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Recent Advances in the Tracer Technology Used for Sentinel Lymph Node Biopsy in Breast Cancer

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Abstract

The high incidence of breast cancer poses one of the greatest risks to female health worldwide. Sentinel lymph node biopsy (SLNB) is the standard of treatment for patients with axillary lymph node-negative early-stage breast cancer. Herein, the precise use of tracers is the key to ensuring the success of SLNB. However, owing to select-few limitations of traditional tracers, their clinical application is limited. New tracer techniques, such as the near-infrared fluorescent dye method (using indocyanine green), contrast-enhanced ultrasound, and superparamagnetic iron oxide nanoparticles are being applied in clinical practice. In this paper, we review the recent progress in SLNB tracer technology.

Keywords

Breast Cancer, Sentinel Lymph Node Biopsy, Tracer

1. Introduction

The 2020 edition of the Global Cancer Observatory (GLOBOCAN) report included 36 cancer statistics from 185 countries and revealed that breast cancer, with the highest incidence rate in 2020, surpassed lung cancer for the first time. The number of breast cancer cases diagnosed annually reaches up to 2.3 million (11.7%) worldwide, and the number of new deaths from breast cancer comes up to 690,000 (6.9%) [1]. The treatment of breast cancer has transformed from local treatment based on surgical strategies to a new era of comprehensive multidisciplinary treatment. Surgery remains a dominant component of this comprehensive treatment strategy. Surgical treatment of breast cancer has witnessed a gradual transition from simple tumor resection to radical mastectomy, extended radical mastectomy, modified radical mastectomy, breast-conserving surgery, and finally, endoscopic surgery for breast cancer.

Axillary lymph node status is the decisive factor for surgeons to judge the prognosis and formulate a follow-up adjuvant treatment. Axillary lymph node dissection (ALND) was first proposed by Halsted and has been the gold standard for axillary staging for more than 100 years [2]. With the development of technology and the popularity of breast cancer screening, the proportion of axillary lymph nodes in early-stage breast cancer patients has decreased from 40% to 20% - 25% [3]. Concurrently, the complications of ALND cannot be ignored: about 10% - 25% of patients were found to have complications such as sensory and functional abnormalities of the upper limb on the affected side, which can considerably reduce the quality of life of patients after the surgery [4].

Krag *et al.* were the first to perform sentinel lymph node biopsy (SLNB) for the surgical treatment of breast cancer. SLNB involves making a small incision under the patient's axilla during the surgery, and accurately removing the sentinel lymph node for biopsy. If the pathology is negative, axillary lymph node dissection can be avoided. If the pathology is positive, it indicates lymph node metastasis and further axillary lymph node dissection is needed. At present, SLNB has replaced AlNB as the standard operation for axillary lymph node treatment [5].

In 1999, the American College of Surgeons Oncology team launched the ACOSOG Z0011 clinical trial. A total of 891 patients were enrolled, of which 856 patients completed the follow-up. Patients with 1 - 2 positive SLN in early primary invasive breast cancer were randomized into ALND and SLND groups. The results showed no significant difference in the overall survival rate, regional recurrence rate, DFS, and OS between the two groups [2]. These results led to experts and scholars questioning the long-standing practice of ALND as a standard of care for breast cancer patients.

International and national guidelines recommend the use of blue dye combined with radionuclide for SLNB. Combined tracing has a high detection rate (>90%) and low false negative rate (<5% - 10%) [6]. Meanwhile, blue dye has a high false negative rate, the location of SLN needs to be determined by the operator's clinical experience, the learning curve is complex, and carries a risk of skin allergy.

The preparation of radionuclides is complex. Moreover, they carry the risk of radioactive pollution and are not approved by the drug and food administration in China; therefore, their clinical application in China is limited. As a result, the discovery of a new type of tracer with high accuracy, visibility, safety, and ease of operation is a research hotspot in the field of surgery. In recent years, new tracers and techniques such as the near-infrared fluorescent dye (indocyanine green, ICG), contrast-enhanced ultrasound (CEUS), and superparamagnetic iron oxide (SPIO) have been developed rapidly. This paper reviews the characteristics and clinical applications of traditional and new tracers.

2. Current Status and Clinical Significance of SLN Detection in Breast Cancer

The pathological stage of axillary lymph nodes is the key factor in judging the clinical stage and prognosis of breast cancer. SLNB is a minimally invasive biopsy technique that can accurately evaluate the staging of axillary lymph nodes. Importantly, ALND can be avoided in early-stage breast cancer when axillary lymph node status is negative [7]. In 1977, Cabanas first proposed the concept of SLN in a study on penile cancer. Soon, this concept was also found to be applicable to breast cancer [8].

A sentinel lymph node is defined as the first lymph node to which the tumor spreads from the primary breast cancer site to the axillary region and other regional lymphatic vessels, through regional lymphatic channels [9]. As in cutaneous melanoma, lymphatic circulation is the main mode of metastasis in breast cancer as well. A series of studies have shown that the lymphatic spread of breast cancer is gradual. If SLN is not affected, the probability of metastasis to the lymph nodes is very small. The National Comprehensive Cancer Network (NCCN) [10] guidelines recommend that SLNB be the first choice for axillary lymph node staging in patients with negative axillary lymph node status. With accumulating evidence from large-scale clinical trials, the previous relative contraindications of SLNB have gradually changed into indications. The 2018 edition of the NCCN guidelines treated inflammatory breast cancer, stage T4 breast cancer, and clinically suspicious or palpable lymph nodes as contraindications to SLNB. Relevant studies have found that some SLN positive patients can also be exempted from ALND. In the NSABPB-32 phase-III randomized trial, 5611 patients with early-stage invasive breast cancer with axillary lymph node-negative status were randomly divided into two groups. In group 1 (n = 2807), ALND was performed regardless of axillary lymph node status. In Group 2 (n = 2804), ALND was not performed if SLN was negative. No significant differences in the overall survival (OS), disease-free survival (DFS), and regional recurrence were observed between the two groups [11]. Similar conclusions have been drawn from large clinical studies such as the AMAROS and ASOCO. SLNB not only improves the detection rate of SLN, but also found to have no significant impact on the survival time of patients. On the other hand, it retains the normal function of the axilla, and has high clinical value and broad scope of application. Because of its high sensitivity, good safety profile, less associated trauma, and fewer complications, SLNB has become the first choice for axillary treatment in patients with early breast cancer and SLN-positive breast cancer.

3. Progress in SLNB Tracer Technology and Clinical Applications

3.1. Blue Staining and Nuclide Method

In 1993, Krag *et al.* [12] pioneered the use of radionuclides to locate sentinel lymph nodes in breast cancer. In 1994, Giuliano *et al.* [13] used biological dyes for sentinel lymph node biopsy for the first time. Blue dyes include methylene blue (MB), patent blue V, and isothioblue. Isothioblue and patent blue V are widely used in European and American countries. Methylene blue is widely used in China due to its advantages such as safety, low cost, and convenient operation. Technetium-99m-labeled (99mTc) sulfur colloid is the most commonly used radionuclide method. The American Society of Clinical Oncology (ASCO) guidelines recommend the use of a dye combined with radionuclide as the preferred technique for SLNB for breast cancer [14]. This method involves injecting 99mTc-labeled sulfur colloids and/or blue dye into the periphery, around the areola, or around the tumor before the operation. The "hot" and "blue" lymph nodes are identified by a handheld scintillation counter (γ-probe) during the operation. These are regarded as sentinel lymph nodes and removed, and their status is confirmed by histopathology. Vipul V *et al.* [15] studied 35 patients with early-stage breast cancer and found that the sensitivity of SLN alone was 90.48%, the accuracy rate was 88.57%, and the specificity was 85.71%. Despite the small sample size of the study, the findings demonstrated the clinical value of methylene blue in patients with early-stage breast cancer. In Italy, a meta-analysis of 4244 patients with early breast cancer enrolled in 35 studies showed that the detection rate of SLNB with 99mTc-labeled sulfur colloid alone (96.5%) was higher than that of blue dye tracer (86.8%); the false negative rate (2.6%) was lower than that of blue dye tracer (18.4%); and the detection rate of combined application of the two was 96.7% [16]. However, this study was limited in the comparison of the detection and false negative rates of each tracer, and lacked comparisons of the measurement and adverse reactions of each tracer. When blue dye is combined with radionuclide tracing for SLN, the average detection rate of SLN is greater than 95% and the false negative rate is less than 10%, thereby constituting the gold standard for SLN detection.

3.2. Near-Infrared Fluorescent Dyes

Fluorescence development technology utilizes the fluorescence tracer's property of absorbing near-infrared light and releasing fluorescence of different wavelengths to image SLNB with near-infrared imaging equipment [17]. Presently, indocyanine green (ICG) is the most widely used fluorescent tracer. It is a water-soluble green dye with strong binding to plasma protein, low toxicity, and strong tissue penetration. The maximum fluorescence excitation is at a wavelength of 765 nm. With the help of the imaging system, the operator can obtain noninvasive, convenient, and immediate observation of the lymphatic drainage and determine the approximate location of SLN. Because ICG is excreted quickly and does not undergo enterohepatic circulation, it is often used as a diagnostic reagent for the examination of liver function and cardiac output, and for retinal angiography [18].

In 1999, Motomura *et al.* [19] used ICG to detect SLN for the first time, and the detection rate was found to be 73.8%. Since then, the curtains for ICG research have been opened. Jeremiasse *et al.* [20] included 55 clinical studies with more than 4900 patients with different types of tumors in their meta-analysis, aiming to compare ICG with the gold standard for the detection of SLN in breast cancer and dermatological and gynecological tumors. They found that ICG had a higher detection rate for different types of tumors compared to the blue dye. Among the 26 breast cancer studies, the detection rate of ICG for SLN was 88.6% - 100%. The overall detection rates with ICG and radiocolloid were similar. Recent studies and meta-analyses have revealed no significant difference between ICG and Radionuclide tracers in the detection rate of SLN, similar to the above results [21]. Wu G *et al.* [22] compared ICG with methylene blue for SLNB and found that the sensitivity of the ICG group was 85.7% (6/7) while the accuracy was 96.43%. Meanwhile, the sensitivity of the methylene blue group was 88.24% (15/17), and the accuracy was 92.86%. There was no difference in the detection accuracy of SLN between the two tracers. Niu M *et al.* [23] included 222 patients with axillary lymph node-positive early-stage breast cancer in their study: the detection rate of SLN using ICG and MB alone was 96.4% and 84.7%, respectively ($P < 0.001$). The differences between ICG and MB in the SLN detection rate, detection number, and positive SLN detection rate were statistically significant ($P < 0.05$), and ICG was superior to methylene blue in all these respects. The above two are the sequential studies carried out by researchers at our institute, and the findings are similar to those obtained within China and abroad. At the same time, the literature shows evidence of a complementary relationship between ICG and radioactive colloids. On the one hand, radioactive colloids can accurately detect SLN through the skin, but have a low spatial resolution. ICG, on the other hand, lacks transdermal sensitivity, but has a high spatial resolution. Therefore, it is suggested that ICG and radioactive colloid be used together to trace SLNB, and ICG can be used as an alternative in countries where the use of radioactive colloid is either limited or lacking [24].

Additionally, the safety of ICG has attracted extensive attention. The FLUOBREAST trial prospectively evaluated the detection rate and toxicity of ICG for SLNB, and found that the detection rates of isotope and indocyanine green were 93% and 96%, respectively, and their combined detection rate was 99%. There was no significant difference in the average number of resected anterior sentinel lymph nodes between the two methods, and no adverse reactions related to ICG or grade 3 or 4 acute skin damage were found intraoperatively or perioperatively [25]. Therefore, ICG is a safe and efficient tracer. It is favored by the majority of healthcare workers because it is easy to operate, safe, provides real-time imaging of the lymphatic system, and aids clinicians in choosing an appropriate surgical incision. However, a recent study found that ICG tends to find more secondary lymph nodes; poor targeting results in the resection of more non-sentinel lymph nodes [24]. The improved detection rate of SLN instigates the excision of too many non-sentinel lymph nodes, which greatly increases the risk of complications in the affected upper limb [26].

The optimal dose of ICG for clinical SLNB is still controversial. A meta-analysis included 513 patients with breast cancer from 15 clinical studies, and found that when the ICG concentration was less than 5 mg/mL and the dose was greater than 2 mL, the sensitivity and detection rate of ICG were higher [27]. The fluorescence emitted by the tracer has limited penetration, and SLN in deeper locations can easily be missed. In addition, it is inevitable for lymphatic vessels to be injured during dissection. The leakage of the fluorescent tracer can also cause fluorescence contamination of the surrounding tissues, making it difficult to identify and locate SLN [28]. Recent studies have found that ICG combined with blue dye for sentinel lymph node detection can solve this problem.

A total of 415 patients with breast cancer were enrolled in the study by Zhang *et al.*, and were divided into the ICG + MB group (197 cases) and a single MB group (218 cases). The detection rate of SLN in the combined group was significantly higher than that in the single MB group (96.9% VS 89.7%; $P < 0.05$), and the average number of SLN (3 VS 2.1; $P < 0.05$) was also greater in the former. Thus, the combination of dyes was better than the blue dye alone [29].

ICG is highly sensitive, safe, easy to operate, and pollution-free, but also has limitations such as the risk of intraoperative fluorescent dye leakage that makes it difficult to locate SLN, weak penetration that may lead to some missed SLN diagnoses, and poor targeting that may lead to the excessive removal of lymph nodes.

3.3. Superparamagnetic Particles of Iron Oxide

Superparamagnetic iron oxide nanoparticles (SPIONs) are negative magnetic resonance imaging (MRI) tracers taken up by the reticuloendothelial system, which can shorten the T2 relaxation time of MRI [30]. According to their particle diameter, they can be divided into two categories: ordinary SPIO (diameter > 50 nm) and ultra-small SPIO (diameter < 50 nm). SPIONs are injected subcutaneously or intravenously into the patient's areola within 27 days before the surgery. After entering the lymphatic vessels, they accumulate in the SLN. Normal or inflamed enlarged lymph nodes show a low signal on T2-weighted MRI due to the degradation of SPIONs by macrophages. However, when cancer cells invade SLN, the function of macrophages fails, which makes metastatic SLN show a high signal on T2-weighted MRI.

SentimagIC was a multicenter, non-inferiority trial involving 146 patients with early breast cancer from six medical centers. The SPIO detection rate of SLN was compared with that of MB combined with nuclide, and was found to be 99.3% and 98.6%, respectively, and the patient detection rates of SLN were 94.3% (348/369) and 93.5% (345/369), respectively. The average number of excised nodules with SPIO was the same as that with blue dye (2.4). However, the detection rate of malignant tumors was higher than that with the radionuclide method [31]. A single-center prospective study in France reached a similar conclusion. This study involved 288 patients who underwent SLNB with SPIONs and received adjuvant radiotherapy; the detection rate of SLN was found to be 99.7% (287/288). SPIO is well tolerated and is not more toxic than nuclide and colorimetry[32]. A meta-analysis found SPIONs to be superior to traditional blue dyes, and comparable to the dual-technology of 99mTc and blue dye [16].

Compared with the traditional tracing method, the most common adverse event with SPIO is breast discoloration or pigmentation. This can, however, be prevented by deep injection. Moreover, if the magnetic tracer stays at the injection site for a long time, it can affect postoperative MRI imaging and cause artifacts [33]. In addition, SPIO is closely combined with MRI, which is not suitable for patients with metallic implants or claustrophobia [30]. Nonetheless, SPIO has good targeting abilities, has no radiation, and has a broad scope of application. The problem of false negative rates, however, needs to be further studied.

3.4. Sentinel Lymph Node Contrast-Enhanced Ultrasound

Contrast-enhanced ultrasound (CEUS) is a new tracer technique that can evaluate the axillary lymph node staging of breast cancer preoperatively. It involves injecting the contrast agent intravenously, into the areola and around the tumor, and using ultrasound to dynamically monitor lymphatic microcirculation in real time to determine the location and size of metastasis [9]. Sulfur hexafluoride microbubbles are most commonly used in SLN-CEUS because their average diameter is 2.5 μm, much smaller than that of red blood cells (average, 7.2 μm). Therefore, these bubbles can freely pass through capillaries and lymphatic microvessels [34]. Moreover, sulfur hexafluoride microbubbles do not contain iodine or protein, which reduces the risk of allergic reactions, thus making it an ideal tracer. The enhancement patterns of lymph nodes are divided into three types: type I SLN is significantly and evenly enhanced; this type is considered negative. Type II SLN is significantly and unevenly enhanced, and type III SLN is slightly enhanced or not significantly enhanced. Types II and III are positive manifestations that occur more often in lymph nodes invaded by cancer cells.

Old Berg reported the injection of the microbubble contrast agent into a pig model with melanoma for the first time. The detection rate of SLN was 90%. After a series of studies, it was also deemed suitable for breast cancer. Li *et al.* [9] used microbubble contrast agents to detect SLN in 453 patients with early-stage invasive breast cancer. The results showed that the sensitivity and specificity of SLN-CEUS in detecting SLN were 96.82% and 91.91%, respectively. Liu *et al.* [35] showed that the sensitivity and specificity of CEUS in the diagnosis of metastatic SLN were 98.04% (50/51) and 49.23% (32/65), respectively. Therefore, CEUS has been demonstrated to be an effective way to detect SLN.

Percutaneous CEUS is a safe and effective technique to locate SLN, and can guide SLNB. This method has good sensitivity for identifying SLN, and is of great significance in identifying the location and characterization of SLN. However, a few limitations exist, such as the high false negative rate and low specificity for metastatic SLN in patients with early-stage breast cancer.

4. Summary and Future Prospects

In the field of breast cancer surgery, axillary treatments have undergone sweeping changes and have witnessed several innovations, having gradually shifted from ALND to more precise and minimally invasive SLNB. At present, SLNB is the standard for axillary treatment of early-stage breast patients in China and several European and American countries. It has guiding significance for the localization and characterization of axillary lymph nodes, though the staging of axillary lymph nodes is based on pathology. Because of their low cost and easy access, blue dyes are easy to carry out in grass-root centers. Meanwhile, the detection rate of radionuclides combined with methylene blue is the highest, and their false negative rate is low. This combination is therefore considered the gold standard for SLNB and is presently included in national and international guidelines. The detection rate of ICG is no different from that of radionuclides, and can be used as a substitute for the latter. The combination of ICG and blue dye can achieve better results in SLN detection. SPIO is a non-radioactive and non-invasive SLNB tracer technology that is comparable to the dual-mode technology using 99mTc and blue dye. CEUS tracer technique has high sensitivity and a low incidence of allergic reactions, but has low specificity for metastatic SLN. In conclusion, with continuous advancements in clinical research, tracer technology is certain to traverse towards a more minimally invasive, safe, visual, convenient, and efficient direction.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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