

Substitution of «sentinel» lymph nodes resection in surgery for breast cancer

I.I. Smolanka, C.Y.Skliar, O.I. Kostryba

National Cancer Institute

Summary. Resection of “sentinel” lymph node (SLN) has been worked out to minimize complications of radical surgery for breast cancer (BC). It has been proven that SLN resection in patients with early stages of BC, in particular N₀, allows to achieve results similar to those after a complete regional lymph node dissection. The article presents data obtained in randomized trials that allow using of preserving surgery on lymph efflux pathways in complex treatment for BC, experience of authors according to the data of National Cancer Institute.

Key words: breast cancer, resection of the sentinel lymph nodes, regional lymph node dissection, effectiveness of treatment.

The advantage of preserving surgery compare to extensive surgery in patients with breast cancer (BC) is an important factor that determines optimal social rehabilitation of patients. Individualization of surgery on lymphatic trunks and identification of regional lymph nodes (LN) are currently important issues. Complete regional LN dissection (CRLND) in treatment for BC is conducted to determine the status of lymph nodes, to control regional metastases, for accurate staging (pN) and to improve the survival of patients. Recommendations for CRLND in BC treatment are based on lymphatic drainage of tumor cells and the opinion of majority experts that there are no accurate methods of tumor cells detection in LN. Current methods of regional LN assessment in BC patients did not allow to recognize adequately presence or absence of metastatic lesions in 47-50% of cases [1].

The most accurate method of identification of LN status is a fine-needle aspiration biopsy under ultrasound control (US), the accuracy of a combination of

these techniques is up to 87%, but in LN less than 1 cm it can reach only 40% at maximum [1].

It is known that removal of regional LN I-III levels during surgery leads to early and long-term postoperative complications, manifested as prolonged seromas, pain in axillary area, limited mobility in the shoulder joint, edema of upper extremity (lymphostasis) and other complications in almost 30% of cases [2-5].

Methods of “sentinel” lymph node (SLN) mapping and resection are carried out for minimization of complications in radical surgery and for achieving the same results as in CRLND.

Various methods of “sentinel” or “signal” LN (which is first LN draining from the breast tumor) mapping have been developed in the past 10 years. To visualize the tumor a dye or specific radioisotopes are inserted directly in the tumor area before or after tumor itself is removed. This appeared to determine regional “sentinel” nodes in 95% of patients with primary BC. The results of numerous randomized studies have demonstrated the ability to perform preserving lymph tract surgery in BC patients.

In the ALMANAC study [6] (1031 patients with BC - T₁₋₃N₀) “sentinel” LN (SLN) biopsies were compared to CRLND. Only biopsy of SLN or SLN biopsy with axillary lymphodissection in cases of metastatic lesions of SLN was performed in patients with resectable BC. Radiopharmaceuticals, portable gamma counter and intraoperative blue dye injection were used for SLN detection. The number of complications, quality of patients’ life and long-term outcomes were evaluated in the study. It was noted that a large body mass index (>30), localization of tumor in interior quadrants of breast, invasive lobular carcinoma are potential statistically significant risk factors for errors in detection of SLN. At the same time, tumor size and LN status of LN may not be the factors important in identifying the location of SLN. According to the results of ALMANAC study, SLN resection alone leads to a significant reduction in number and course of complications, improves quality of life and has no effect on survival in the initial

stages of the disease [6]. Peintinger F. et al. [7] compared quality of life and mobility of upper extremity after CRLND and SLN resection and made a conclusion that the patients who underwent preserving surgery had significantly less pain and greater range of motion in the shoulder joint. Quality of life was assessed with the scale survey of the European Organization for Research and Treatment of Cancer (EORTC) C30 and B24, as well as McGill and visual analogue Pain Scale. The rates were much better in patients that underwent SLN resection alone. Based on this data the authors recommended resection of SLN as radical surgery for treatment of patients with BC N₀.

Now a lot of researchers are looking for factors that can reliably prove the absence of metastatic involvement of regional LN. Sharp et al. [8] have proven that a high degree of tumor differentiation (GI), tumor size $t < 1$ cm have a low probability of regional LN involvement and CRLND should not be performed.

Veronesi U. et al (2006) [3] published results of complex treatment of 506 patients, 247 patients were in CRLND group and underwent a complete axillary lymphodissection regardless of SLN status, and 259 were in the second group, where lymphodissection was performed only if SLN status was positive. There were 18 relapses, 7% with a median follow-up 79 months (a period from 15 to 97 months) in the first group and there were 16 relapses, 6% in the second group. 5-year overall survival rates were respectively 96.4% and 98.4%. The second study of Veronesi U. et al (2009) (observation of 3548 patients) has confirmed these results [4]. Thus, the authors did not reveal significant difference in outcomes between the treatment groups, but the quality of life of patients with intact axillary lymph collector was much better and even did not differ much from that of healthy women.

Kim H.J. et al. [5] analyzed the results of treatment of 1626 BC patients, in 1196 of them with negative SLN. 709 patients in this group underwent only resection of SLN and axillary lymphodissection was not performed (the group with SLN resection alone), in others 487 patients additional complete axillary lymphodissection was performed (Group CRLND). The median follow up was

70.2 months in the first group and 71.5 months in the second group. Long-term outcomes were evaluated in both experimental groups: 5-year regional relapse free survival was 98.9% in the first group and 99.3% in the second, 5-year progression-free survival rates were 95.1% and 95.2 % respectively. 5-year overall survival rates were 98.36% in the first group and 98.75% in the second group. These data also confirm the lack of significant difference between the results of treatment by different methods of dissections.

Zavagno G. et al. observed 697 patients, in 662 (95%) of them successful detection of SLN was performed [9]. 189 patients with metastatic involvement of SLN (28.5%) were included into the first group, who underwent axillary lymphodissection. There was no involvement of LN in 508 patients (71.5%), they did not undergo axillary lymphodissection. Estimated 5-year relapse free survival was 89.9% in the first group and 87.6% in the second. The difference was not significant.

At the conference of the American Association of Clinical Oncology (USA, Florida, 2009) the results of treatment of 3205 patients were presented; 2680 of these patients had no macrometastases in LN (Tjan-Heijnen, et al, ASCO 2009). Resection of SLN without regional lymphodissection was performed in 1218 patients, with regional lymphodissection – in 1314 patients, 148 patients received only radiotherapy (RT) to axillary area. The results of treatment (5-year study) are shown in the Table.

Table

The results of treatment according to Tjan-Heijnen, et al. (ASCO 2009)

Variant of SLN	Number of patients	Relapses (%)*	HR
pN ₀ (sn) - CRLND	125	1,6	1,00
pN ₀ (sn) - only SLN	732	2,3	1,08
pN ₀ (i+)(sn) CRLND +	450	0,9	1,00

RT			
pN ₀ (i+)(sn) only SLN	345	2,0	2,39
pN ₀ mi(sn) CRLND + RT	887	1,0	1,00
pN ₀ mi (sn) only SLN	148	5,0	4,39

* - percent of relapses in axillary region

HR-"hazard ratios" – hazard of relapse

The authors underlined that the presence of metastatic lesions in SLN raised the risk of relapse when performing only SLN resection. Metastatic lesions of non-SLN largely depend on the level of destruction of SLN. Neoplastic lesions of SLN were observed only in 40% of patients. Non-SLN were involved in 40-58% of cases if there were macrometastases (> 2mm) [9, 10]. If there were micrometastases (0.2-2 mm) in SLN the probability of cancer involvement of non-SLN was 20%. If isolated tumor cells (<0.2 mm) were present in SLN this rate decreased to 12% [11,12]. Micrometastases and isolated tumor cells can be successfully destroyed by adjuvant RT, chemotherapy or hormone therapy. Their presence in LN is not an indication to perform CRLND, but it is an indication for RT, which has been proven by the low rate of recurrence in this group of patients. The possibility of skipping the CRLND even in case of confirmed SLN involvement was proven in ACOSOG Z0011 study (891 patients); according to its results, preserving surgery with resection of SLN alone did not reduce survival of patients compared with the preserving surgery with CRLND [13]. Progression-free survival (82.2% and 83.8%) and overall survival (91.9% and 92.5%) of patients in both groups did not differ significantly. The authors underlined that this was true only for a limited group of patients with following parameters: primary tumor <5 cm, N₀, preserving surgery, adjuvant irradiation of the whole breast [13].

According to the results of a randomized clinical trial NSABP V32 (efficacy parameters of treatment of 5611 patients with BC $T_{1-3}N_0$ were analyzed) there was no significant difference in local recurrence, progression-free and overall survival in patients with complete regional dissection and without it (performed only resection of SLN) provided SLN negative results (5-year overall survival rate was 95.8% and 94.6% respectively).

It was noted that patients who underwent SLN resection alone had significantly lower rate of complications (pain, sensory-motor disturbances, decrease in range of motions, swelling) and better quality of life compared with patients who underwent CRLND.

The authors suggested that biopsy or resection of SLN was a safe and effective technique in the treatment of patients with BC N_0 ; it is possible to avoid complete dissections without risk for the patient and facilitate the process of rehabilitation provided SLN status is negative [14,15,16]. It was also noted that micrometastases in LN, which were identified only during immunohistochemical studies (IHC) were not clinically significant and IHC test in case of N_0 could be optional.

Thus, biopsy and resection of SLN is a minimally invasive procedure that allows to identify the status of regional LN and make tumor staging according criterion N, to avoid postoperative complications that often occur after CRLND. The results of randomized trials ACOSOG Z-0011, NSABP V32, ALMANAC and research of leading oncologists during many years (St. Gallen, 2009, 2011, 2013) have changed the conventional surgery practice in treatment for BC. Following conclusions were made:

- For patients with pN_0 (sn) performing axillary lymphodissection does not make sense, and this issue should be documented in the guidelines.
- For patients with pN_0 (i +) (sn) performing axillary lymphodissection does not make sense provided favorable tumor characteristics.

- For patients with pN₁mi (sn) and in patients with pN₁mi (sn) it is recommended to perform axillary lymphodissection to reduce the risk of recurrence.
- When making a decision whether to perform complete lymphodissection for patients with pN₀ (and +) (sn) and pN₁mi (sn) tumor size, malignancy grade, receptor status must be taken into account.

To sum up, CRLND cannot be performed in patients with the following parameters:

- Tumor size less than 3 cm
- (T₁-T₂), G1 with negative SLN or with one positive LN of five investigated LNs without spreading of tumor beyond capsule
- No contraindications to RT in postoperative period
- No contraindications to adjuvant chemotherapy
- ER/PgR-positive
- HER2-negative

These recommendations do not apply to cases when the tumor is larger than 3 cm, when there are clinically and radiographically enlarged LN, there is an intraoperative diagnosis of micrometastases in more than 1 LN, when radical mastectomy is planned and in patients who received neoadjuvant antitumor therapy.

Since the development of organ-preserving operations, **biopsy of "sentinel" lymph node is the second most significant achievement in surgical treatment for BC**. Biopsy and resection of SLN is a safe and an effective method for the surgical treatment for early stages of BC. The results of the above-mentioned studies demonstrate the possibility to avoid complete excision of regional LN in radical surgery for BC to facilitate the rehabilitation of patients without risk of declining of their survival's rates.

References

1. Семиглазов В.Ф. (2013) Новые подходы к лечению рака молочной железы. Вопросы онкологии, 59(3): 288–291.
2. Schwartz G.F. (2004) Clinical Practice Guidelines for the use of axillary sentinel lymph node biopsy in carcinoma of the breast: current update. *Brest J.*, 10: 85–98.
3. Veronesi U., Paganelli G., Viale G. et al. (2006) Sentinel-lymph-node biopsy as a staging procedure in breast cancer: update of a randomised controlled study. Scientific Direction, European Institute of Oncology, Milan, Italy. *Lancet Oncol.*, 7(12): 983–90.
4. Veronesi U., Galimberti V., Paganelli G. et al. (2009) Axillary metastases in breast cancer patients with negative sentinel nodes: a follow-up of 3548 cases. *Eur. J. Cancer*, 45(8): 1381–1388.
5. Kim H.J., Son B.H., Lim W.S. et al. (2010) Impact of omission of axillary lymph node dissection after negative sentinel lymph node biopsy: 70-month follow-up. Department of Surgery, University of Ulsan College of Medicine and Asan Medical Center, Seoul, Korea. *Ann. Surg. Oncol.* [Epub ahead of print].
6. Mansel C.D. (2001) On behalf of ALMANAC Trialists Group. The learning curve in sentinel node biopsy (SNB) in breast cancer: results from the ALMANAC trial. *Breast Cancer Research Treatment. Special Issue: 24th Annual San Antonio Breast Cancer Symposium*, 69: 212. Abstract 15.
7. Peintinger F., Reitsamer R., Piswanger C., Stranzl H. (2001) Quality of life and arm mobility after axillary lymph node dissection versus sentinel lymph node biopsy. *Breast Cancer Research Treatment. Special Issue: 24th Annual San Antonio Breast Cancer Symposium*, 69: 220. Abstract 115.
8. Sharp C., Wilson C.R., Doughty J.C., George W.D. (2001) Incidence of lymph node metastases in infiltrating breast cancers of less than 10 mm. *Breast Cancer Research Treatment. Special Issue: 24th Annual San Antonio Breast Cancer Symposium*, 69: 219. Abstract 110.

9. Zavagno G., De Salvo G.L., Scalco G. et al. (2008) A Randomized clinical trial on sentinel lymph node biopsy versus axillary lymph node dissection in breast cancer: results of the Sentinella/GIVOM trial. *Clinica Chirurgica II, University of Padova, Italy. Ann. Surg.*, 247(2): 207–213.

10. Bergkvist L., de Boniface J., Jönsson P.E. et al. (2008) Axillary recurrence rate after negative sentinel node biopsy in breast cancer: three-year follow-up of the Swedish Multicenter Cohort Study. Department of Surgery and Center for Clinical Research, Uppsala University, Central Hospital, Västerås, Sweden. *Ann. Surg.*, 247(1): 150–156.

11. van Deurzen C.H., de Boer M., Monnikhof E.M. et al. (2008) Non-sentinel lymph node metastases associated with isolated breast cancer cells in the sentinel node. *J. Natl. Cancer Inst.*, 100(22): 1574–1580.

12. Grube B.J., Giuliano A.E. (2001) Observation of the breast cancer patient with a tumor-positive sentinel node: implications of the ACOSOG Z0011 trial. *Semin. Surg. Oncol.*, 20(3): 230–237.

13. Shah-Khan M., Boughey J.C. (2012) Evolution of axillary nodal staging in breast cancer: clinical implications of the ACOSOG Z0011 trial. *Cancer Control.* 19(4): 267–276.

14. Krag D.N., Anderson S.J., Julian T.B. et al. (2010) Sentinel-lymph-node resection compared with conventional axillary-lymph-node dissection in clinically node-negative patients with breast cancer: overall survival findings from the NSABP B-32 randomised phase 3 trial. *Lancet Oncol.*, 11(10): 927–933.

15. Land S.R., Kopec J.A., Julian T.B. et al. (2010) Patient-reported outcomes in sentinel-node negative adjuvant breast cancer patients receiving sentinel-node biopsy or axillary dissection: National Surgical Adjuvant Breast and Bowel Project Phase III Protocol B-32. *J. Clin. Oncol.*, 28(25): 3929–3936.

16. Ashikaga T., Krag D.N., Land S.R. et al. (2010) Morbidity results from the NSABP B-32 trial comparing sentinel lymph node dissection versus axillary dissection. *J. Surg. Oncol.*, 102(2): 111–118.

17. Tjan-Heijnen V.C. et al. (2009) Sentinel lymph node biopsy and axillary recurrence. *J. Clin. Oncol.*, 27(18): 506.