SENTINEL LYMPH NODE BIOPSY IN BREAST CANCER (literature review)

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Summary. Axillary lymph node dissection (ALND) is a standard procedure in surgical treatment of breast cancer patients. It can cause such complications as lymphedema, pain and sensorimotor disturbances. Sentinel lymph node biopsy (SLNB) – ALND's safe alternative in treatment of breast cancer patients. It allows to save a maximum of intact tissue and to improve cancer control. Its efficiency has been already proven by numerous randomized multicenter studies. Interdisciplinary approach (collaboration of surgeon, radiologist and pathologist) underlies in successful realization of SLNB conception.

Keywords: breast cancer, axillary lymph node dissection, sentinel lymph node biopsy.

History

The term "sentinel node" was used for the first time in 1960 by Gould E.A., Winship T., Philbin P.H., Kerr H.H. in their published work dedicated to the parotid cancer [25]. 15 years later Schein C.J. and Hasson J. publish article «The sentinel lymph nodes of the abdomen» [58].

Cabanas's R.M. publication (1977) is considered to be a fundamental for SLNB. One hundred cases were studied in detail using lymphangiograms, anatomic dissections and microscopic evaluation. Forty-six SLNB were performed, 15 of them were positive for metastatic disease; in 12 of them there were no involvement of other lymph nodes. Based on this findings author recommend to avoid inguinofemoroiliac dissection when bilateral SLNB is negative for metastatic disease [8]. These results were confirmed and supplemented by two more publications in 1980 [9,26].

Morton D.L. et al. published results of performed SLNB in melanoma patients (stage I) in 1992. New methodic allow to identify patients with metastases in sentinel lymph nodes (SLN). They are more likely to benefit from radical lymph node dissection. Blue dye was used for visualization of SLN. It was injected peritumoraly just before operative intervention. Contrast was successful in 194 of 237 cases (82%), false-negative rate – <1% [49].

Alex J.C. and Krag D.N. succeed in experimental usage of Tc^{99m}-colloid as a contrast with preoperative lymphoscintigraphy and intraoperative gamma probe detection of SLN (1993). Than they start pilot projects with Tc^{99m}-colloid in breast cancer and melanoma patients. Results confirmed experimentally obtained preliminary data [3,4,39].

First results of isosulfan blue (Lymphazurin, Hirsch Industries, Inc., Richmond, Virginia, USA) usage in SLNB appeared in 1994. Levenback et al. reported about SLN 77% identification

rate and 0% false negative rate in patients with vulvar cancer [42]. According to Giuliano et al. SLN were identified successfully in 114 of 174 (65,5%) breast cancer patients. SLN status was determined correctly in 109 (95,6%) of them. 3-5 ml of contrast was injected peritumoraly in 5 minutes before axillary incision [24].

Albertini J.J. et al (1996) proved that combined use of radionuclide (Tc^{99m}-colloid) and contrast-visual (blue dye) methods can increase SLN identification rate up to 92% [2].

The rapid development of the SLNB conception started in 90^{th} years of XX century. It resulted in widespread adoption of SLNB in clinical practice. This is confirmed by the number of published works during this period. For example, here is PubMed's data. Search combination - «sentinel node». Result: total 9873 publications, 17 are dated 1995, 437 - 2000, 757 - 2005, 861 - 2012. SLNB is included in melanomas' and breast cancer's treatment standards of such organizations as ESMO, ASCO, SSO, NCCN and others.

Evidence based medicine and SLNB in breast cancer.

The data of major multicenter trails devoted to the various aspects of SLNB performance in breast cancer is summarized in table 1. In those studies blue dye and radiocolloid were used to determine the SLN.

According to the NSABP B32, the largest-scale randomized surgical trial, overall survival, disease-free survival, regional control among patients with ALND and SLNB only were statistically equivalent in both groups. Recurrence rates were the same also. The rate of complications (sensorimotor disturbances, reduced range of motion, swelling, pain) was significantly lower in patients who underwent SLNB only. Also they had a better quality of life in comparison with patients who underwent ALND. SLNB – ALND's safe alternative in treatment of breast cancer patients with clinically negative axilla. So it is possible to avoid ALND in SLN negative patients without risk and to facilitate rehabilitation [5,38,40].

In the SNAC trial SLNB sensitivity was 94.5%, negative predictive value - 98%, the false-negative results - 5.5%. SLNs were successfully identified in 95% of patients with SLNB (29% positive) and 93% with ALND (25% positive). As in NSABP B32, it was found that patients who underwent SLNB only had less extremity edema and dysfunction rate [22].

According to the ALMANAC trail, SLNB make it possible to decrease a complication's number and severity. By this way it can improve the quality of patient's life. Based on the above, SLNB was recommended as the method of choice in the treatment of breast cancer patients with early-stage and clinically negative axilla [46].

The AMAROS research team reported SLN's successfully detection in 97% of patients. SLNB is more effective in young people with T1-T2, lobular and ductal breast cancer, with the

combined usage of blue dye and radiocolloid. 65% of patients had negative SLN, 35% - positive SLN (63% - macrometastases, 25% - micrometastases, 12% - isolated tumor cells). Non sentinel lymph node involvement in the pathological process in patients who underwent ALND with macrometastases in SLN was observed in 41% cases, micrometastases – 18%, isolated tumor cells - 18% [62].

The presence of metastatases in non sentinel lymph nodes depend on the level of SLN involvment. Neoplastic lesions of SLN only is present in 40-60% of patients. If there is macrometastases (more than 2 mm) non sentinel lymph nodes are involved in the tumor process in 40-58% of cases. If in SLN is micrometastases (0,2-2 mm), the likelihood of non sentinel lymph node involvement is 20%. With the presence of isolated tumor cells (less than 0,2 mm) this figure reduce to 12%. Micrometastases and isolated tumor cells can be successfully treated by adjuvant radiotherapy, chemotherapy or hormone therapy. Their presence in SLN do not indicate to perform ALND. It is confirmed successfully by low recurrence rate [16,27,31,34,41,44,50,67].

It is evidenced by the results of the multivariate data analysis ACOSOG Z0010 that the presence of metastases in SLN and bone marrow according to immunohistochemical study with their negative status according microscopy using hematoxylin and eosin has no statistically significant effect on overall survival. Overall survival is reduced by the presence of occult metastases in the bone marrow [23].

It was observed (data ACOSOG Z0010 and ACOSOG Z0011), that within 30 days after the immediate ALND paresthesia occurred in 51% of patients versus 35% for delayed ALND ($p < 0,001$), reduced range of motion in the limb was in 49% and 36% patients respectively ($p < 0,001$). By 1 year, the difference reached statistically not significant level. Long-term complications were similar after delayed and immediate ALND in patients with positive SLN. Taking into account staging and complications, there is no clear evidence of harm for patients with positive SLN to undergo the second intervention with the aim to perform ALND [52].

It is possible to opt-out of ALND in patients with positive SLN. Results of the ACOSOG Z0011 trail confirm it. This trial is actively debated, criticized by some scientists and confirmed by others. Mechanistic conception of gradual spread of breast cancer (W. Halsted) gives way to the concept of systemic disease (B. Fisher). ALND performance has no effect on survival rate in patients who undergo organ preserving surgery and adjuvant irradiation of the whole breast with primary tumor less than 5 cm, clinically negative regional lymph nodes and 1-2 SLN with metastases (according to the SLNB results) [60].

Indications and contraindications for SLNB.

Allergic reaction to the dye or radiocolloid is the only *absolute contraindication.* There was no reports about cross-reactivity between them in clinical practice. Blue dye (methylene blue, patent blue, isosulfan blue) can cause anaphylactic reactions in 2,7% of patients [59,66]. Methylene blue is approved for intravenous injections for methemoglobinemia and hemolysis treatment. Subcutaneous injections may cause necrosis. The structure of methylene blue is not similar to patent blue or isosulfan blue, so cross-reactivity is impossible between these dyes. Methylene blue do not bind to plasma proteins due to absence of sulfonic groups. It results in complicated lymphatic drainage, so it diffuses directly in the blood capillaries [66]. Isosulfan blue and patent blue are structural isomers, cross-reactivity is possible between them [59]. Preoperative antiallergic drug usage does not prevent anaphylactic reaction but significantly mitigates it [56].

Other contraindications are relative and actively studied.

Males. The vast majority of studies dedicated to the SLNB were designed for women`s breast cancer. There are research results that prove the effectiveness of SLNB technique in males with breast cancer. Breast cancer is diagnosed in males in older age ($p = 0.005$) and with larger tumor size ($p = 0,04$) than in females. Non sentinel lymph node metastases are diagnosed in 62,5% of males versus 20,7% of females ($p = 0,01$). The average size of lymph node metastases is 10 mm and 3 mm, respectively ($p = 0,03$). SLN detection rate range from 93,7% to 100%, false-negative results - 0%. SLN metastases are detected in 33,3-49,0% of males. SLN are effected by metastases in 56% of patients [6,11,18,37,54,57].

Pregnancy. Breast cancer is usually diagnosed late in pregnant. Approximately half of breast cancer patients during pregnancy have clinically negative regional lymph nodes and could potentially benefit from SLNB. Surgery with general anesthesia is safe, but although it is associated with an increased risk of spontaneous abortion. Chemotherapy is safe during the second and third trimester. Irradiation is contraindicated during pregnancy. Based on the above, it is possible to preserve breast in pregnant women with breast cancer, which was diagnosed in late pregnancy, by usage adjuvant chemotherapy before radiotherapy, which will be performed in the postpartum period. It is important to keep in a mind, that methylene blue is teratogen and limphazuryn can cause an anaphylactic reaction, which increases the risk of fetal loss. Fetus exposure of Tc^{99m} which is used to identify SLN is safe. As follows, the usage of radiocolloid and gamma probe to determine the SLN is an acceptable method in pregnant women [15,19-21,35,53,55,61].

Clinically positive axillary lymph nodes. It is believed that lymph passage can be distorted due to the blocked by tumor masses lymph nodes, obstructed or infiltrated lymph

vessels. SLNB performance in such conditions can cause a significant level of false-negative results. That`s why clinically negative regional lymph nodes are the main criteria for selecting patients for SLNB in the vast majority of the researches. Preoperative fine-needle aspiration biopsy (followed by cytology) controlled by ultrasound can help to determine SLN status and to plan further surgical intervention. In this manner 41% of patients with clinically positive regional lymph nodes can be detected for the metastatic lesion in lymph nodes. Other 59% of patients are potential candidates for SLNB. All palpable lymph nodes should be removed and examined for the metastases presence, the level of absorption of the dye or radiocolloid has no effect on the subsequent approach [14,44].

Absence of metastases in the clinically positive regional lymph nodes can be explained as a reaction to the tumor lesions. It can occur in two ways. First - hyperplastic changes (hyperplasia of reticular and lymphatic elements, enlargement of the reactive centers in the follicles, augmented sinus). Second - compensatory changes (alteration or distortion of lymph flow). In addition, it is possible lymph node formation de novo (including unusual location), as a manifestation of impaired lymph flow compensation. There are the following stages of lymph node formation de novo: perivascular lymphoid infiltrate, perivascular lymphoid follicle, grouping of lymphoid follicles (lymphoid plaque), non bagged lymph node, mature lymph node [1].

The lymph nodes visualization by ultrasound by the time after performed radical surgery with axillary lymph node dissection in breast cancer patient may indicate compensatory reaction rather than partial removal of axillary lymph nodes.

Previous biopsy. Previous breast biopsy has no effect on the success and accuracy of SLNB. It is highly sensitive and specific method in breast cancer patients despite the type of previous biopsy (stereotactic core-biopsy, fine needle aspiration biopsy, excisional biopsy), time interval between its performance and SLNB and the volume previously removed tissue. The level of false-negative results and regional recurrences are similar in fine-needle aspiration and excisional biopsy performance groups [7,12,28,29,43,44,48,51].

Previous surgery on the breast or axillary area. Similarly to the any type of previous biopsy, previous surgery for breast cancer is not a contraindication to SLNB and does not distort the results. If the tumor is in the intact quadrant of the breast, previous reducing procedures does not affect the SLNB result. Researchers from Memorial Sloan Kettering Cancer Centre have shown in their studies that SLNB can be performed more successfully in patients with less than 10 lymph nodes removed during previous interventions. Thus, in this study, the rate of SLN identification in patients with primary breast cancer was 94-97%. In re-intervention patients who

have been removed at least 10 lymph nodes during previous intervention the rate was 87%, more than 10 – 44% [32.63].

Reduction and augmentation mammoplasty through axillary access and quadrantectomy may be associated with higher levels of false-negative results and decreased sensitivity SLNB. In the world literature there is no data to indicate against SLNB performance in breast cancer patient, whom in the past has been done reducing or augmentation mammoplasty. Lymphatics of upper and lateral breast quadrant usually are not damaged after reduction mammoplasty and cosmetic breast implantation in submammary or subpectoral position, especially if surgery was performed more than 6-12 months ago [29,32,44].

Multicentric and multifocal tumors. The absence of significant differences in sensitivity and false-negative results in patients with multicentric or multifocal tumors versus solitary breast cancer is proved. These rates were 90-97% and 0-8%, respectively [36.65].

Locally advanced disease and neoadjuvant chemotherapy. Results of a prospective randomized trial NSABP B-27 indicate that the level of SLN identification is 85%, the false-negative rate - 12% after neoadjuvant chemotherapy. Similar values can vary in the range of 85-94% and 0-33%, respectively according to the literature. Other authors report the absence of a statistically significant difference in the amount of localization and absorption radiocolloid by SLN in patients who received neoadjuvant chemotherapy compared with those who did not [17,30,45,64].

The tumor size. Researchers point to significant differences in the identification and false-negative rates at T1 and T3. Tumor size more than 4 cm is not a contraindication for SLNB. Given evidence that the identification rate and sensitivity is the same for tumors more or less than 4 cm [10,33].

Ductal carcinoma in situ. SLNB is recommend for patients with high risk of invasive component for more accurate staging [7].

Body mass index (BMI) and age. Advanced age and significant increase of BMI is not a contraindication, although somewhat it reduces the SLNB efficiency. There is a strong feedback between BMI and SLNB. When BMI was less than 20 sensitivity was 99%, BMI = 30 - 96.6%, BMI = 40 - 94.2%. SLN detection rate is 87.6% for patients older than 50 years in comparison with 92.6% for younger [5,7,13,47].

Conclusions.

Based on the above, SLNB is recommended as the method of choice for patients with early-stage breast cancer and clinically negative regional lymph nodes. Allergic reaction to the dye or radiocolloid is the only absolute contraindication to the performance of SLNB. More and more countries are implementing this technique in the standards of treatment, the necessity of

SLNB implementing in the practice of Ukrainian oncology hospitals according to their material and technical capabilities for SLN identification.

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