or inward indentation to the medulla) and/or disproportionate enlargement of a lymph node that forms an abnormal "rounding" shape.[24,58-61]

The FNR of only 1.39% is similar to the series in which the SN biopsy was performed for breast cancer, and furthermore, detecting patients with locally advanced breast cancer without SN metastasis, and being unable to localize nodes in the non-SN level using IOUS after NAC, Yu et al recommended that sequential axillary dissection is unnecessary.[24]

Contrast-Enhanced Ultrasound Using Microbubbles

Although we could not find any literature on the use of CEUS in SLNB after NAC, SLN identification using intradermal microbubbles and CEUS has been recently reported in swine models and patients with breast cancer by Sever et al.[62] Nielsen et al[63] also used a blood pool contrast agent SonoVue (Bracco SpA, Milan, Italy) consisting of sulfur hexafluoride microbubbles with a mean bubble size of approximately 2.5 μm (range, 1-10 μm), and showed that the distances from the injection site did not affect the ability to detect the contrast-enhanced SLNs.

Sever and colleagues[64] studied CEUS in 54 patients with the periareolar injection of 0.2 to 0.5 mL SonoVue (Bracco SpA). The breast was massaged and lymphatic channels were visualized immediately resulting in SLN identification in 89% of patients, which was later repeated by Schrenk et al.[65]

Cox and colleagues[66] did a larger study of 347 patients, but the technique could not visualize or successfully biopsy 13.3% of patients with the sensitivity and specificity of 61% and 100%, respectively.

Tattooing of Biopsied Axillary Lymph Nodes

Ultrasound or mammography might not be able to identify metallic clips placed in the axilla, especially after neoadjuvant treatments. Because labeling methods like 125I radioactive seeds and sonographically visible bioresorbable polymers (Hydromark, Devicor Medical Products, Lecia Biosystems, Cincinnati, OH) have the disadvantages of their resource-intensive and potentially more

expensive methodologies,[30,36,67] Choy et al[25] reported tattooing positive nodes with a sterile black carbon suspension at the time of biopsy. In the initial experience with 12 patients who had neoadjuvant therapy, the tattooed node was successfully identified in 10 patients. Because no radioactive materials are used in this approach, it might be a more accessible technique for some centers. Also, it does not require additional localizing procedures. However, one disadvantage is the inability to see the tattooed node at the time of surgery, causing more dissection.

Spot is the first and only non-India ink Food and Drug Administration-approved product for marking or tattooing the gastrointestinal tract. It is a sterile, nontoxic, suspension containing water, glycerol, polysorbate 80, benzyl alcohol, simethicone, and high-purity carbon black.[68]

Intraoperative pigment was detected up to 211 days after injection, with an average time interval of 130 days. In the study of Choy et al,[25] suspected nodes were identified and sampled and tattooed before treatment and correlated 96.4% with those identified as SNs at the time of definitive surgery.

Conclusion

Some of the restrictions of the SLNB techniques, forced the researchers to develop alternative methods like fICG, SPIO, indigocarmine blue dye, IOUS, CEUS using microbubbles, and tattooing. Some methods were also used to be sure about removal of the initially biopsy-proven positive node at the time of surgery like clip placement to the suspected or involved nodes before NAC, and removing it with the guidance of radioactive seed or guide wires. However, further methods facilitating the evaluation of SNs, especially after NAC and studies including larger numbers of patients improving the techniques mentioned are still needed.

Disclosure

The authors have stated that they have no conflicts of interest.

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