

RESULTS OF SENTINEL LYMPH NODE BIOPSY IN PATIENTS WITH BREAST CANCER IN 10-YEAR OWN MATERIAL OF THE 4TH MILITARY TEACHING HOSPITAL WITH POLYCLINIC IN WROCLAW

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At present, sentinel lymph node biopsy is a standard procedure to assess the advancement of breast cancer and cutaneous melanoma.

The aim of the study was to assess the role of the sentinel lymph node biopsy in the treatment of patients with breast cancer in our own material.

Material and methods. Analyzed was medical documentation of 258 patients with initially operable breast cancer, qualified for operation with sentinel lymph node biopsy in 2004-2014 in the Department of Surgery of the 4th Military Teaching Hospital. A few hours prior to the planned surgery, radioisotope (technitium-99 sulfur colloid) was applied in the area of tumor or under the areola. 1-2 hours after administering the tracer, the lymphoscintigraphy with the labelling of the sentinel lymph node on the skin was performed.

Results. On the basis of the gathered material, obtained were the following parameters: sensitivity – 100%, and specificity – 94.6%. Four cases were false negative (5.5%).

Conclusions. 1. Marking the sentinel lymph node in breast cancer, based on the single visualisation method with the use of radioisotope, is a useful and effective technique. 2. The factor influencing the results of the sentinel lymph node biopsy (true positive and negative results and false negative result) was the number of the excised lymph nodes except for the sentinel lymph node. 3. Patients with estrogen receptor expression had often metastases to sentinel lymph node (145 cases – 56%). 4. The false negative rate, i.e. 5.5% in our material, is within the limits of acceptability given in the literature. 5. The sentinel lymph node biopsy performed by the experienced surgical team is a reliable diagnostic tool with a low complication rate.

Key words: breast cancer, sentinel lymph node, radioisotope, lymphoscintigraphy

In 1977, Cabanas performed lymphography in patient with penile cancer and showed gradual concentration of the contrast in the lymphatic system (1). He also gave the following definition of the sentinel lymph node: the sentinel lymph node is the first node on the way of lymphatic pathway from the primary tumor area and thus the first area of gathering the metastatic cancer cells. If there are no

metastases in the sentinel lymph node, metastases should not occur in other nodes. However, if there are metastases in the sentinel lymph node, they may occur in other nodes of the sentinel node group.

In 1994, Giuliano et al. applied sentinel lymph node biopsy in the treatment of breast cancer (2). He also pointed out to the learning curve: the failure rate of identifying the senti-

nel lymph node decreases with the growing number of biopsies performed. Turner et al., in his 1997 study, demonstrated the presence of only one metastasis in 1,087 examined lymph nodes in 60 patients suffering from breast cancer after a negative sentinel lymph node biopsy and elective lymph node dissection, and thus confirmed the value of sentinel lymph node biopsy as a method for assessing the regional lymphatic system (3).

At present, sentinel lymph node biopsy is a standard procedure to assess the advancement of breast cancer and cutaneous melanoma.

The objectives of the study were the following:

1. Assessing the sensitivity and specificity of the biopsy of the sentinel lymph node visualised with the radioisotope method in breast cancer.
2. Analysing the factors for the obtained sentinel lymph node biopsy results.
3. Analysing clinical and histopathological factors predisposing the sentinel lymph node to be occupied by cancer cells.
4. Analysing the false-negative results.
5. Assessing the results of breast cancer treatment based on the sentinel lymph node biopsy.

MATERIAL AND METHODS

Analyzed was medical documentation of 258 patients with initially operable breast cancer, qualified for operation with sentinel lymph node biopsy in 2004-2014 in the Department of Surgery of the 4th Military Teaching Hospital.

In all 258 patients qualified for operation with sentinel lymph node biopsy due to breast cancer, a pre-operative lymphoscintigraphy was performed in the Department of Nuclear Medicine. The Department of Surgery adopted a standard procedure to apply radioisotope (technetium-99 sulfur colloid) in the area of tumor or under the areola a few hours (sporadically a day) prior to the planned surgery. 1-2 hours after administering the tracer, the lymphoscintigraphy with the labelling of the sentinel lymph node on the skin was performed.

During the operation, with the use of a portable gammacamera Neo2000 Gamma De-

tection System Model 2100, the sentinel lymph node, most often single (sometimes 2-3 active nodes) was identified and biopsied; sometimes single, inactive lymph nodes, identified by palpation at the sentinel lymph node biopsy, were sampled. The last stage was the histopathological examination of the sampled material in the Department of Pathomorphology.

RESULTS

On the basis of the gathered material obtained were the following parameters: sensitivity – 100%, and specificity – 94.6%. Neither the day of marking the sentinel lymph node (the day prior to or the day of the procedure), type of the procedure performed prior to sentinel lymph node biopsy (mammotome biopsy MMT, guided fine needle aspiration biopsy BACC, surgical biopsy), number of identified lymph nodes nor the surgeon's experience influenced the obtained results (true negative and positive, and false negative). However, for a large number of excised lymph nodes, apart from the sentinel lymph node false negative results were confirmed more often than true positive ones.

The patients' age, location and size of the tumor, grade of histopathological malignancy and the histopathological kind of breast cancer had no influence on the obtained results. Yet, metastasis to the sentinel lymph node was confirmed more often in the presence of the estrogen receptor. For the remaining receptors: progesterone and HER2, no interdependency was confirmed between the obtained results. Four cases were false negative (5.5%). Metastases to a few lymph nodes apart from the sentinel lymph node were then confirmed, which shows that the cancer was locoregionally advanced and patients were wrongly qualified for the sentinel lymph node biopsy. In the researched group of patients who underwent only the sentinel lymph node biopsy, in 3 (1.3%) cases a relapse in the lymph nodes in axilla was identified.

Factors having NO influence on the results

- day of marking the sentinel lymph node (the day prior to or the day of the procedure)
- patient's age,

- grade of histopathological malignancy,
- histopathological kind of breast cancer.

Factors influencing the results

- number of excised lymph nodes apart from the sentinel lymph node,
- presence of the estrogen receptor,
- location and size of the tumor,
- surgeon's experience,
- type of the procedure performed prior to sentinel lymph node biopsy (mammotome biopsy MMT, guided fine needle aspiration biopsy BACC, surgical biopsy).

DISCUSSION

Histopathological examination of axilla lymph nodes is the principal requirement for forecasting and determining the way of treatment in patients with breast cancer. It allows for assessing the advancement level of the disease; it also is the main prognosis factor and sets the way of systemic complementary treatment.

Until the beginning of 1980s, radical mastectomy, described by William Halsted in 1894, and radical modified mastectomy (modified by Patey, Madden, and Auchinclos) had been the main surgical techniques in the treatment of breast cancer. Although inevitably effective, the procedures were physically and mentally mutilating the woman. Because of this fact, for many years oncologists focused on attempts to replace mastectomy with a different, yet effective, way of treatment. Research by Veronesi proved to be a breakthrough, which directed breast cancer surgery towards limiting the scope of the procedure to the breast area (4). Wider access to screening, such as mammography, and the growth of society's oncological awareness nowadays allow for detecting breast cancer in an earlier stage than previously. Yet, removing the lymphatic system of the axilla still remains an inseparable part of surgical breast cancer treatment. A question arises as to why axillary lymph node dissection is being performed. First, it is performed due to the necessity to remove metastases located in the axillary lymph nodes, which reduces the number of relapses and has a positive impact on patients' long-term survival (5). Second, histopathological examination of the removed lymph

nodes is a condition necessary to determine the cancer advancement level and is one of the basic factors when making a decision regarding the possible complementary treatment (6).

In treating early stages of breast cancer, apart from limiting the scope of surgical intervention in the breast area (the so-called breast-saving procedures), a tendency arises to limit the scope of resection in the axilla. The sentinel lymph node biopsy, when compared to elective lymph node dissection, is not burdened with the possible long-term complications (lymphatic obstruction, pain, mobility and sensory disturbances within the shoulder girdle, long-term chylothorax (7). After the axillary lymph node dissection, the long-term lymphatic obstruction occurs in 10% of the cases and pain – in 80% of the cases (8). The quality of life after the sentinel lymph node biopsy is significantly better. Complications which may occur after the sentinel lymph node biopsy amount to 0-3% of the cases (9, 10). Early complications include: lymph accumulation at the sentinel lymph node biopsy site, wound infection, hematomas, and parasthesias. In rare cases, patients who underwent sentinel lymph node biopsy experience lymphatic obstruction of the arm or mobility disturbances within the shoulder girdle.

Some authors point out to the fact that there is more than one sentinel lymph node for a single change in the breast. That is why, 1 to 4 lymph nodes in which radioactive tracer accumulates are excised during the procedure. Removing 4 lymph nodes allows for identifying 99% of the sick with changes in the nodes, whereas excising more nodes only slightly improves the sensitivity of the test while significantly increasing the possibility of complications (11).

Also, the possibility of a false negative must be taken into account when in the histopathological examination of the excised lymph node, identified as the sentinel lymph node, no metastases are identified, whereas in reality there are not present in the wrongly removed lymph node. The reasons of a false negative result may include: technical mistakes of the team performing the biopsy; tumor cells emboli present in the vessels or lymph nodes which obstruct the flow of the tracer from the primary tumor to the lymph node; and wrongly performed histopathological examination. The effectiveness and credibility of the sentinel lymph node biopsy is a derivative of the team

performing the biopsy's experience (12). It has been demonstrated that as the experience grows, the rate of the procedures with identified sentinel lymph node increases and the rate of false negatives decreases. In the past, the training cycle, i.e. the learning curve, consisted in performing an appropriate number of sentinel lymph node biopsies with concurrent axillary lymph node dissection. Whenever the level of false negatives dropped below 5%, the training cycle was finished. Nowadays, assuming that the surgeon is trained in a site with extensive experience in sentinel lymph node biopsy, elective lymph node dissection is not performed. The reason for false negative may be the presence of tumor cells emboli in lymph pathways from the primary tumor to the sentinel lymph node or emboli in the sentinel node itself. The tracer may then omit the blocked lymphatic vessel going to the sentinel lymph node and move to other lymph nodes. In turn, these nodes may not contain metastases. In order to limit the risk of mistake and obtaining a false-negative result, upon identifying and excising the sentinel lymph node, palpation of the wound for the presence of clinically suspicious lymph nodes. The literature confirms the impact of palpation and excising lymph nodes clinically suspected of metastases on the increase of the sentinel lymph node biopsy sensitivity and the decrease of the false negatives rate (13).

Obtaining a false negative result may carry some consequences, such as resigning from axillary lymph node dissection which should be performed. As a result, relapse may take place in axillary lymph nodes which were left and which contain metastases. Apart from that, the false negative of the sentinel lymph node biopsy may be the cause of resigning from the complementary treatment. What is the risk of that? Relapses in the axilla after a standard dissection of lymph nodes are rare and occur in 1-1.5% of the cases. It was shown that resigning from axillary lymph node dissection basing on the negative result of the sentinel lymph node biopsy has no impact on the increase of the number of metastases in this location (1.4%) (14).

Some sites perform intraoperative histopathological examination of sentinel lymph nodes by imprint cytology or examination of frozen sections. These methods may be characterised with a rather low sensitivity (respec-

tively 67-71% and 66%) and specificity (15). Furthermore, these methods did not help to detect any case of micrometastases to the sentinel lymph node. Reports on detecting metastases in sentinel lymph nodes by immunohistochemical tests (IHC) or reverse transcription polymerase chain reaction methods (RT-PCR) result in resigning from intraoperative tests. These techniques allow for identifying isolated tumor cells (ITC < 0.2 mm pN0i0 and micrometastases (> 0.2-2 mm pN1mi). If isolated tumor cells are detected in the sentinel lymph node, there is no indication for axillary lymph node dissection. Detecting micrometastases is an indication for axillary lymph node dissection. If a micrometastasis is detected (> 2 mm) in the sentinel lymph node, a classic axillary lymph node dissection should be performed, although there is research demonstrating that 50% of the patients with a positive sentinel lymph node will not have tumors in other axillary lymph nodes, otherwise removed. Studies are being conducted to assess the necessity to perform the axillary lymph node dissection in patients with metastases to the sentinel lymph node. The American College of Surgeons Oncology Group (ACOSOG) study compared the full axillary lymph node dissection with observation. No differences were shown in the frequency of occurrence of the axilla relapse. In turn, the After Mapping of the Axilla Radiotherapy of Surgery (AMAROS) study compares lymph node dissection with radiotherapy of the axilla for relapse.

It should be taken into account that the sentinel lymph nodes are located differently in breast cancer than in the axilla. Incidental sentinel lymph nodes are located in the infraclavicular fossa and on the inner area of the arm; in tumors located in the central part or in the area of inner quadrants they flow to the prasternal lymph nodes. The sentinel lymph node biopsy in this location is technically difficult and may involve resection of the prasternal part of the rib, after which the sentinel nodes might still not be identified. Dissection of these nodes is difficult and involves a great risk of complications, which does not justify the procedure. No benefits of complementary radiotherapy in this area were shown.

Breast cancer may occur in specific clinical presentations as both breasts cancer, hidden breast cancer, cancer accompanying Paget's disease of the breast; it may affect pregnant

women or women of advanced age while it extremely rarely occurs in men. It may be a metastatic cancer from the other breast or a metastasis from a different organ. Breast tumors may be of various histological type: most often epithelial, i.e. cancers, but also non-epithelial (phyllodes tumor, sarcoma, lymphoma or joint epithelial and non-epithelial metaplastic breast cancer).

In bilateral breast cancer (5-10% of all breast cancers) patients are qualified for sentinel lymph node biopsy based on the same criteria as in single breast cancer, but the criteria are examined for each breast separately (16). Performing the sentinel lymph node biopsy is indicated especially in bilateral breast cancer because of the importance of avoiding bilateral axillary lymph node dissection and limiting the possible complications, chronic bilateral lymphatic obstruction or bilateral upper limb pain, which may be the cause of patients' serious disability.

Paget's disease is adenocarcinoma in situ of the nipple epidermis (Tis Paget). It may occur as isolated Paget's disease (only on the nipple epidermis) or jointly with concomitant breast cancer, either pre-invasive or invasive. There are no indications for sentinel lymph node biopsy in the isolated Paget's disease or Paget's disease with concomitant pre-invasive cancer. Sentinel lymph node biopsy is indicated in the invasive breast cancer unless axillae are suspicious or clinically confirmed (17).

Hidden breast cancer amounts to 0.3-1% of all breast cancers. Diagnosis is based on identifying breast cancer metastases in the axillary lymph nodes. Due to this fact, sentinel lymph node biopsy is not logically justified and thus – not performed (18).

Sentinel lymph node biopsy is not performed in pregnant patients with cancer due to the lack of reliable clinical research on the impact of radioactive tracer on the fetus and the described allergic reactions to the tracer (19).

Indications for the sentinel lymph node biopsy in advanced-age patients with cancer are the same as in younger women. Also, in male patients, indications for biopsy are to meet typical criteria.

In the case of metastases to breasts (most often the other breast cancer) the surgeon's role is limited to dissecting the metastasis from the breast; no sentinel lymph node biopsy is performed (20).

Phyllades tumor is a malignant epithelial-mesenchymal cancer. The mesenchymal component is responsible for the clinical course while the epithelial component is not malignant. Metastases to the lymph nodes are very rare (< 5% of the cases), thus neither the sentinel lymph node biopsy nor the axillary lymph node dissection is a routine procedure (21). In breast sarcoma (< 1% of breast cancers), the metastases spread mainly through the circulatory system, therefore neither the sentinel lymph node biopsy nor the axillary lymph node dissection is performed (22).

In lymphomas, the surgeon's role is usually limited to performing the biopsy; here also neither the sentinel lymph node biopsy nor the axillary lymph node dissection is performed. In metaplastic breast cancers (0.25% of breast cancers), apart from infiltrating ductal cancer, also other types of tissues are present. Epithelial elements are responsible for spreading via the lymphatic system. Surgical procedure is the same as in invasive ductal cancers. If lymph nodes are not suspicious, the sentinel lymph node biopsy is indicated and further treatment depends on its result.

The sentinel lymph node biopsy performed by the experienced clinical team: surgeon, clinical oncologist and nuclear medicine specialist, is a useful and reliable diagnostic tool with a low complication rate in the breast cancer surgery.

CONCLUSIONS

1. Marking the sentinel lymph node in breast cancer, based on the single visualisation method with the use of radioisotope, is a useful and effective technique.
2. The factor influencing the results of the sentinel lymph node biopsy (true positive and negative results and false negative result) was the number of the excised lymph nodes except for the sentinel lymph node.
3. Patients with estrogen receptor expression had often metastases to sentinel lymph node (145 cases – 56%).
4. The false negative rate, i.e. 5.5% in our material, is within the limits of acceptability given in the literature.
5. The sentinel lymph node biopsy performed by the experienced team is a reliable diagnostic tool with a low complication rate.

REFERENCES

1. Cabanas RM: An approach for the treatment of penile carcinoma. *Cancer* 1977; 39: 456-66.
2. Giuliano AE, Kirgan DM, Guenther JM, Morton DL: Lymphatic mapping and sentinel lymphadenectomy for breast cancer. *Ann Surg* 1994; 220 (3): 391-98.
3. Turner RR, Ollila DW, Krasne DL, Giuliano AE: Histopathologic validation of the sentinel lymph node hypothesis for breast carcinoma. *Ann Surg* 1997; 226 (3): 271-78.
4. Veronesi U, Saccozzi R, Del Vecchio M et al.: Comparing radical mastectomy with quadrantectomy, axillary dissection and radiotherapy in patients with small cancer of the breast. *N Eng J Med* 1981; 305 (1): 6-11.
5. Orr RK: The impact of prophylactic axillary node dissection on breast cancer survival—a Bayesian meta-analysis. *Ann Surg Oncol* 1999; 6 (1): 109-16.
6. Goldhirsch A, Ingle JN, Gelber RD, Coates AS et al.: Thresholds for therapies: highlights of the St Gallen International Expert Consensus on the primary therapy of early breast cancer 2009. *Ann Oncol* 2009; 20 (8): 1319-29.
7. Piekarski J, Pluta P, Jastrzębski T i wsp.: Ocena węzła wartowniczego w raku piersi. W: Jeziorski A (red.) Węzeł chłonny wartowniczy. Wyd. 1. ViaMedica, Gdańsk 2014.
8. Petrek JA, Heelan MC: Incidence of breast carcinoma-related lymphedema. *Cancer* 1998; 83 (12 Suppl): 2776-81.
9. Schijven MP, Vingerhoets AJ, Rutten HJ et al.: Comparison of morbidity between axillary lymph node dissection and sentinel node biopsy. *Eur J Surg Oncol* 2003; 29 (4): 341-50.
10. Mansel RE, Fallowfield L, Kissin M et al.: Randomized multicenter trial of sentinel node biopsy versus standard axillary treatment in operable breast cancer: the ALMANAC Trial. *J Natl Cancer Inst* 2006; 98 (9): 599-609.
11. Piekarski J, Pluta P: Biopsja węzła wartowniczego w klinicznych postaciach specjalnych raka piersi i w złośliwych nowotworach nienabłonkowych piersi. W: Jeziorski A (red.) Węzeł chłonny wartowniczy. Wyd.1. ViaMedica, Gdańsk 2014.
12. Tafra L: The learning curve and sentinel node biopsy. *Am J Surg* 2001; 182 (4): 347-50.
13. Pluta P, Nejc D, Piekarski J et al.: Intraoperative palpation of the axilla as a part of sentinel node biopsy in breast cancer patients. *Nowotwory – J Oncol* 2008; 58 (2): 92e-94e.
14. van der Ploeg IM, Nieweg OE, van Rijk MC et al.: Axillary recurrence after a tumour-negative sentinel node biopsy in breast cancer patients: A systematic review and meta-analysis of the literature. *Eur J Surg Oncol* 2008; 34 (12): 1277-84.
15. Treseler P: Pathologic examination of the sentinel lymph node: what is the best method? *Breast J* 2006; 12 (5 Suppl): S143-51.
16. Piekarski J: Bilateral breast cancer – two primary cancers or one primary cancer and its metastasis. *Nowotwory – J Oncol* 2005; 55 (5): 395-400.
17. Jeziorski A, Sęk P, Nejc D, Piekarski J: What do we know about Paget's disease? *Nowotwory – J Oncol* 2005; 55 (6): 463-65.
18. Piekarski J, Pluta P, Nejc D, Jeziorski A: Mastectomy is an over-treatment in patients with occult breast cancer. *Nowotwory – J Oncol* 2003; 53 (6): 630-34.
19. Loible S, von Minckwitz G, Gwyn K et al.: Breast carcinoma during pregnancy. International recommendation from an expert meeting. *Cancer* 2006; 106 (2): 237-46.
20. Jeziorski A, Piekarski J: Przerzuty do piersi – opis przypadków. *Nowotwory – J Oncol* 1999; 49: 445-47.
21. Telli ML, Horst KC, Guardino AE et al.: Phylloides tumors of the breast: natural history, diagnosis and treatment. *J Natl Compr Canc Netw* 2007; 5 (3): 324-30.
22. Bousquet G, Confavreux C, Magne N et al.: Outcome and prognostic factors in breast sarcoma: a multicenter study from the rare cancer network. *Radiother Oncol* 2007; 85 (3): 355-61.

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