UDC 616.428-02:618.19-006.6]-07

The role of sentinel lymph nodes in breast cancer

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Abstract

Introduction. The problem of improving early diagnosis and prognosis of breast cancer remains one of the most actual for current oncological practice. Taking into account a close correlation between the general prevalence of breast neoplasms and mortality from breast cancer, this problem is not only of professional interest, but also has medical-social and socio-economic significance.

The purpose of the study is to improve the quality of the sentinel lymph node detection in patients with breast cancer using ICG.

Material and methods. At the period 2009–2016, 400 patients with T1-T3N0M0 breast cancer were operated on. All the patients were divided into two groups using two dyes
– Patent Blue and ICG. The patients after mastectomy with a sentinel lymph node biopsy had a clinical diagnosis of T2-T3N0M0 breast cancer more often.

In group I, 100 patients had the sentinel lymph node biopsy. Lymph node staining was performed using Patent Blue dye.

In group II, sentinel lymph nodes biopsy was conducted with the Patent Blue dye and another fluorescent dye — ICG, which was also injected on the affected side of the breast. After ICG dye introduction, in 15 minutes the stained green lymph nodes were detected using special equipment.

Criteria for inclusion of patients in the clinical trial:
1) breast cancer patients of any age with T1-3N0M0, I-II AB disease stage;
2) patients with clinically unaffected lymph nodes N0 after examination.

Criteria for exclusion of patients from the clinical trial:
The exceptions were T3-T4 tumors > 5 cm in diameter, or the skin and chest wall invasion, as well as palpable axillary lymph nodes, 3 or more affected lymph nodes with sentinel lymph node biopsy;
3) patients after radiation therapy.

**Results.** The tumor histology was performed after the node trephine biopsy. The main aims of sentinel nodes detection were staging and improving the breast cancer patients’ life quality after surgical treatment. The post-mastectomy syndrome, the main manifestation of which is swelling of the upper extremity is a big problem for patients because it affects their life quality and disturbs their usual lifestyle. The sentinel lymph node detection, in contrast to axillary lymph node dissection of I-II level, significantly minimizes all the risks of postmastectomy syndrome, in particular, impaired lymphatic drainage in the form of lymphatic edema of the upper extremity, impaired venous outflow in the form of stenoses or the axillary and/or subclavian veins occlusion, rough scars which limit the function of the extremity in the shoulder joint, and brachioplexitis.

**Conclusions.** The study of sentinel lymph nodes significantly improves the results of surgical treatment of breast cancer patients. Based on the clinical-laboratory and histological examinations, new data were obtained concerning the sentinel lymph node detection using two dyes, the choice of the surgical intervention volume and reduction of complications rate at the postoperative period. We found that fluorescent lymphography is highly effective, which allows to recommend it for implementation into the clinical practice. The frequency of sentinel lymph node detection in breast cancer patients is 98% in the control group, 100% – in the main group.
On the basis of the obtained results, the sentinel lymph node detection algorithm and the surgical management of patients with breast cancer was developed and implemented into practice, which allowed to reduce the number of complications with using two dyes for the sentinel lymph node detection from 19% to 2% ($\chi^2 =15.37$, $p<0.001$). Recurrence of breast cancer fell from 13% to 8%.

**Key words:** sentinel lymph nodes; breast cancer; ICG.

**Actuality.** The problem of improving early diagnosis and prognosis of breast cancer remains one of the most important for current oncological practice [1, 6, 9, 15, 18, 26, 36]. Taking into account a close correlation between the general prevalence of breast neoplasms and mortality from breast cancer, this problem is not only of professional interest, but also has medical-social and socio-economic significance [2, 8, 13, 18, 24, 30, 38]. Breast cancer in Ukraine, like in most countries of the world, is one of the most common tumors in women and ranks first in the structure of mortality from malignant neoplasms (25% of all cancers in women) [1, 5, 10, 14, 20, 27, 37]. The number of women with breast cancer in Ukraine has significantly increased [2, 7, 12, 19, 25, 34]. A new case of breast cancer is detected every 35 minutes, and one woman dies from this disease every hour [3, 16, 23, 33, 38, 39]. Every woman who has breast cancer loses on average 17–18 years of life, which is 53–62% of all losses of the female population in Ukraine [1, 4, 11, 22, 28, 32, 35].

According to statistical data of the Ukrainian Mammological Center at the Institute of Oncology of the National Academy of Sciences of Ukraine, the Odesa region ranks first in morbidity and mortality from breast cancer among women [26, 31, 38]. So, in the Odesa region, the standardized mortality rate from breast cancer reached 90.3 cases per 100,000 female population (National Cancer Registry, 2011).

Today, the only real way to successfully reduce mortality from breast cancer is to improve the quality of diagnosis by the way of sentinel lymph node detection [2, 10, 17, 21, 26, 36]. A thorough study of the metastasis mechanisms revealed that in breast cancer, certain lymph nodes of the first order are first affected, and then, after their involvement, cancer cells spread to other lymph nodes of the first and second order [6, 15, 29, 35]. Such lymph nodes which are affected first and are a certain barrier to further spread of cancer cells are called sentinel lymph nodes [7, 13, 26, 38]. In the 1990s the leading oncologists formulated the sentinel lymph node doctrine [8, 17, 25, 38]. If no cancerous lesion is detected in the sentinel lymph nodes, their detection in the lymph nodes of the second and third order is relatively unlikely [2, 12, 19, 28, 39]. This logically led to a reduction in the volume of surgery. If there
are no cancer cells in the sentinel lymph nodes, there is no need to perform extended lymph node dissection [10, 18, 27, 34].

The cancer treatment doctrine exists and is currently relevant [1, 9, 16, 20, 26, 38]. It has received brilliant clinical confirmation in breast cancer. Mastectomy with large and small pectoral muscles and simultaneous radical lymphadenectomy was the most common operation, and since the 1990s surgical management has experienced radical changes according to currently existing protocols [10, 19, 26, 32].

With early breast cancer, a biopsy with staining and removal of sentinel lymph nodes with emergency histology are conducted [4, 10, 18, 24, 35]. If cancer cells in the sentinel lymph nodes are not detected, the operation is limited to local excision of the tumor in order to preserve the beauty of the mammary gland, followed by radiation and chemotherapy [9, 12, 19, 27, 30]. The conducted multicentric studies in different countries have confirmed that the new breast cancer surgical management by oncological radicality is as good as the old superradical interventions, but the main criterion was the sentinel lymph node detection using special dyes [6, 15, 20, 28, 33].

Currently, sentinel lymph nodes assessment is used in breast cancer, when clinical examination (palpation, ultrasound and FNAB) shows no signs of axillary lymph node metastases, and there is a need in in situ ductal carcinoma biopsy when such patients have a high probability of invasive component and they are indicated mastectomy [1, 8, 16, 26, 32].

**The purpose of the study** is to improve the quality of the sentinel lymph node definition in patients with breast cancer using ICG.

**Material and methods.** At the period 2009–2016, 400 patients with T1-T3N0M0 breast cancer were operated on at the Odesa Regional Clinical Hospital. All the patients were divided into two groups using two dyes – Patent Blue and ICG. The patients after mastectomy with sentinel lymph node biopsy had more often a clinical diagnosis of T2-T3N0M0 breast cancer.

In group I, 100 patients had sentinel lymph node biopsy. Lymph node staining was performed using Patent Blue dye.

In group II, sentinel lymph nodes biopsy was performed using the Patent Blue dye and another fluorescent dye – ICG, which was also injected on the affected side of the breast. After ICG dye introduction, in 15 minutes, the stained green lymph nodes were detected using special equipment. The preoperative examination of the breast consisted of clinical examination, ultrasound and mammography. The tumor histology and the level of malignancy were indicated after the trephine biopsy. The next step was the immunohistochemical
examination, tumor phenotype determination which included the values of estrogen and progesterone receptors, the level of Her2/neu protein expression and Ki67 proliferation index.

Criteria for inclusion of patients in the clinical trial:
1) breast cancer patients of any age with T1-3N0M0, I-II AB disease stage;
2) patients with clinically unaffected lymph nodes N0 after examination.

Criteria for exclusion of patients from the clinical trial:
The exceptions were T3-T4 tumors > 5 cm in diameter, or the skin and chest wall invasion, as well as palpable axillary lymph nodes, 3 or more affected lymph nodes with sentinel lymph node biopsy;
3) patients after radiation therapy.

The middle age of breast cancer patients did not differ practically (Table 1). In patients of the control group, it ranged between (47.1–51.1) years in 95%. In the main group the age ranged between (49.5–54.0) years in 95% (Table 1).

Table 1 - The average age of patients in the control and main groups

<table>
<thead>
<tr>
<th>Groups</th>
<th>Age of patients, years</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>M±m</td>
</tr>
<tr>
<td>I (n=100)</td>
<td>49.1±13.2</td>
</tr>
<tr>
<td>II (n=100)</td>
<td>51.7±12.8</td>
</tr>
</tbody>
</table>

*Note. * – compared to group I (P > 0.05).

All the patients received an injection of Patent Blue dye subdermally along the outer edge of the areola in amount of 2 ml of diluted dye, to allow spread through the lymphatic system (Fig. 1).

Fig. 1. Injection of Patent Blue dye subdermally along the outer edge of the areola
The time of a standard interval for a stained lymph node appearance was 15–20 minutes. The stained lymph node (lymph nodes) was sent for pathomorphological examination.

A cytological examination of stained lymph nodes was carried out intraoperatively (Fig. 2, 3).

Fig. 2. Lymph nodes stained with ICG dye

Fig. 3. The stained sentinel lymph node with Patent Blue and ICG
Pathomorphological examination was performed according to the hematoxylin-eosin standard, false-negative sentinel lymph nodes were examined using immunohistochemical analysis. Our study showed an excellent result in detection of important lymph nodes using the ICG fluorescent dye. All patients with sentinel lymph node involvement received adjuvant therapy at the postoperative period according to ESMO/NCCN recommendations [5, 18, 24, 26, 38].

Results and discussions. Tumor histology was performed after trephine biopsy of the lymph node. The results of the histological examination of the lymph nodes in the control group are presented in Table 1.

When dividing the patients of the control group according to malignancy of the lymph nodes, histologically unfavorable forms prevailed: moderate (G2) and high grade (G3) – 68% and 24% respectively (Table 2.).

Table 2. - Distribution of patients of the control group according to tumor grade (G) according to Ellson-Ellis modification of Scaff-Bloom Richardson grading system

<table>
<thead>
<tr>
<th>Tumor grade</th>
<th>Number of patients, abs. (%)</th>
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<tbody>
<tr>
<td>G1</td>
<td>8 (8%)</td>
</tr>
<tr>
<td>G2</td>
<td>68 (68%)</td>
</tr>
<tr>
<td>G3</td>
<td>24 (24%)</td>
</tr>
<tr>
<td>Total</td>
<td>100 (100%)</td>
</tr>
</tbody>
</table>

When dividing the patients of the main group according to the degree of malignancy of the tumor process, histologically unfavourable forms prevailed: moderate (G2) and high (G3) degree of malignancy – 67% and 27% respectively.

Table - Prognostic effectiveness of the sentinel lymph nodes detection method in breast cancer patients of the control and the main group

<table>
<thead>
<tr>
<th>Groups</th>
<th>Sensitivity (95% CI)</th>
<th>Specificity (95% CI)</th>
<th>Positive result probability ratio (95% CI)</th>
<th>Negative result probability ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group 1</td>
<td>0.93 (0.71–0.98)</td>
<td>0.93 (0.87–0.96)</td>
<td>14.59 (7.05–30.22)</td>
<td>0.06 (0.01–0.44)</td>
</tr>
<tr>
<td>Group II</td>
<td>0.94 (0.71–0.98)</td>
<td>0.94 (0.87–0.97)</td>
<td>16.68 (7.05–39.47)</td>
<td>0.06 (0.01–0.44)</td>
</tr>
<tr>
<td>Total</td>
<td>0.93 (0.82–0.97)</td>
<td>0.93 (0.89–0.94)</td>
<td>12.74 (8.73–18.60)</td>
<td>0.07 (0.02–0.21)</td>
</tr>
</tbody>
</table>
The main goals of sentinel nodes detection are staging and improving of breast cancer patients’ life quality after surgical treatment [2, 18, 26, 35]. The post-mastectomy syndrome, the main manifestation of which is swelling of the upper extremity is a big problem for patients, because it affects their life quality and disturbs their usual lifestyle [4, 15, 26, 38]. The sentinel lymph node detection, in contrast to axillary lymph node dissection of I-II level, significantly minimizes all the risks of postmastectomy syndrome, in particular, impaired lymphatic drainage in the form of lymphatic edema of the upper extremity, impaired venous outflow in the form of stenoses or the axillary and/or subclavian veins occlusion, rough scars which limit the function of the extremity in the shoulder joint, and brachioplexitis [9, 13, 18, 20, 26, 39]. The mentioned manifestations can be minimized by the sentinel nodes detection by fluorescent lymphography with indocyanine green [8, 17, 22, 26, 30].

After the clinical trial carried out, it is no doubt in simplicity of the method, the absence of side effects, and the most important – in the successful sentinel nodes detection with green indocyanine [9, 12, 21, 26].

All existing methods of sentinel lymph nodes detection according to the sentinel nodes concept, in fact, perform the only function – they show the priority path of lymph outflow from the sentinel node to regional lymph nodes [7, 14, 24, 26, 39]. These can be not only axillary, but also supra- and subclavian and even sternal lymph nodes, therefore the method of fluorescent lymphography with indocyanine green is also a universal method of sentinel nodes detection, which evaluates all ways of lymph drainage [3, 20, 26].

So, the search for sentinel lymph nodes by the fluorescent lymphography method in patients with breast cancer is effective for staging the disease, as well as a minimally injured factor in breast cancer surgery. At the same time, it is both a prognostic factor and a reference point for the further treatment of breast cancer patients of I-II (A-B) stages and can be recommended to patients who are indicated radical surgical treatment in the absence of absolute contraindications to fluorescent lymphography with green indocyanine [11, 26, 35].

Conclusions. So, the study of sentinel lymph nodes significantly improves the results of surgical treatment in breast cancer patients. Based on the clinical-laboratory and histological examinations, new data were obtained concerning the sentinel lymph nodes detection using two dyes, the choice of the surgical intervention volume and reduction of complications rate at the postoperative period.

We found that fluorescent lymphography is highly effective, which allows to recommend it for implementation into the clinical practice. The frequency of sentinel lymph
nodes detection in breast cancer patients is 98% in the control group, 100% – in the main group.

The use of the two dyes method in patients with breast cancer of the main group made it possible to reliably ($\chi^2=15.38$, $p<0.001$) reduce postoperative complications from 19% to 2%.

On the basis of the obtained results, the sentinel lymph node detection algorithm and the surgical management of patients with breast cancer was developed and implemented into practice, which allowed to reduce the number of complications with using two dyes from 19% to 2% ($\chi^2=15.37$, $p<0.001$). Recurrence of breast cancer fell from 13% to 8%.

Another advantage of fluorescent dyes – simplicity – allows this method to be implemented in the daily work of oncologist-surgeons.

References


