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Trends and future perspective in Sentinel Node Biopsy in Breast Cancer Patients

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Abstract

The current approach to lymph node staging in early breast cancer is sentinel lymph node biopsy (SLNB), which is essential for prognosis and regional control of the disease. No imagining method is capable to detect lymph node metastasis and only SLNB is considered a gold standard to identify even the smallest metastatic foci in regional lymph nodes. Nevertheless, despite years of experience in this procedure, important clinical aspects and some variabilities are still under investigation. Also, for SLNB procedure, new techniques and indications are explored if a more precise and individualised approach is possible for the tailored treatment of our patients. This review aimed to discuss selected questions about modern and possible future directions in SLNB for breast cancer.
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Introduction

Breast cancer is the most commonly diagnosed malignant disease worldwide, with an estimated number of around 2.3 million new cases in 2020 [1]. In Poland, in 2020, the detection rate of breast cancer, according to world health organisation data, is 24,644 cases [2]. Sentinel lymph node biopsy (SLNB) for many decades showed its clinical usefulness, improving staging diagnosis in many cancer patients [3]. Using this method, we can visualise the lymphatic anatomy and get information about the cancer metastasis to the lymphatic system. Not only the stage of the disease but also regional control of cancer might be observed. Historical term, „sentinel", was described for lymphatic nodes in 1923 by Braithwaite, later by Gould et al. in 1960, and by Sayegh in 1966 [4-6]. The term „Sentinel Lymph Node" (SLN), for the first time was proposed by Cabanas et al. [7]. The details of the physiological concept of "sentinel lymph node biopsy "was published in melanoma patients in 1992 by Morton and Cochran [8].

The concept of SLN is based on hypothetical lymph node drainage from the primary tumour. Currently, no imaging system can detect lymph node metastasis in the early stage of breast cancer. However, by performing SLNB, we can stage regional lymph nodes and diagnose not only macro- but also micrometastasis of the lymphatic system. By drainage of the lymphatic area, the cancer cells flow towards the sentinel lymph node(s) and subsequently are transported to higher tiers of lymphatic system [8].

Today SLNB is a standard alternative technique to axillary lymph node dissection (ALND) for breast cancer staging. This surgical approach reduced the postoperative complications associated with ALND-like lymphedema, pain, nerve damage, postoperative serum collection, thromboembolic events, and infections.

The beginning of SLNB was based on the usage of methylene blue as a visible blue dye during the SLNB procedure [8]. The current gold standard is based on a dual method procedure using radioactive nanocolloide with an addition of a blue dye [9].

The detection rate of the double dye technique is about 96%, and using only blue dye is around 91% [10].

This paper aims to describe the current methods and trends for selected subjects in SLNB for breast cancer.

One or two metastatic sentinel nodes

ACOSOG Z0011

This trial was proposed to prove whether SLNB impacts survival compared to ALND in breast-conserving therapy (BCT) [11]. For early-stage breast cancer, presenting one or two metastatic lymph nodes after

SLNB, the patients were randomised to ALND vs whole breast irradiation therapy, with standardised adjuvant treatment either way.

The first results revealed no benefit in ALND vs SLNB and radiation therapy in case of locoregional recurrence in patients with BCT.

This trial's long-term follow-up showed no significant difference in local recurrence free survival and overall survival. Ten-year cumulative locoregional recurrence was similar for both groups (6.2% for ALND and 5.3% for sentinel node biopsy p=0.36)

As a result of this trial, a new standard was set for T1/T2 breast cancer with SLNB, where we can omit ALND when radiotherapy is given afterwards.

Still, three and more metastatic lymph nodes, or macroscopically suspicious lymph nodes, remain an indication for ALND [12].

AMAROS Trial

In another clinical trial (AMAROS), after surgical staging of the axilla, it was proven that postoperative radiotherapy compared to ALND showed similar oncological outcomes, with significantly lower morbidity and reduced risk of postoperative lymphedema [13].

Based on the results of these trials, still the group of selected patients with only 1-2 positive lymph nodes after SLNB procedure, with tumours greater than 3 cm, lymphovascular tumour invasion, and sentinel nodes microscopic extra capsular extensions, are a group of patients where an optimal adjuvant treatment plan is required [14].

Similar results were presented in another clinical trial (OTOASOR trial) [15].

NEW DYES

However, the standardised dual tracer technique in SLNB in breast cancer staging presents excellent results in terms of detection and false negative ratio. New dyes are being developed to improve some aspects of this procedure.

Fluorescent Dyes

From 2005, indocyanine green (ICG) has proved to be a valuable dye for breast cancer SLNB [16].

Using the fluorescent properties of this fluorophore, we can visualise the lymphatic vessels between the injection site and the sentinel lymph node in real time. A relatively cheap method is a good alternative for hospitals without access to nuclear medicine department. It is especially important because the detection rate is higher than nanocolloid and blue dye alone, similarly to the dual technique [17].

The advantages of this tracer include the visualization of lymphatic vessels through the skin, long-term proven safety profile, high-resolution real-time tracking and simple administration protocol with a short learning curve.

The main disadvantages are possible iodine allergy risks, relatively low fluorescence brightness, and skin discolouration. The detection of deeper sentinel nodes also seems problematic, ultimately due to the quick dispersion and then shortening of the detection time [18].

Not only ICG but also other fluorophores showed the feasibility of lymph node biopsy using fluorescent properties of these dyes like methylene blue or fluorescein [19,20].

Using different fluorophores during the same operation - a multispectral imagining - is possible to differentiate specific structures during operation [21].

Superparamagnetic iron oxide (SPIO)

With this tracer, non-invasive magnetic properties are used for handheld magnometer detection. Preoperative magnetic resonance imaging can visualise sentinel lymph nodes preoperatively and handheld magnometers intraoperatively. A non-inferiority of this technique in comparison to the dual tracer technique was proven in a meta-analysis by Zada et al. [22]. Like ICG, this procedure stains more lymph nodes [23]. We must remember that if using this approach, the surgical field must not be covered with any tools with magnetic properties.

Contrast-enhanced ultrasound (CEUS) with microbubbles

The idea behind this technique is based on dispersion with sulphur hexafluoride gas, stabilised by phospholipids [24].

The SLNB together with lymphatic vessels, are visualised by contrast-enhanced ultrasound (CEUS). The live visualisation using live ultrasound imaging can help in marking by guide wire of SLN(s) before operation. Identification rates ranged from 92.8%, with no statistical difference between CEUS and blue dyes [17]. We must keep in mind that this technique is highly dependent on ultrasound skills and requires a long

learning curve. The main advantage of this method is its cost effectiveness.

Micrometastasis and isolated tumour cells

According to sentinel node histopathological classification, we can distinguish three types of metastases based on the size of metastatic foci: macrometastasis, micrometastasis and isolated tumour cells.

The first clinical question in case of pN0(i+) or pN0(mi) is an additional non-sentinel involvement in other lymph nodes. For pN0(i+) the involvement varies from 4.9-16% [25,26], and for pN0(mi) involvement varies from 0-21% [27].

The second clinical question is the prognosis for pN0(i+) or pN0(mi) after SLNB. In the MIRROR study, patients with pN0(i+) or pN0(mi), did or did not receive systemic adjuvant therapy, and 10% decrease in 5-year disease-free survival was found in these patients in comparison to the pN0 group [28]. Nevertheless, with additional systemic therapy, 10% improvement in 5-year disease-free survival was observed for pN0(i+) or pN0(mi).

In another research additional pathological section of histological negative sentinel lymph nodes resulted in finding occult metastasis in 15.9% of patients, including 11.1% of ITC, 4.4% of micrometastasis and 0.4% macrometastasis [29]. Statistically significant less disease-free and overall survival was observed. However, the presence of occult metastasis was found not to be a predictor for cancer recurrence.

In the IBCSG 23-01 trial micrometastatic sentinel lymph nodes with or without lymphadenectomy showed similar disease-free survival rates [30]. Similar results were presented in AATRM 048/13/2000 trial [31]. The omission of axillary lymphadenectomy should be proposed for patients with or without radiotherapy afterwards.

Neoadjuvant Treatment

Due to new advancements in neoadjuvant treatment and an increasing number of patients qualified for this procedure, new challenges occur. Neoadjuvant therapy can change the axillary stage status and helps classify more patients eligible for SNB. Primary systemic therapy is responsible for up to 30-40% of complete pathological remission in the axillary lymph nodes [32].

We need to analyse two different subgroups of patients for SLNB, with or without positive axillary lymph nodes in preoperative settings.

Sentinel node biopsy after neoadjuvant treatment in node-negative patients (cN0)

The SENTINA trial showed that after neoadjuvant treatment, SLNB is feasible and showed a lower detection rate and higher false negative rate, as if the SLNB was done before the neoadjuvant treatment [33]. The false negative rate of SLNB in cN0 patients, who underwent neoadjuvant chemotherapy, was 5.9% vs 4.1% with the surgery-first approach [34].

A meta-analysis based on 23 studies proved an excellent identification rate and false negative rate [34].

Sentinel node biopsy after neoadjuvant treatment in node-positive patients (cN1)

In an ACOSOG Z1071 trial, the false negative rate of axillary involvement was less than 10% after prior treatment of cN1 status patients.

The false negative rate was 20.3%, and for the dual technique, 10.8% [35]. With the removal of at least three or more lymph nodes, the false negative rate dropped to 9.1% compared to 21.1% if two nodes were removed.

The GANEA 2 Trial showed independent predictor factors associated with a higher false negative rate after neoadjuvant chemotherapy for SLNB if the residual tumour size was ≥5 mm and lymphovascular invasion was present [36].

In the SENTINA trial, similar to ACOSOG Z1071, the reduction in false negative rate from 16-8.6% was found if the dual method was used instead of one tracer [37].

Moreover, the false negative rate decreased when more sentinel lymph nodes were removed (24.3% for one node, 18.5% for two nodes, and less than 10% for three or more lymph nodes). Another factor involves pathological immunohistochemical evaluation of the lymph node. Using this specific method, the false negative rate dropped to 8.7%. Interestingly, 6.8% of false negative ratio could be achieved if lymph nodes were marked by a clip, via ultrasound, prior neoadjuvant treatment [36].

The other useful tool for localising pre-neoadjuvant treatment positive lymph nodes is pretreatment labelling by clip [38].

The feasibility and placement of a clip into the most suspicious biopsy-proven lymphatic nodes were

investigated with a postoperative identification rate of 87.8% in the specimen.

The false negative rate for these patients was 4.2 % when the marked node was found as a sentinel node; however, if this clip node was not a sentinel node, the false negative rate was 16.7% [39]. In some cases, the clip-marked lymph node can be found preoperatively by ultrasound. If not, there is the possibility of marking via a guide wire in the department of radiology. The lymph node can be found during surgery. After performing SLNB, the presence of the clip in the lymph node can be confirmed by X-Ray mammography.

Many of the questions may be resolved by the results of ongoing clinical trials [40-42].

Omission of SLNB in Elderly patients

Older patients with estrogen receptor positive tumours, treated with hormonal therapy, showed that omission of SLNB in tumours with a good prognosis is possible [43,44].

In an Italian study, patients aged 65-80 years, who underwent BCT were randomised to ALND vs. no axillary intervention at all. All patients received five years of treatment with tamoxifen. No difference was found in case of cancer-specific mortality, overall mortality or crude cumulative incidence of breast events.

In another retrospective study in cN0, patients aged 70 years and older who underwent ALND vs no--ALND showed no difference in breast cancer mortality in 15 years of follow-up [45].

In the IBCSG Trial 10-93 in patients aged 60 years and older, randomised with or without ALND followed by five years of tamoxifen, similar results in terms of disease-free survival and overall survival was achieved, with significantly better quality of life, in the subgroup of patients without axillary surgery [43].

According to the Recommendation of Society of Surgical Oncology, SLNB should not be routinely used in women older than 70 years with hormone positive receptor breast cancer.

Omission of SLNB/Avoidance in Axillary staging

Following low recurrence rates for SLNB negative and selective SLNB positive cases, the rate of lymphedema after SLNB may impact the patients' outcome. Currently, ongoing trials are investigating the feasibility of omitting SLNB in patients with cN0 and biologically not aggressive tumours after BCT. The SOUND trial, INSEMA Trial and BOOG 2013/08 are under investigation [40-42].

The primary endpoint of these studies is a disease--free survival with secondary ones including morbidity and quality of life.

Conclusions

Recently, an evident trend toward deescalation of axillary surgical treatment in breast cancer patients is observed. Additionally, new technologies are being helpful for pre- and intraoperative sentinel node visualisation. ACOSOG Z0011 trial changed the dogma in some cases of positive sentinel nodes, where one or two metastatic sentinel nodes are no longer an indication for axillary lymph node dissection in patients qualified for breast-conserving therapy.

Indocyanine green and other fluorescent dyes, like methylene blue or fluorescein, might be useful tools for intraoperative visualisation of sentinel nodes and lymphatic vessels. Also, other new techniques for SLNB, like SPIO and CEUS found their place in clinical research.

The presence of ITC or micrometastasis in the lymph nodes is a risk factor for non-sentinel lymph node involvement. Moreover, the presence of ITC or micrometastatic sentinel lymph nodes is responsible for a 10% decrease in 5-year disease-free survival; however, this difference disappears with additional systemic therapy.

Occult sentinel node metastases are not predictive factors for cancer recurrence. Following IBCSG 23-01 trial, ALND seems to be an overtreatment in case of patients with micrometastatic sentinel lymph nodes.

Also, after neoadjuvant therapies, a sentinel node biopsy is offered for all cN0 patients and in case of clinical downstaging to ycN0 cases. Still positive and palpable lymph nodes remain an indication for ALND.

Older patients with estrogen receptor positive cancer, together with anti-hormonal therapy, are good candidates for the omission of SLNB. Ongoing clinical trials will probably find a subgroup where omitting axillary staging in younger subgroups also will be possible.

In the last years, the revolution and evolution of SLNB in breast cancer has become a fact.

A tailored axillary approach will help improve disease staging and patient quality of life.

Conflict of interest
None

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