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REVIEW ARTICLE

Techniques for sentinel lymph node biopsy in breast cancer patients

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Summary

Breast cancer is the most frequent cancer among women worldwide. Cancer cells primarily spread through the lymphatic vessels, with axillary lymph node status being one of the most reliable prognostic factors in breast cancer patients. Axillary lymph node staging in breast cancer patients was initially performed by axillary lymph node dissection. Sentinel lymph node biopsy is the standard of care in clinically and radiologically negative axilla.

According to the current guidelines, double contrast is a recommended procedure for identifying the sentinel lymph node. Nowadays, several new tracers are in clinical practice with a high identification rate and low false negative results. Due to technological and resource limitations, many medical centers worldwide lack the facilities to apply new radioactive tracers. The use of blue dye alone is a reliable and effective diagnostic and surgical technique, offering a high identification rate and low false-negative results.

Key words: breast cancer, biopsy, sentinel lymph node

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INTRODUCTION

According to The Cancer Registry of the Republic of Serbia, breast cancer (BC) is the most common cancer affecting women in Serbia. Every year, 4,600 women get diagnosed with BC, and 1,600 women die from this disease. Every eighth woman in Serbia is diagnosed with BC (1).

Breast cancer is a heterogeneous disease with multiple subtypes. A fundamental step in breast cancer progression and metastasis is the invasion of the basal layer (2). There are several classifications of BC. The fundamental classification involves the histological categorization of BC. Invasive ductal carcinoma is the most common histological subtype, accounting for 70%–80% of all invasive breast carcinomas, followed by invasive lobular carcinoma at approximately 10%. The remaining cases are rarer subtypes, including mucinous, cribriform, papillary, tubular, medullary, metaplastic, and apocrine carcinomas (3). The immunohistochemical classification is the most widely used method for defining the molecular subtypes of breast cancer. Immunohistochemistry assesses the presence of estrogen receptors (ER), progesterone receptors (PR), and human epidermal growth factor 2 (Her2). Based on the expression of these receptors, breast cancer is classified into the following subtypes: Luminal A, Luminal B, Her2 positive, and triple negative. The molecular classification of BC holds significant clinical importance as different subtypes exhibit distinct characteristics and prognoses, thereby guiding oncological treatment based on molecular subtypes (4,5).

Diagnostic and staging process of breast cancer is based on physical examination, ultrasound, mammography, and magnetic resonance imaging of the breast (6,7). It is important in terms of diagnosis of the primary tumor as well as the evaluation of the stage of axillary disease.

One of the most accurate prognostic factors in breast cancer is the presence of axillary lymph node metastasis (8). Detailed knowledge of the anatomy of the lymphatic system of upper extremities and the breast is fundamental in the adequate assessment of the axillary lymphatic status (9).

Axillary lymph node staging in breast cancer patients was initially performed by axillary lymph node dissection. This technique was accurate, but it had significant morbidities such as upper extremity numbness, surgical site and surrounding soft tissue infection, and lymphedema of the unilateral upper extremity. (10) Sentinel node biopsy for breast cancer was introduced by Krag in 1993 (11). The sentinel lymph node (SLN) is the first to receive drainage directly from the tumor. Sentinel lymph node biopsy (SLNB) is a minimally invasive technique to confirm regional lymph node metastasis in cancer patients. SLN biopsy is the gold standard for axillary lymph node metastasis assessment in patients with clinically and radiologically negative axilla (N0 status) (12).

Among the biological subtypes of breast cancer, positive lymph nodes were most frequently observed in luminal cancer, while the lowest frequency was found in triple-negative breast cancer (13)

The most frequent localization of the sentinel node is the lower medial part of the axilla alongside the lateral thoracic vein, below the second intercostobrachial nerve (87%) or above the nerve (11.5%) (14).

The most commonly used SLNB techniques are dual-the modality method with radioactive isotope technetium-99m (Tc)- labeled nano colloid and blue dye, blue dye alone, radioactive isotope technetium-99m (Tc)- labeled nano colloid alone, indocyanine green fluorescence, super-paramagnetic iron oxide (SPIO) nanoparticles, contrast-enhanced ultrasound imaging using microbubble (CEUS) (15).

Dual-modality method with radioactive isotope technetium-99m (Tc)- labeled nano colloid and blue dye

The dual-modality method with radioactive isotope and blue-dye method are considered the gold standard for SLNB. This is an expensive method that requires a nuclear medicine facility; thus, it is not available in every hospital. (16)

Sentinel lymph node biopsy technique using radioactive isotope is conducted through the preoperative administration of a radioisotope solution, specifically 99mTc colloidal, injected into the subareolar region of the breast or the peritumoral area. Following this injection, lymphoscintigraphy is performed a few hours later using a gamma camera to visualize the lymphatic drainage. Surgical intervention is generally scheduled for the day after lymphoscintigraphy. The procedure begins with injecting the blue dye into the same anatomical location as the radioactive isotope. During this procedure, a handheld intraoperative probe is used to identify radioactive sentinel lymph nodes. Subsequently, all labeled or stained nodes are excised individually and subjected to pathological examination for further analysis (10,12). Disadvantages of using radioactive isotopes for SLN marking include the need for preoperative injection hours before surgery, reliance on nuclear medicine personnel, and exposure to radiation for both patients and healthcare staff. Lymphoscintigraphy does not provide real-time visualization of lymph nodes; once the gamma camera is removed, surgeons dissect areas previously identified as radioactively hot (17).

The identification of the dual-modality method with a radioactive isotope and blue dye is up to 99.6% (18).

Blue dye alone

In many countries, the dual modality approach for sentinel lymph node biopsy (SLNB) is not feasible; therefore,

the use of blue dye alone is a prevalent alternative for performing SLNB (5 Zhou). The application of blue dye is considered acceptable and can be effectively utilized in institutions with limited access to nuclear tracers (9, 19).

The procedure is performed in an operating room setting. Following the administration of general endotracheal anesthesia, 2 mL of methylene blue is injected subdermally around the areola and peritumorally, accompanied by a brief massage to facilitate lymphatic drainage from the breast. Access to the axilla is achieved through a transverse incision, and upon the identification of the sentinel lymph node (SLN), it is excised for ex tempore histopathological evaluation.

The SLNB procedure is recognized as safe and accurate and recommended when nuclear tracers or alternative modalities are unavailable. This method demonstrated an identification rate of 94.74% (8, 20).

Indocyanine green fluorescence

Indocyanine green (ICG) is used to assess liver function and cardiac output and to monitor free flap perfusion. Unlike fluorescein, ICG is entirely bound to plasma proteins and fluoresces in the near-infrared spectrum. This fluorochrome absorbs light at approximately 800 nm, emitting a fluorescent signal when subatomic particles transition from an excited state to a ground state.

Indocyanine green fluorescence is one of the most well-known alternative methods for SLN localization. It offers a comparable SLN detection rate to radioisotope or blue dye. The procedure is performed with a 1-5 mL volume of ICG, administered subdermally or intradermally into the retroareolar or periareolar breast tissue. The breast tissue is then massaged for 2 minutes to facilitate distribution (21, 22).

The fluorescence is not visually detectable; therefore, the operating room lights are typically dimmed, and the Photodynamic Eye (PDE: Hamamatsu Photonics, Hamamatsu, Japan) system is used to capture the black-and-white images of fluorescent lymphatics and sentinel nodes on a monitor. ICG administration is contraindicated in patients with iodine allergies due to the presence of sodium iodide. Transcutaneous fluorescence of lymphatic vessels aids in identifying the location of axillary incision. After the incision, sentinel nodes are localized using an infrared torch PDE and excised. This technique may be used independently or in combination with blue dye or radioisotope techniques (22).

Superparamagnetic iron oxide (SPIO) nanoparticles

Supermagnetic iron oxide (SPIO) nanoparticles are used as contrast agents in magnetic resonance imaging (MRI). Sienna+® (Endomagnetics Ltd, Cambridge, UK) is a brown liquid SPIO tracer with an average particle size of 60 nm and has been used for sentinel node mapping. To prepare the solution, 2 mL of Sienna is diluted with 5 mL of saline and injected subcutaneously in the breast. Following injection, the site is massaged for approximately five minutes to facilitate the movement of SPIO nanoparticles through the lymphatic system, where they accumulate in the sentinel lymph node. The sentinel node/s may stain brown and the tracer can be detected using the hand-held magnetometer- Sentimag® (Endomagnetics Ltd) magnetometer probe, which functions similarly to a gamma probe for radioisotope detection after a migration period of 20 minutes. It is important to note that metal instruments can disrupt the ferromagnetic signal, and these need to be removed or replaced with plastic alternatives during localization. This technique is contraindicated in individuals with allergies to iron or dextran compounds, iron overload diseases, pacemakers, or ferrous metal-containing devices in the chest wall (22,23).

Detection rates of sentinel nodes using this method range from 94.4 to 98%.

The SPIO tracer is not radioactive, which simplifies implementation by avoiding the regulatory challenges associated with radioisotopes. It is available in approximately 30 countries, and reassuringly, data from multiple studies indicate that its detection rates are non-inferior to those of standard trace techniques (22).

Contrast-enhanced ultrasound imaging using microbubbles (CEUS)

Contrast-enhanced ultrasound (CEUS) utilizing microbubbles dispersed in sulfur hexafluoride gas, injected intradermally around the areola, was first documented in 2013 for sentinel lymph node biopsy. This technique employs an ultrasound contrast agent in conjunction with a contrast-specific mode of the ultrasound machine, allowing dynamic contrast-enhanced ultrasound imaging to facilitate non-operative identification and biopsy of sentinel nodes.

Second-generation ultrasound contrast agents comprise microbubbles filled with various gases encased in a lipid shell. While no adverse effects have been reported in breast applications, these agents may be perceived as foreign by the immune system, which raises the possibility of hypersensitivity reactions. The contrast agent is administered intradermally or subdermally at the upper outer periareolar region or directly under the areola. Following injection, the breast is gently massaged for several seconds. Visualization of the lymphatic channels is achieved through contrast pulse sequencing, enabling tracking into the axilla to locate the sentinel node that accumulates the contrast agent.

Repeated injections may be performed in cases where localization fails. This raises safety concerns regarding potential damage to the microvasculature. After successful localization, fine needle aspiration or core needle biopsy of the draining node is conducted using conventional grayscale ultrasound to assess axillary staging (24).

The CEUS procedure offers several benefits, including the elimination of radioisotope use, avoiding potential irradiation, eliminating the necessity for a nuclear medicine facility, providing real-time visualization of sentinel lymph nodes (SLN), and utilizing a low-cost contrast agent. However, drawbacks of this technique include extended procedure duration relative to alternative methods, the necessity for proficiency in axillary ultrasound examination, a prolonged learning curve, and dependence on operator skill. CEUS has a lower detection rate and sensitivity compared to the blue dye method (24). The Ceus detection rate is 96.3% (25).

CT lymphography (CTLG)

Computed tomography lymphography offers a novel way of localizing SLN, with possible combinations with other techniques (ICG fluorescence) allowing for a non-invasive highly accurate localization process compared to the radioisotope/ blue-dye method (21).

CTLG is a method in which computed tomography (CT) scans are obtained after local injection of a mixture of iodine contrast and local anesthetic into the areola to identify contrast-enhanced lymphatic vessels and sentinel lymph nodes. Contiguous 2-mm-thick CT images are obtained 3 minutes after the massage from the upper thorax to the axilla. After detection of the SLN –which is the LN enhanced with the dye-, its location can be mapped on the skin by marking the point of crossing of the vertical & horizontal lines of the red laser light beam of the CT machine. That laser beam is moved according to the SLN site on the CT. CTLG was performed 1–2 days before surgery (26, 27).

During surgery, 1.5–3 ml of dye (blue dye, Indigo carmine, etc.) was injected into the same site. Sentinel lymph node biopsy was then performed, relying on the images and markings obtained on CTLG. The identification rate of sentinel lymph nodes with CTLG is 92.9% (26, 27).

CONCLUSION

SLN biopsy is the gold standard for axillary lymph node metastasis assessment in patients with clinically and radiologically negative axilla. The gold standard for SLNB is the Dual-modality method with radioactive isotope and blue-dye method. Applying blue dye alone is a reliable and effective procedure in institutions with limited access to nuclear tracers. There are some new tracers with high identification rate and low false negative results.

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TEHNIKE BIOPSIJE "STRAŽARSKOG" LIMFNOG NODUSA KOD PACIJENTKINJA SA KARCINOMOM DOJKE

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Sažetak

Karcinom dojke je najčešća maligna bolest kod žena. Limfogeni put je primarni način širenja karcinoma dojke, što je slučaj i kod drugih karcinoma. Status regionalnih limfnih čvorova je jedan od najvažnijih prognostičkih parametara obolelih od karcinoma dojke. Aksilarna disekcija je bila primarni način procene aksilarnog statusa kod klinički i radiološki negativnih limfnih čvorova. Danas, biopsija stražarskih limfnih čvorova predstavlja proceduru izbora kod ovih pacijenata.

Prema važećim preporukama, metoda dvostrukog kontrasta (kombinacija radioaktivnog koloida i metilenskog plavog) predstavlja proceduru izbora. U novije vreme, u svakodnevnu praksu se uvode i drugi obeleživači. U velikom broju ustanova u svetu nema mogućnosti za korišćenje radioaktivnog koloida kao i novih obeleživača čija upotreba je povezana sa tehnološkim poteškoćama i materijalnim izdacima. Korišćenje metilenskog plavog kao jedinog kontrasta od strane obučenog hirurga predstavlja pouzdanu metodu sa prihvatljivim procentom identifikacije stražarskog limfnog čvora i niskom stopom lažno negativnih rezultata.

Ključne reči: karcinom dojke, biopsija, stražarski limfni čvor

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