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PERSPECTIVES

Classic and novel approaches to sentinel lymph node detection in patients with invasive breast cancer

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ABSTRACT
Sentinel lymph node biopsy is a revolutionary approach used in a complex management of patients with invasive breast cancer. Only a few decades ago, all patients diagnosed with this condition underwent a radical removal of all axillary lymph nodes to determine the stage of the cancer and to prevent further lymphatic metastasis. This surgery has been associated with numerous side effects, sometimes even more serious than complications after the removal of the primary tumour. The growing understanding of lymph circulation and its drainage patterns led to the concept of sentinel lymph nodes, which in turn led to the development of assorted techniques used for their mapping/detection. This review paper discusses the classic methods of sentinel lymph node detection, their status in clinical practice and novel emerging approaches. The classic is a "gold standard" combination of lymphoscintigraphy and blue dye. Although dominant in practice, it has numerous drawbacks. Novel techniques implement superparamagnetic iron oxide nanoparticles, indocyanine green fluorescence and contrast-enhanced ultrasound. These have a potential to establish a new gold standard, which will meet all the most important criteria in this regard – optimal sensitivity, specificity, economic and technical availability and least burden for a patient *(Ref. 60)*. Text in PDF *www.elis.sk*

KEY WORDS: breast cancer, sentinel lymph node biopsy, gold standard, superparamagnetic iron oxide nanoparticles, indocyanine green fluorescence, contrast-enhanced ultrasound.

Introduction

There has been an enormous progress in the management of breast cancer patients in the course of history. Ancient Egyptians "treated" breast cancer with a fire drill, surgeons of ancient Rome performed a form of proto-surgery, even though the aetiology was misattributed to mysterious "black bile". In the middle ages, the Catholic Church condemned the surgery or any reasonable treatment for that matter, due to a belief in divine intervention (1). Breast cancer treatment attempts performed in our homeland can be traced back to 17th century to a work of Professor Wenzel Trnka von Krowitz (Czech translation: Václav Trnka z Křovic), who experimented with mercury application and inoculation of causative agent of malaria (2). To see at least some contours of procedures, which can be considered evidence-based, we must fast-forward several centuries. In the 19th century, influenced by other famous surgeons of that time, Sir William Stuart Halsted started to perform his radical mastectomy – at that time, a *lege artis* approach. More than 50 years had to pass for surgeons to review their experiences and start to implement more conservative approaches (3). The topographic knowledge of lymph draining certain regions of the body through a specific set of lymph nodes predated the concept of sentinel lymph node (SLN) and its possible application in cancer diagnostics by more than a century. Even though the presence of cancer tissue in lymph nodes (LN) had been previously observed, it wasn´t until the middle of the 19th century, when the mechanism was finally conceived by Rudolf Wirchow (4). The first studies published on the concept of SLN occurred in the 1960s in patients with parotid gland cancer (5), later in the 1970s, SLNs were described in penile cancer (6) and eventually in the 1990s, the concept was applied also to breast cancer patients (7).

According to guidelines of that time, axillary lymph node dissection (ALND) was routinely performed as soon as invasive breast cancer was diagnosed. The main indications of this surgery were cancer staging, but also a prevention of lymphatic metastasis. Krag et al (7) were among the first to point out an ironical and rather paradoxical situation, that breast-conserving surgeries with a low incidence of postoperative complications, already firmly established in clinical practice at that time, were in striking contrast with a highly invasive and radical ALND. Even though this procedure was often performed "only" as a preventive measure or as a cancer staging approach in clinically negative LNs, it was usually associated with much frequent and more serious postoperative complications than the breast cancer surgery itself (7). Apart from the risks associated with general anaesthesia, a number of other

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complications were commonly reported, from short-lasting, e.g. infection of the surgical wound, seroma, or motility impairment in the shoulder joint, to long-lasting and disabling complications such as: lymphedema, or chronic pain. These complications occurred in about 25–30 % of patients (8). In contrast, the preoperative assessment of axillary lymph node (ALN) status by means of physical examination is the least invasive; however, this approach has an unacceptable false negative rate (9). The concept of SLN as the first regional LN to drain particular tributary region, thus serving as the first line of defence during lymphatic metastasizing, has gradually started to gain support as a feasible and moderately invasive method with less complications in comparison to ALND, with only 5 % false negative rate (10).

The purpose of this paper was to provide an overview of the current approaches and future perspectives in the SLN detection.

Sentinel lymph node biopsy – basic concepts

The key initial requirement in successful bioptic evaluation of the SLN is its unequivocal identification/detection. The methodology in this endeavour rarely rests upon a single technique, the most common approach is double or triple mapping (combination of two, alternatively three methods) to achieve an optimal result (11).

The most important prerequisite of a successful staging of invasive breast cancer using the method of sentinel lymph node biopsy (SLNB) is a proper erudition and sufficient amount of practical experience of the team of experts carrying out this procedure. If this is not fulfilled, the lack of experience can lead to an excessively high false negative rate, leading to understaging of the cancer, what can potentially jeopardize a patient´s life due to an inadequate therapeutic strategy (12). Before this method was routinely implemented into clinical practice at given workplace, it was recommended to perform at least 30–40 SLNBs followed by obligatory complete ALND for evaluative purposes – i.e. checking-up whether the maximum potential of sensitivity and specificity was reached (12).

From its inception, the most frequently used method of SLN detection has been the combination of blue dye injection and radiocolloid technique (lymphoscintigraphy). As of today, these canonical techniques are still considered first-choice methods (gold standard), although newer approaches have been emerging. These novel techniques attempt to optimize the most important variables in this regard – invasiveness, safety, sensitivity and specificity (13).

After properly identified SLN is excised, the bioptic sample is further evaluated using different methods, as well. Apart from the “classic” histological (histopathological) examination of formalin-fixed paraffin-embedded tissue samples stained with haematoxylin and eosin, modern methods are also used, e.g. immunohistochemical identification (14), or methods for quick perioperative evaluation, such as imprint cytology (15), or frozen sections technique (16). The principal criterion for the selection of bioptic modality is preferred (or feasible) diagnostic-therapeutic strategy. Those methods, which enable a perioperative assessment of bioptic samples, are advantageous, because in case of positive SLN, there is no need for a patient to undergo reoperation; however, a major drawback of this approach is an excessive duration of the surgery. Decision-making regarding the perioperative evaluation is mainly dependent upon personal, technical, and logistical resources of given workplace (12, 17).

Radiolabelled colloid technique (lymphoscintigraphy)

This method of nuclear medicine was tested for the first time in the pilot study in 1993. The authors used technetium-tagged sulphur colloid in a cohort of 22 patients, with 82 % rate of successful detection of the SLN (7). Over the following years, this modality was researched and elaborated until it reached the status of “gold standard” in SLN detection. This holds valid to this day, even though a plenty of new approaches have been continuously developing (18).

The principle of lymphoscintigraphy is the injection of radioisotope-labelled colloid or other suitable substance into a region nearby the primary tumour site, which travels through the system of lymphatic vessels until it reaches the SLN, where it is captured and subsequently detected using specialized devices. Among the most commonly used substances utilized in lymphoscintigraphy (radiopharmaceuticals) belong 99-mTc (99-mTc – metastable nuclear isomer of technetium-99) pertechnetate, 99-mTc sulphur colloid, 99-mTc albumin nanocolloid (Nanocoll) popular in Europe, and 99-mTc tilmanocept (Lymphoseek). These radioisotope-tagged pharmaceuticals represent substances with optimal pharmacokinetic properties, particularly ample penetration and distribution throughout the lymphatic circulation. 99-mTc tilmanocept is a recently registered drug, whose pharmacodynamics rests upon binding to CD206 receptor on the surface of macrophages and dendritic cells (19). Perioperative identification of the radioactive emission is carried out using a handheld gamma probe, which can be complemented by an additional imaging apparatus, e.g. a gamma camera, or a combination of multiple imaging devices (20). There are also different modern techniques available, which can refine the SLN detection even more, e.g. hybrid sentinel lymphoscintigraphy. Compared to “classic” planar lymphoscintigraphy, this technique uses a combination of imaging modalities, namely single photon emission computed tomography/computed tomography (SPECT/CT). The main advantage of this hybrid method is the possibility of 3D reconstruction and superior spatial orientation, which enables precise anatomical localization of the SLNs (21).

For the purpose of unification and standardization, The Society of Nuclear Medicine and Molecular Imaging (SNMMI) in cooperation with The European Association of Nuclear Medicine (EANM) published guidelines in 2013, with the main objective to ensure the state-of-the-art quality of radiodiagnostic methods used in the diagnostics of breast cancer. The most common inconsistencies in the procedure, which had to be resolved, concerned the size of the radioisotope particles, an optimal route of administration, proper timing of scintigraphy and perioperative detection, as well as the issue whether the ALN evaluation ought to be extended also to the evaluation of extraaxillary LN. The use of imaging technique is also important before the actual surgery due to interindividual anatomical variations in axillary lymphatic drainage and corresponding extraaxillary regions. This approach rises the odds of successful coverage of all the relevant areas, leading to a higher success rate of identifying all the SLNs in question (22).

Radiolabelled colloid technique has also its drawbacks and pitfalls. From the logistical point of view, this method is feasible only if the hospital has the department of nuclear medicine at disposal, what can be an issue, especially for smaller, regional hospitals. Another disadvantage is a relatively short half-life of 99-mTc, narrowing the time span between radiocolloid administration and surgery deadline, after which the gamma radiation is no longer detectable. Finally, yet importantly, the potentially harmful radiation exposure of a patient and staff is also a major drawback (23).

Blue dye mapping

This method is one of the most frequently used along with lymphoscintigraphy. The technique of blue dye mapping in patients with invasive breast cancer was used for the first time in the 1990s. Giuliano et al (24) reproduced the technique they previously used for lymphatic mapping and lymphadenectomy in patients with malignant melanoma, only modifying it in order to be applicable also to breast cancer patients. One of the key findings of this experimental study was that only experienced experts should perform this procedure. The so-called learning curve always has to be taken into consideration to reach the maximum diagnostic potential and minimize the false negative rate. The success rate of the SLN detection was directly proportional to the experience level – in the first 87 patients, the successful identification was achieved in only 58.6 % of cases, while from the last 50 patients, the authors succeeded in 78 % of cases (24).

It is important to note that the ALN status is not an exclusive determinant of the invasive breast cancer prognosis. Highly relevant in this matter is also the immunocytochemical analysis of the expression of the oestrogen receptor α and progesterone receptor. The oestrogen receptor α expression is an important prognostic marker, which is used to estimate the probability of the success of antihormone therapy (25). The progesterone receptor serves as the marker of functionality of the oestrogen receptor α. Those tumours, which display the positivity for these two receptors, have much better susceptibility for antihormone therapy (26). The SLN detection via blue dye mapping plays an important part in this regard. The hypothesis, which postulated that application of dyes could interfere with the analysis of these receptors in the neoplastic tissue, was tested in 2007. The authors concluded that some types of commonly used dyes, for example methylene blue can worsen the detection of oestrogen receptor α and progesterone receptor (27). Another drawback is hardly removable skin tattooing at the site of dye injection, as well as potential risk of allergic reaction (anaphylaxis in the worst-case scenario) (28). There is also an issue with a massive popularity of decorative tattoos these days. In 2014, Soran et al published a case report, which described a patient with a tattoo in tributary region drained by ALNs. The drainage of tattoo pigment to regional LN, in this case ALNs, caused their discoloration, which produced an image of pseudo-SLN (29). Considering that sole utilization of blue dye mapping has a suboptimal sensitivity, thus it is normally used exclusively in combination with radiocolloid mapping, some authors put forward a suggestion that, taking into account the aforementioned side effects, it is worth considering whether this method shouldn´t be omitted from the diagnostic process altogether (30). Despite this opinion, the authors concluded that the combination of blue dye mapping and lymphoscintigraphy still represents a suitable and preferred technique whose positive identification rate is as high as 98.8 %. This conclusion was consistent with the results of large studies ALMANAC (31) and AMAROS (32). Nevertheless, the expert consensus on this matter states that in regard of the aforementioned risks associated with the radiocolloid/blue dye double mapping, there should be an ongoing ambition and endeavour to test novel techniques, which can potentially become the new "gold standard" with even a higher rate of identification, and importantly also lower rate of deleterious effects (30). From among these novel approaches, worth mentioning is a technique utilizing superparamagnetic nanoparticles commercially known as Sienna+/SentiMag (33, 34), fluorescence method utilizing indocyanine green known as fluorescence image-guided surgery (35) and contrast-enhanced ultrasound (36).

Superparamagnetic iron oxide (SPIO) nanoparticles

The application of SPIO nanoparticles as contrast agents in magnetic resonance imaging was documented as early as 1980s (37), however the usage of these particles in cancer metastasis surveillance and SLNB detected by a prototype of handheld magnetometer has been known only for about a decade (38). From today´s perspective, and in the light of scientific knowledge growth rate within the biomedical field, a decade can be considered as relatively long time, so this technique shouldn´t be considered novel. Yet, it is still one of the newer approaches, although it stays in the shadow of the routine "gold standard", despite its numerous advantages. Douek et al (39) authored a multicentre trial, which attempted to evaluate the application of SPIO nanoparticles detected with handheld magnetometer, in comparison to "classic" double mapping – lymphoscintigraphy and blue dye. This method dealt with the issue of radiation exposure during lymphoscintigraphy. It represents something like a fusion of gold standard techniques. From the methodological standpoint, Sienna+/SentiMag is a system based on colour visualization (brown dye) of the SLN combined with its localization using a handheld probe. This study concluded that Sienna+/SentiMag has comparable success rate of SLN detection as the "classic" approach, so it can be potentially a game-changer of the clinical practice in this regard (39).

Practical feasibility and identification success rate of this method was also tested in 2016 French multicentre prospective trial. Conclusion was similar as in previously cited study. Interestingly, the identification rate of Sienna+ /SentiMag was even a bit higher (97.2 %) compared to the standard method (95.4 %) (40). Over the last 4 years, similar studies have been performed in different countries including Czech Republic (34). Most authors agreed that this method using SPIO nanoparticles is a feasible alternative to established "gold standard" (23).

Indocyanine green (ICG) fluorescence

ICG is a fluorescent indicator, which is visualized after administration and subsequent capture inside the SLN using a specialized camera capable of detecting fluorescence emission. ICG has been in medical use since the half of 1950s. It has a broad spectrum of applications in different medical fields including cardiology, ophthalmology, or neurosurgery. Only recently, this dye has also been employed as a method of perioperative evaluation of the tissue perfusion, but also as a suitable alternative for SLN identification. The main benefit of ICG is an almost absent toxicity, what makes it a promising low-risk option compared to other methods (41). Utilization of ICG in SLN diagnostics in breast cancer patients was already tested in 1999. This technique was rated as easy-to-use with a potential to become a part of routine diagnostic process. However, this pioneering study used ICG only as a dye, without exploiting the full potential of its fluorescent properties (42). First studies utilizing the perioperative identification of ICG fluorescence in the near infrared spectrum, were published several years later. This method was evaluated as suitable and safe (43). Highly beneficial is also its learning curve, which is steep (short) in contrast with the "classic" method, meaning that ICG fluorescence is far less demanding with regard to technical expertise (44). Another advantage is that in case of unavailability of the department of nuclear medicine, this technique can be combined with the blue dye mapping without any difficulty, and without any risk of losing appropriate level of sensitivity (45). On the other hand, a pilot study, which tested ICG fluorescence using a system called HyperEye on a cohort of patients from Czech Republic, concluded that it was inferior to classic radioisotope approach (46).

Contrast enhanced ultrasound (CEUS)

Another approach is contrast-enhanced ultrasound (CEUS), which uses gas-filled microbubbles as contrast agents. The applicability of this imaging technique in SLN detection was confirmed in animal model study, which evaluated swine with naturally occurring melanoma (47). The diameter of these bubbles is smaller than that of an erythrocyte, so they are readily cleared through the blood and lymphatic microcirculation. The bubbles often contain an inert gas, so there is a little risk of allergic reaction (48). Apart from its safety, this technique is also advantageous because it is convenient from the economical perspective and is widely accepted by patients (49). CEUS also provides real-time image, is less dependent on the skilfulness of the medical staff and prevents the occurrence of side effects associated with the "gold standard" approach (radioactivity exposure, skin tattooing, anaphylaxis). This technique is also more available from the technical perspective (50). To augment the sensitivity of CEUS, which can be suboptimal, when used exclusively (51), CEUS was also tested in a double mapping study, which combined CEUS and blue dye. This combination can enhance the sensitivity substantially (up to 98.4%) (52). One of the newest techniques to detect the SLNs is derived from CEUS and uses a three-dimensional (3D) approach. 3D-CEUS as an imaging modality is indeed not that new. In clinical setting, it was used back in the first decade of the new millennium, e.g. in a study of blood supply of liver tumours (53). Despite that, the first study of 3D-CEUS in the SLN detection was published online only a few months ago. Even though the authors of this study concluded that 3D-CEUS has a lower sensitivity compared to CEUS, the specificity was higher. 3D-CEUS has been presented as a new promising approach in the SLN detection, nevertheless there is a necessity to perform additional multicentre trials to test and reproduce these results (54).

In 2019, Mok et al authored a meta-analysis, which compared the performance of classic vs. novel approaches. The best detection rate was described in ICG, followed by superparamagnetic iron oxide nanoparticles, radiocolloid, gold standard, CEUS and blue dye alone (55).

Fluorescein fluorescence

One of the most recent approaches to SLNB is based on the same principle as ICG fluorescence, but it implements different fluorophore known as fluorescein, as well as different source of excitation. Fluorescein mapping technique uses blue light of wavelength of 480 nm, compared to near-infrared light in the case of ICG fluorescence. The main advantage is the lower cost of the former, which makes this technique more available in low to middle-income countries. When combined with blue dye mapping, the identification rate has been reported as comparable to the gold standard – 95.4 % vs 97 %, what makes it a cost-effective and widely applicable approach (56, 57). One of the biggest advantages is that the blue light is in the visible electromagnetic spectrum, so it can be seen with the naked eye and no specialized machine is necessary to visualize it (58).

Conclusion and future perspectives

Sentinel lymph node biopsy in patients with breast cancer is an up-to-date issue, what is documented by more than 250 articles published on the topic over the last year from different perspectives, according to PubMed search engine of the MEDLINE database. From the historical perspective, the progress in the management of axilla in patients with breast cancer has been massive in a relatively short time. In a few decades, we have moved from ALND as a fit-for-all standard procedure to SLNB, which has been performed by modalities continuously refining the risk vs. benefit ratio. The concept of SLNB, regardless of the method applied has been revolutionary in its own right. It has substantially decreased the morbidity of patients undergoing the management of ALNs. Currently, there is a tendency to diminish the potential complications of the SLNB even more by implementation of techniques dealing with the risks of the "gold standard" procedure, which is still dominant in clinical practice. The above-discussed approaches are all substantiated by multiple experimental studies, but there is also a body of state-of-the-art approaches, which are not yet validated, but the preliminary results showed that their performance is non-inferior compared to the gold standard. These include multimodal imaging techniques as well as hybrid methods operating via chemical conjugation of tracers based on different physical phenomena. For instance, a promising approach is the hybrid optical-gamma modality, referred to as gamma-NIR (near-infrared) fluorescence, which uses chemically conjugated ICG-99-mTc-nanocolloid as a single tracer (59). Another example of modern and highly promising approach is the use of artificial intelligence (AI). Nowadays, it is widely applied in the entire biomedical field, and SLNB is no exception. The principal applicability of AI is to the evaluation of bioptic samples. Liu et al tested an AI algorithm called LYNA (Lymph Node Assistant). The system could detect all the metastases, ignore the common artefacts, and very importantly, save time and diminish the workload of a pathologist (59, 60).

We can conclude that it is only a matter of time until some of these techniques will become a new gold standard, with optimal sensitivity, specificity, economic and technical availability, and finally yet importantly, with minimal occurrence of side effects a patient would have to endure.

Learning points

- sentinel lymph node biopsy has been a huge contribution to a complex management of patients with invasive breast cancer
- sentinel lymph node detection is performed by various techniques based on different physical phenomena
- gold standard double mapping (lymphoscintigraphy and blue dye) has numerous drawbacks
- novel methods are emerging with a potential to replace the double mapping in routine clinical practice

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