ARTYKUŁ POGLĄDOWY / REVIEW PAPER
Otrzymano/Submitted: 25.08.2019 • Zaakceptowano/Accepted: 22.09.2019

The latest trends and future development of sentinel node biopsy in breast cancer patients

Najnowsze trendy i przyszłe kierunki rozwoju biopsji węzła wartowniczego u pacjentów z rakiem piersi

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Abstract

During the last few decades, sentinel lymph node biopsy (SLNB) in breast cancer patients became a gold standard for staging of the disease. Radiocolloid and blue dye are used for sentinel lymph node (SLN) identification. With a change of clinical indications for this procedure, we are also witnesses of implementations of new dyes and technologies. Recently a new option appeared and we are able to use alternative tracers to identify these nodes. In this review, we delineated current knowledge and future directions of SLNB in breast cancer patients with indocyanine green (ICG), superparamagnetic iron oxide nanoparticles (SPIO) and microbubbles. Ever since the new techniques reached a fair standard in clinical practice, they seem to be a good alternative for the traditional ones. *(Farm Współ 2019; 12: 129-133)*

Keywords: biopsy, sentinel lymph node, indocyanine green, superparamagnetic iron oxide nanoparticles, microbubbles, breast cancer

Streszczenie

Przez ostatnie dekady biopsja wartowniczego węzła chłonnego (SLNB) u pacjentów z rakiem piersi stała się złotym standardem w ocenie zaawansowania choroby. Radiokoloid oraz błękitny barwnik są używane do identyfikacji węzła wartowniczego (SLN). Wraz ze zmianą wskazań klinicznych do wykonywania tej procedury, jesteśmy także świadkami stosowania kolejnych barwników oraz technologii. W ostatnim czasie pojawiły się możliwości, dzięki którym możemy stosować nowe znaczniki do identyfikacji tych węzłów. W tej pracy poglądowej opisaliśmy obecną wiedzę oraz przyszłe kierunki rozwoju procedury biopsji wartowniczego węzła chłonnego u pacjentów z rakiem piersi z wykorzystaniem zieleni indocjaninowej (ICG), superparamagnetycznych nanocząsteczek tlenku żelaza oraz tzw. "microbubbles". Jakość danych stojących za stosowaniem nowych technik w praktyce klinicznej, pozwala na uznanie ich za alternatywne wobec tradycyjnych metod. *(Farm Współ 2019; 12: 129-133)*

Słowa kluczowe: biopsja, węzeł wartowniczy, zieleń indocjaninowa, nanocząsteczki tlenku żelaza, microbubbles, rak piersi

Introduction

Sentinel lymph node biopsy is one of the landmarks that improved surgical oncology care for many patients. Using this procedure, we are able to improve our knowledge of lymphatic anatomy and tumour spread via lymphatics. By performing sentinel node biopsy, we are able to get information about proper staging of the disease, we can better control the regional disease and finally improve the survival of patients with different malignancies [1]. Even though the concept of sentinel node biopsy has a long history, the first details of the procedure were published in 1992 by Morton and Cochrane [2]. The term "sentinel lymph node" was used for the first time by Cabanas et al., but it was only based on anatomical patterns, which stands in contrast to the physiological concept presented by Morton and Cochrane [2,3]. Historically the term "sentinel" node was described by Braithwaite in 1923, Gould et al. in 1960 and Sayegh et al. 1966 [4-6].

Sentinel lymph node is the first lymph node or lymph node that drains the cancer site. The cancer cells from the primary site reach at the beginning the

sentinel lymph node/-s and afterwards the other tiers of lymphatic areas [2]. At the beginning, methylene blue as a blue dye visible by naked eye was used for sentinel node biopsy. Currently, the gold standard is radioactive nanocolloid with blue dye [7]. In this case, we use a naked eye and handheld gamma camera for intraoperative visualization.

Using combined technique improved sensitivity of sentinel node biopsy up to 96%, whereas when applied single method - blue dye like methylene blue or radioisotope (RI), the reported level of positive biopsy was 85.6% [7].

Last years gave us a considerable possibility to improve the procedure of SLNB by using different techniques. We will describe shortly three of them that represent a scientific potential for future development. Indocyanine green represents a fluorescent dye that uses near-infrared camera for detection. The Superparamagnetic Iron Oxide nanoparticles are detected by the handheld magnetometer (Sentimag®). The last technique uses contrast-enhanced ultrasound that visualizes microbubbles.

ICG

ICG is a fluorescent molecule that initially was used as a visible dye marker for sentinel node biopsy [8]. The first publication that used its fluorescent properties for SLNB in breast cancer patient was proposed by Kitai et al. in 2005 [9]. The fluorescent signal is detected by the near-infrared camera using a light-emitting diode that emits light at the wavelength of 778 nm. It activates ICG and the camera detects the wavelength that is emitted by this fluorophore below 830 nm, the diameter of the molecule is 1.2 nm [10]. Using this camera for ICG detection, we can visualize intraoperatively subcutaneous lymphatic flow in real-time (real-time lymphography) and additionally the sentinel lymph node. One of the limitations of this technique is the penetration depth of about 1 cm. It also varies with different types of cameras [10]. The main advantage of ICG is the real-time visualization of the lymphatic vessels between the injection site on the breast to the sentinel lymph node. This tracer was used for many decades in different specialities like ophthalmology for ophthalmic angiography, gastroenterology for hepatic function and many more and proved safety profile [11]. We are obliged to highlight that it is relatively cheap method and might be a good option for centres without access to nuclear medicine department. ICG allows to identify more SLNs than radiotracer, probably due to the lower molecular weight of the last, which results in unnecessary dissection of additional nodes.

The limitation of this technique is time, that should not be too long between injection of ICG and dissection of SLN, preferably ICG should be injected just before the operation. There is also the issue of spreading of the dye after cutting first lymphatic vessel when the dye leaks out and spreads in the operating field. However, dose reduction may prevent that leakage. What is more, the iodine allergy cannot be neglected as the molecule compounds iodine.

ICG allows to identify SLN with better results than blue dye (BD), as Ahmed et al. affirmed, but there was no significant difference between radioisotope and ICG. Also, there was no difference observed between dual technique and ICG only [12].

Sugie et al. found that the overall detection rate (DR) of SLNs between RI and ICG is significantly higher than RI alone [13]. Hirano et al. reported that ICG and BD combined gives better results in finding SLNs than BD alone, additionally combined technique lowered false negative (FN) results [14]. Ji et al. asserted that using ICG with BD allows to improve efficiency and sensitivity of SLNB, cause usage of BD shortens the time to identify SLN and increases the amount of SLNs detection [15]. ICG was better or equal than RI in detecting SLNs, as reported by the newest meta-analysis in this subject [16].

Superparamagnetic iron oxide (SPIO)

This tracer represents non-invasive magnetic properties that are detected by handheld magnetometer. The particle of Sienna+ (injectable magnetic tracer) is about 60 nm. The dye injected subcutaneously into the breast in the amount of 2 ml of this traced diluted in 3 ml; flows to SLNs and deposits only in sinuses and macrophages. In the case of metastatic node, it can be detected in non-metastatic parts of the node [17]. Preoperatively we can detect SLNs with this probe by using magnetic resonance imagining (MRI). Intraoperatively the nodes are dyed in brown or black colour. The handheld magnetometer is a detector that modifies magnetic field that causes magnetisation of the SPIO and recognizes magnetic response [18]. After injection, the minimal time reserved for a flow of the tracer is about 20 min. The detection with Sentimag has to be performed in the surgical field without any metal retractors. We have to follow the same rule of

10% as we use for nanocolloid. Currently available trials confirm its safety and high detection rate. Central-European SentiMag study reports almost identical detection rate (DR) between magnetic technique and the standard RI (98.0 *vs*. 97.3%) [18]. Although, SPIO technique allows to achieve higher number of resected nodes [18]. Similar DR between RI and SPIO was also reported by the "IMAGINE" Spanish multicentre study [19]. SPIO allowed achieving higher malignancy DR per patient [19]. The French Sentimag Feasibility Trial confronted SPIO with the standard RI technique [20]. The DR was 95.4% for standard and 97.2% for magnetic technique with less SLNs detected with RI (90.2 *vs* 97.2%). Moreover, the N+ status wasn't an obstruction for Sienna+, which allows identifying more engaged SLNs. This tendency was already described by Thill et al. [18].

The meta-analysis by Zada et al. proved non-inferiority of SPIO in comparison to standard techniques (97.1 *vs* 96.8%) [21]. This technique, similarly to ICG, represents higher number of stained lymph nodes [21].

SPIO technique requires less time to prepare than RI, has convenient timeframe and the tracer is well maintained in the engaged SNLs. The surgeon can inject Sienna+ right at the operating theatre. In contrary to other techniques, the learning curve seems to be quite short. Tracer has long shelf-time, it can be kept several years with no special conditions and causes no radiation. Magnetic tracer technique may be a good option for centres without Nuclear Medicine Departments. On the contrary, the magnetometer is bigger than gamma camera. What's more, this technique needs constant rebalancing after each received signal. Using plastic surgical instrumentation is necessary during the procedure because of ferromagnetic signalling. Also, long-lasting Sienna+ molecules can impede the interpretation of postoperative MRI. Another limitation of SPIO technique is the exclusion of patient with pacemakers, metal implants or with hypersensitivity to iron.

Microbubbles

The idea of microbubbles as a contrast agent for SLNB is based on usage of dispersion with sulphur hexafluoride gas stabilised by phospholipids [22]. It is injected intradermally around breast areola. The lymphatic vessels and SLNs are visualised by contrast-enhanced ultrasound (CEUS). The mean diameter of the molecule is about 2.5 μm [23]. After injection, the lymphatic vessels are promptly seen just after a short massage of the injection site. It is reported that the dye flows from the injection site to SLNs in 15-45 s. Areas of contrast accumulation were visualised with greyscale or live dual images by ultrasound imaging. After CEUS identification, the sentinel lymph nodes were marked by guidewire before standard SLNB procedure. In a recent meta-analysis, the SLN identification rate ranged from 9.3-55.2% and sensitivity varied from 61-89% [24]. Better results are presented when we use totally intravenous injection of the tracer for preoperative detection of metastatic SLN [25]. In a meta-analysis, the identification of metastatic SLNs with this technique is 54% and pooled specificity 100% [26]

This method isn't expensive and doesn't bring radioactive risk as it requires only US and contrast agent that is easily accessible on the market. Number of SLNBs and axillary lymph nodes dissections in a woman with breast cancer (BC) can be potentially decreased by CEUS guided biopsy. SLN identification rate with CEUS and RI with BD are proven to be very similar. As written, CEUS may become a practical option for countries with no access to nuclear medicine departments or with complex nuclear regulations. Microbubbles are also a safe alternative for allergic patients, as they don't include proteins and iodine. The main disadvantage in our opinion is relatively long learning curve and ultrasound is still very subjective examination. Further trials are needed to standardize the CEUS technique.

Conclusions

Although we still have to wait for high-quality data acquired from randomized clinical trials, sentinel node biopsy with the new agents may revolutionize the current practice. We are witnesses of the technological development and probably in the nearest future will be able to improve the detection of SLNs by ameliorating above mentioned techniques. Encouraging results obtained by all of the aforementioned techniques suggest its potential value not only in research but also in clinical practice. Keeping in mind limitations of mentioned techniques, in particular circumstances, they may favourably substitute traditional methods of SLN detection.

Conflict of interest
None

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