

## **Detection of "sentinel" lymph nodes in surgery for breast cancer. View on the issue**

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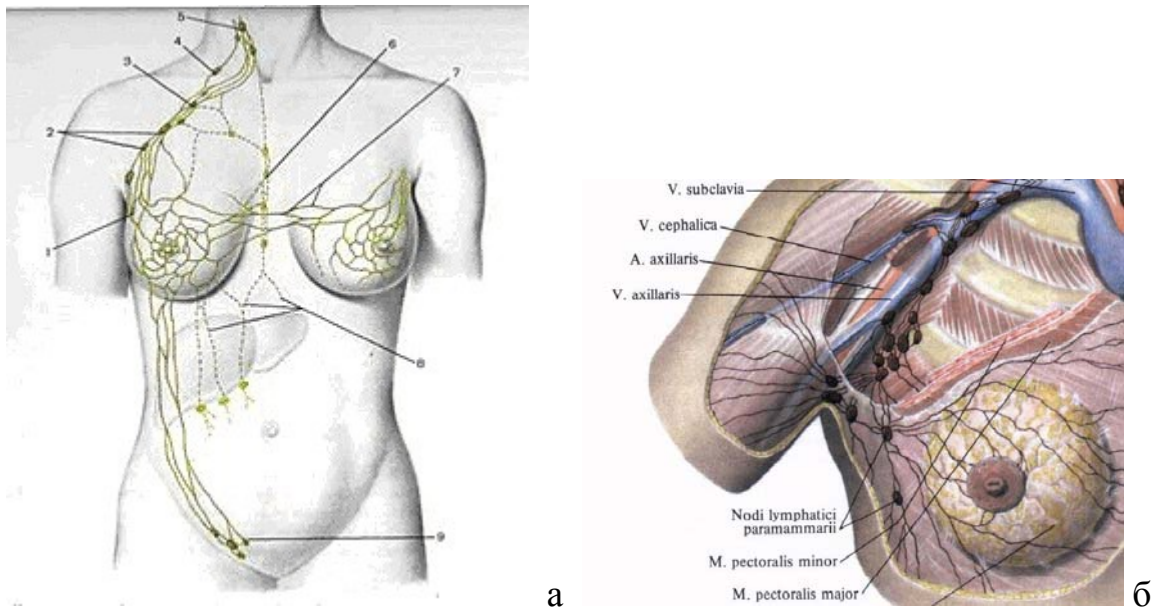
**Summary:** Methods of identifying “sentinel” lymph nodes (SLN) have been worked out to minimize the complications of radical surgery for breast cancer (BC). However, the results after SLN resection at early stages of the disease are similar to those when the full lymph node dissection is performed. The article presents the recommendations and indications for this method and the current standards of treatment of early stages of BC.

**Key words:** breast cancer, lymph nodes, treatment efficiency.

Despite significant advances in modern oncology, improved methods of diagnosis and treatment, breast cancer (BC) is still an important issue. According to WHO database, more than 1.2 million new cases of BC are registered every year in the world. BC ranks No.1 in structure of cancer of the female population in Ukraine since 1990. According to the National Cancer Registry Ukraine the incidence of BC is 70.9 per 100 thousands in female population and is constantly growing [1].

During the last decade the treatment of patients with BC has been changed dramatically. First of all, extended radical surgery in early stages was changed into organ-preserving surgery. Secondly, there has been a revision of indications for complete regional lymph nodes (LN) dissection in early stages of disease. Modern conservative treatment allows reducing the extent of operation in order to preserve breast (B) and regional lymph node basin that significantly improves quality of life of patients with BC. Individualization of lymph efflux tract surgery and identification of regional LN are important issues in this regard.

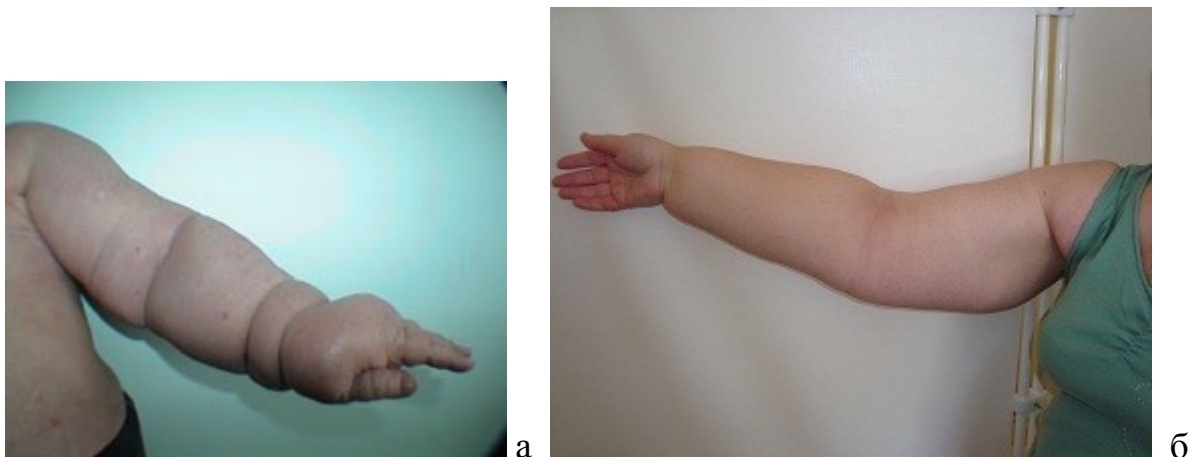
Taking into account zonal anatomical variant of lymphogenous distribution of metastases in BC (see Figure 1a, b) radical surgery (including organ-preserving) had always included a complete regional dissections, even in clinically intact ("negative") LN. It is known that regional LN dissection of I-III levels during surgery causes postoperative complications, prolonged lymphorrhea, pain in auxiliary region, limited mobility in shoulder joint, upper extremity edema (lymphostasis) in almost 30% of cases (see Figure 2a, b) [2,4].



**Fig. 1**

a – Lymphatic drainage from the breast

b – The most common localization of SLN in BC



**Fig. 2 (a,b)** - Lymphoedema of the arm after complete LN dissection in patient with BC

In 1977 after a series of studies R.M. Cabanas made a publication regarding the existence of the so-called "sentinel" lymph node (SLN) which is primarily reached by lymph from tumour tissue. Considering the mechanism of involvement in the metastatic LN process, D.L. Morton and A.J. Cochran renewed concept of sequential lymphogenic dissemination, which had been introduced by W.S. Halsted earlier in describing breast surgery. It has been recently shown that 90% of primary metastases are in the SLN, and then the cancer cells are spread to other

LNs and distant organs. E. Holmes recommended a lymphoscintigraphy as a method for SLN imaging in the preoperative stage in 1977. In the 90s of last century it was decided to evaluate SLN in order to identify the presence or absence of regional LN metastases and plan regional dissection. In 1991 D.L. Morton suggested using of dyes for SLN imaging, namely «Isosulfan blue due», in 1994 J.C. Alex suggested to use the radioactive lymphotropic colloid, that is able to penetrate into lymphatic capillaries. Results of numerous studies showed that 3- and 5-year progression-free survival (PFS) in patients with early stage BC (with negative SLN) who were treated without complete dissections are as good (and sometimes even better) as PFS in patients after extended surgery. Theoretically, the absence of tumour cells in SLN suggests intact lymphatic collector and allow its preservation. It is known that in early stages of BC and absence of metastatic involvement of the SLN likelihood of further metastasis is not more than 3% [2,3,5]. Since the development of organ-preserving operations, biopsy of "sentinel" lymph node is the second most significant achievement in surgical treatment for BC. Nowadays the statement regarding the necessity of complete LN dissection for radical surgical treatment is disproved for cases when there are no metastases in SLN [5]. Therefore the detection and SLN resection are based on the peculiarities of lymphogenous tract of BC dissemination and is developed for tumour staging and minimization of tissue trauma. It is proved that the SLN is a filter for contrast agents and therefore can be primarily detected during lymphography.

### **Indications for detection of SLN**

Not every case of surgical intervention in patients with BC requires the use of detection and resection of SLN. Taking into account international experience and experience of our clinic, criteria for SLN detection were developed, namely:

- early stages of breast cancer (tumour size — T<sub>in situ</sub> , T<sub>1</sub>, T<sub>2</sub> (tumour 3 cm);
- histological (preferably immunohistochemical) verification of BC diagnosis;
- absence of clinical, radiological and histological regional LN metastases (N<sub>0</sub>);
- no previous treatment (neoadjuvant therapy) and previous breast surgery;

### **Contraindications for detection of SLN**

- No previous treatment (neoadjuvant radiation or polichemotherapy).
- Multicentral tumour growth.
- Metastases to LNs (N +).
- Inflammatory BC.

- Presence of scars in the breast and axillary region (surgery, injury, inflammations).

### **Methods of SLN detection in the BC treatment**

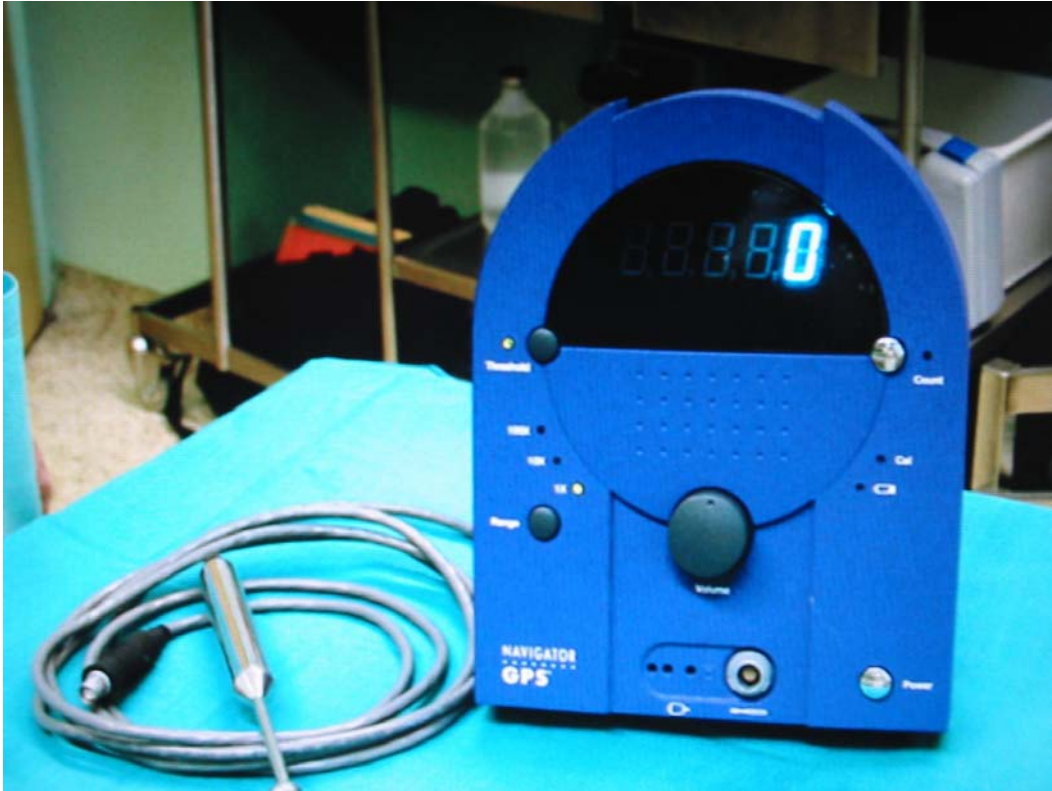
Implementation of intraoperative detection of SLN in clinical practice requires close cooperation between surgical oncologists and histopathologists of oncological institution. Histopathologist should have sufficient experience and equipment in order to make an instant testing of SLN to identify the presence or absence of metastases. There are two methods of the intraoperative SLN evaluation: using radiopharmaceuticals (RP) and by means of chrome lymphography (dye) - for example, 1% aqueous methylene blue. SLN detection with RP conducted together with radiological department of medical institution and only if all necessary equipment, details on which will be described below more broadly, is in place.

For testing SLN detection it is recommended to perform a complete regional LN dissection in no less than 20 - 30 patients in order to compare the histology results of SLN assessment (express histological test) and other regional LN (final histological conclusion). The rate of false-negative results of express histological assessment of SLN should be less than 5%, the accuracy and specificity rates of SLN detection should be more than 85-90%. It should be mentioned that there can be from 1 to 4 or more SLN in some cases.

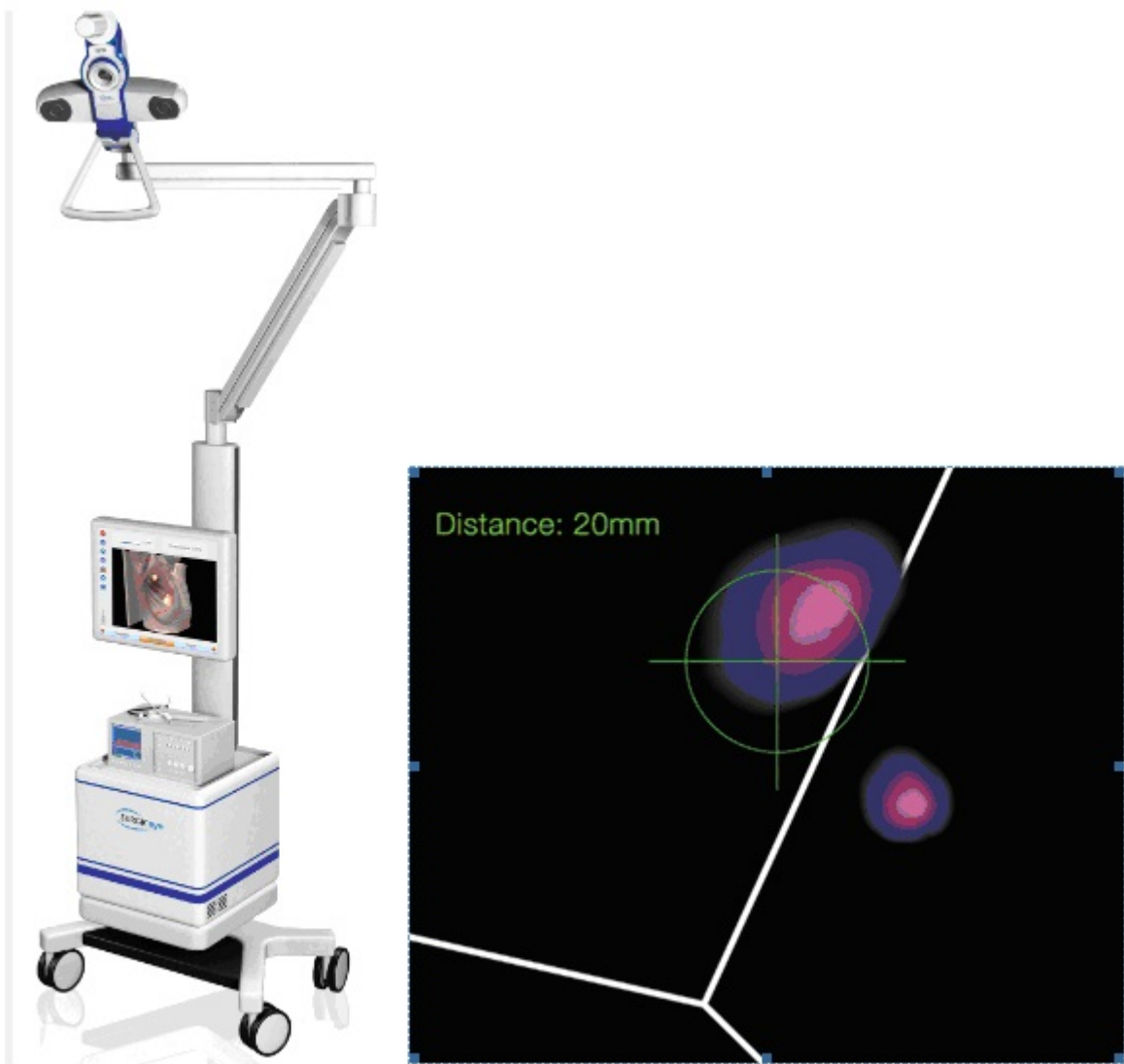
Methods using RP consists of two stages – lymphoscintigraphy and intraoperative detection of SLN by means of gamma counter. From 0.4 to 2 ml labeled  $^{99m}\text{Tc}$  nanocoll or nano Cys (colloidal isotope carriers) (activity of 200-400 MBq of particle size of 3-5 nm) are used for the lymphoscintigraphy as peritumoural, subcutaneous, subareolar or over the tumour injections.

Scintigraphy is recorded in static mode after 20-30 min. and 1.5-2 h. after injection using a gamma camera. Parameters for data collection in gamma camera are as follows: matrix size –  $256 \times 256$ , set should not be less than 200 thousand pulses per image matrix; photopeaks of radiation energy of  $^{99m}\text{Tc}$  (140keV) with 15% energy window. Static scintigraphy is performed in frontal, lateral, and anterior-lateral ( $45^\circ$ ) projections. In case of SLN imaging is successful its projection is pointed and marked on patient's skin. Intraoperative detection of SLN is performed in a day along radial-type lines from the injection site toward the regional lymph collectors using portable or stationary gamma counter (fig. 3, 4).. Skin incision is performed on the marked area, after detection of SLN it is necessary to control it during the surgical approach. During the intraoperative detection low-energy detector with high resolution power is used; gamma counter is set to radiation

energy photopeaks of  $^{99m}\text{Tc}$  with 50% energy window. Removed LN is sent to intraoperative histological examination on frozen sections. Meanwhile breast surgery is performed (usually quadrantectomy is performed, in case of T<sub>in situ</sub> lumpectomy is performed). After receiving the histological test results, a decision regarding further volume of LN dissection is made.

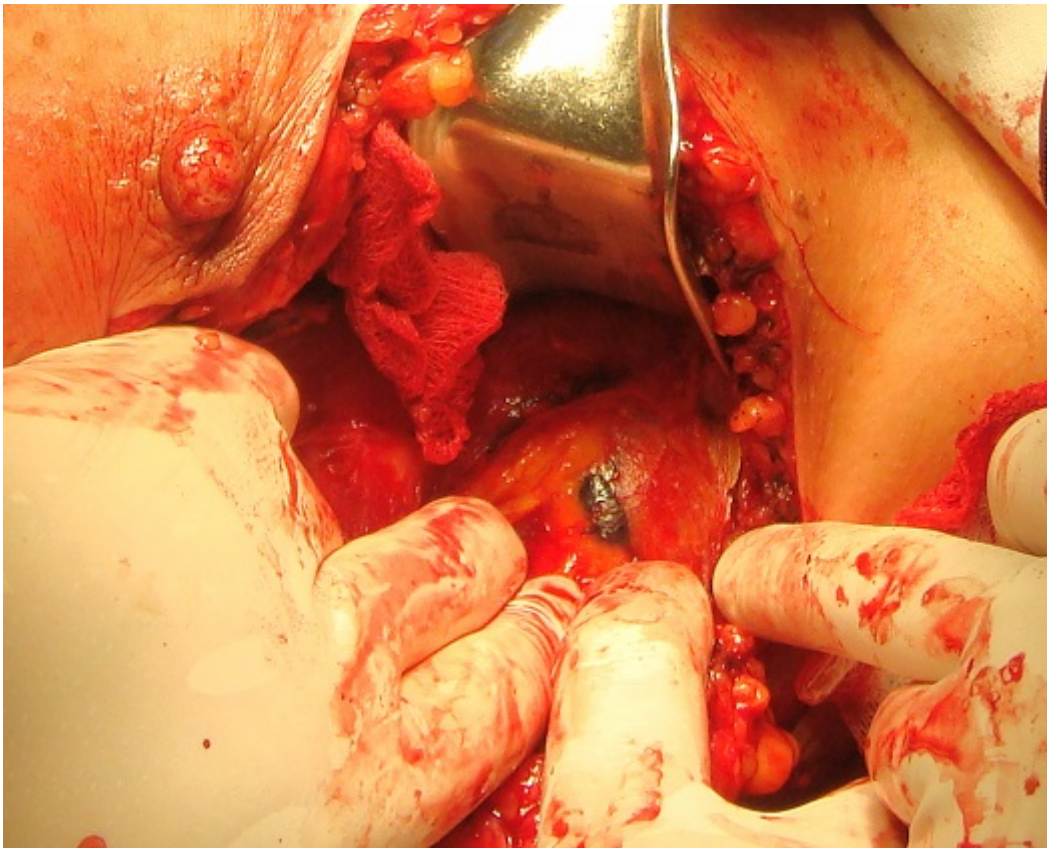


**Fig. 3.** Portable gamma-counter for SLN imaging



**Fig. 4.** Stationary gamma-counter for SLN imaging

Second method consists of preparing and autoclaving of 1% aqueous solution of methylene blue, 2.3 ml sterile solution aseptically injected around the tumour. In 15-20 minutes the drug accumulation is observed in areas of SLN. After mobilization of the closest to the tumour LN it is necessary to find and remove marked one. When the tumour is localized in the outer quadrant of the breast, usually LNs of axillary areas are affected in the first place operation may begin with detection of SLN. Skin incision is performed above the possible dye accumulation and stained LN is removed and sent to express histological test. Afterwards radical surgery for breast cancer is performed (usually quadrantectomy, in case of *Tin situ* lumpectomy is performed), After receiving the histological test results, a decision regarding further volume of LN dissection and its zoning are made.



**Fig. 5.** Sentinel LN

For improving the results of SLN detection in many institutions around the world where these techniques were implemented, dual method of using both RP and chrome lymphography is recommended. This approach increases the accuracy and specificity of detection of SLN. Removed stained LNs are immediately sent for express histological test, the results are available before the end of surgery. In case of metastases LNs complete regional LN dissection is recommended. In case of early stages of BC and absence of tumour cells in SLN no complete regional LN dissection is recommended, but surgery is still considered radical.

The final histology conclusion (HC) regarding status of removed LNs is always made after paraffin processing and assessment of sections, stained with hematoxylin-eosin and immunohistochemical analysis. Upon receiving the final HC appropriate adjuvant anticancer treatment is planned.

**Pathologic classification of regional LNs (6-edition, 2002) for SLN detection:**

pN(sn) – “sentinel” lymph node

pN0 – no regional lymph node metastasis were identified, no additional tests for identification of tumour cells were performed.

pN0(i-) – no regional lymph node metastases histologically, negative immunohistochemistry

pN0(i+) – no regional lymph node metastases histologically, positive immunohistochemistry, malignant cells in regional lymph node(s) no greater than 0.2 mm (detected by immunohistochemistry)

pN0(mol-) – no regional lymph node metastases histologically, negative molecular findings (RT-PCR)\*

pN0(mol+) – no regional lymph node metastases histologically, positive molecular findings (RT-PCR)\*

\* - RT-PCR: reverse transcriptase/ polymerase chain reaction.

pN1 –metastases in 1–3 axillary lymph nodes and/or in internal mammary nodes with metastases detected by sentinel lymph node biopsy

pN1mi – micrometastases (greater than 0.2 mm and/or more than 200 cells, but none greater than 2.0 mm).

### **To date, there are following recommendations:**

- for patients with pT<sub>in situ</sub> та T1, N0(sn) it is reasonable to avoid axillar LN dissection and to put this approach into the clinical practice of medical institution;  
- for patients with pN0(i+)(sn) good practice is to avoid axillar LN dissection only in good prognosis features of tumour (it is necessary to make prior immunohistochemistry on trephine biopsy of tumour).

- when decision regarding LN dissection in patients with pN0(i+)(sn) is made it is necessary to take into account tumour size, grade and receptor status.

During the 11th and 12th International Conference dedicated to BC treatment (St.Halen 2011, 2013), it was decided that it is reasonable to avoid axillary LN dissection in patients with BC with low risk of recurrence, such as the early stages of disease, N0, G1, with max. one affected SLN of 5 assessed, with ER / PgR-positive and HER2-negative, Ki 67 in less than 14%.

The detection and biopsy of SLN lead to a significant decreasing in the frequency of complications, reducing the time and cost of hospitalization, adequate planning of adjuvant anticancer treatment. Reduced regional LN dissection in patients with early BC stages may be recommended for implementation into clinical practice of oncology institutions in Ukraine. It is important to note that the quality of life of patients with intact axillary lymph collector in combination with organ-preserving surgery is much better and can be compared with that of a healthy person.

### **Conclusions**

1. Intraoperative SLN assessment should be carried out only in patients with early stages of BC (no regional LN metastases clinically and radiographically).

2. Intraoperative assessment of SLN is a modern and effective method of BC staging,

which allows to define the indications and extent of regional LN dissection.



3. Detection of SLN allows avoiding unnecessarily traumatic surgery in the early stages of BC and intact LNs, prevents postoperative complications, shortens the treatment time and improves the quality of patients' life.
4. The results of studies show that for improving the outcomes, the accuracy of staging process and adequate planning of LN dissection in patients with early stages of BC it is recommended to use dual method of SLN detection: both radiopharmaceuticals and chrome lymphography methods.

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