ANALYSIS OF SENTINEL NODES BIOPSY IN BREAST CANCER – 12 YEARS AFTER INTRODUCTION INTO CLINICAL PRACTICE

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Summary

Introduction. Sentinel node biopsy in breast cancer has been a standard procedure at the Institute for Oncology of Vojvodina since 1999 and we have done more than 700 biopsy. Before the introduction of axillary sentinel lymph node biopsy, lymph nodes were routinely dissected, and this approach was the gold standard in surgical treatment of breast cancer. The study was aimed at presenting our results in performing sentinel node biopsy in clinical practice for operative treatment in breast cancer.

Material and Methods. All patients (n=791) were women with clinically T1-2, N0-1, M0 breast cancer. Sentinel lymph node marking was performed by both contrast blue dye (Patentblau V) and radiotracer (antimony sulfide marked with Tc99m). Both contrast media were applied peritumorally or periareolarly. After sentinel lymph node biopsy all patients underwent breast-conserving surgery or mastectomy with or without lymph node dissection of level I and II (depending on sentinel lymph node status).

Results. Sentinel lymph node biopsy was negative in 543 (68.7%) patients, and positive in 248 (31.3%) patients. Solitary tumor was present in 722 (91.2%) cases, multifocal tumors in 36 (4.57%), multicentric in 28 (3.55%) and bilateral in 5 (0.68%) patients. The mean duration of follow-up was 60.59 months (median 65, range 12-132). Distant metastases were mostly found in bones (39.13%).

Conclusion. The number of complications related to axillary dissection can be reduced and the patient’s quality of life can be improved by avoiding complete axillary lymph node dissection.

Key words: Sentinel Lymph Node Biopsy; Breast Neoplasms; Female; Quality of Life; Neoplasm Metastasis; Lymph Node Excision + adverse effects; Axilla + surgery

Original study

ORIGINAL STUDIES

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ANALIZA BIOPSII STRAŽARSKIH LIMFNIH ČVOROVA KOD KARCINOMA DOJKE – 12 GODINA NAKON UVODENJA U KLINIČKU PRAKSU

Sažetak

Uvod. Biopsija stražarskih limfnih čvorova kod karcinoma dojke uvedena je kao standardna procedura 1999. godine u Institutu za onkologiju Vojvodine i do danas je izvedeno preko 700 biopsija. Cilj ove studije bio je da se prikažu naši rezultati u sprovođenju metode biopsije stražarskih limfnih čvorova na Klinici za operativnu onkologiju Instituta za onkologiju Vojvodine u terapiji karcinoma dojke. Materijal i metode. Sve pacijentkinje (n = 791) bile su žene s klinički T1-2, N0-1, M-0 karcinomom dojke. Markiranje stražarskih limfnih čvorova kod svih pacijentkinja je usklopljeno sa postupcima kojim je oblikovan cilj kliničkog ispitivanja. Rezultati. Rezultati biopsije stražarskih limfnih čvorova kod svih pacijentkinja su u skladu sa izdvojivim načinom. Pol ogleda operativna institucija dojke ili mastektomija, s kompletnom disekcijom limfnih čvorova aksile I i II nivoa ili bez nje (u zavisnosti od statusa stražarskih limfnih čvorova). Završni rezultati. Rezultati biopsije stražarskih limfnih čvorova bili su negativni kod 543 (68,7%) a pozitivni kod 248 (31,3%) pacijentkinja. Pojedinačni tumor bio je prisutan kod 722 (91,2%) pacijentkinja, multifoinalni kod 36 (4,57%), multicentrični kod 28 (3,55%) i obostrano kod 5 (0,68%) pacijentkinja. Srednja vrednost praćenja pacijentkinja iznosila je 60,59 meseci (medijana 65, range 12-132). Distant metastases were mostly found in bones (39.13%).

Ključne reči: Biopsija sentinel limfnog čvora; Karcinomi dojke; Žensko; Kvalitet života; Metastaze; Ekscizija limfnog čvora + neželjeni efekti; Aksila + hirurgija

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of each histologically verified breast cancer. In the mid-twentieth-century surgery of regional lymph nodes was being developed towards more and more complicated dissection procedures, which consisted of removing the potential paths of expansion in order to avoid any possibility of delayed metastases in lymph nodes [6,7]. This resulted in many problems, both intraoperative ones (due to very complicated surgery techniques), and even more after the surgery because of impaired lymph flow (abundant accumulation of seroma, the possibility of inflammation, interstitial islands with the development of lymphedema, compression of adjacent structures, development of contracture etc). By considering these issues in relation to the statistics of survival and financial expenses, it was concluded that something substantial had to be changed in terms of radicality of these operations [8]. Complications after surgical treatment which contained dissection were the reason to consider the axillary lymph nodes preservation.

The concept of sentinel lymph node biopsy in breast cancer was introduced by Giuliano in 1994. Giuliano argues that the analysis of sentinel node (SN) can serve as a predictor of positivity of other axillary lymph nodes status in over 95% of cases.

Sentinel node biopsy (SNB) in breast cancer has been a standard procedure at the Institute for Oncology of Vojvodina since 1999 and we have done more than 700 biopsies.

SN biopsy involves the identification, extirpation and histopathological analysis of SN at fast frozen sections (ex tempore). It is indicated to be performed in all cases of clinically or histologically verified breast cancer, with the maximum dimension of up to 3 cm and no preoperative clinical and ultrasonographic suspicion of axillary lymphadenopathy.

Mapping and identification can be performed by injecting the vital dye and visual identification of the SN (81% accuracy), the application of radioisotopes, and with intraoperative identification with manual gamma counter (accuracy 92%), or the combination of the previous two methods when the accuracy rises to 97%. False negative findings in the SN can be expected in 3 to 7.9% of cases [1-8].

Precise histopathological analysis of SN samples at fast frozen section, if necessary combined with immunohistochemistry (IHC) staining, provides data which can be the basis to decide to abandon axillary node dissection in the absence of metastases with a statistical significance. Thus, in many cases it is possible to avoid complete axillary dissection and the morbidity carried by it [1-3].

The aim of this study is to present the results of a multi-year implementation of sentinel node biopsy method for breast cancer at the Department of Surgical Oncology, Institute of Oncology of Vojvodina.

Material and Methods

This retrospective study was performed at the Department of Surgical Oncology from January 1999 to December 2010. All patients were women with clinically T1-2N0-1M0 breast cancer. The study included 791 patients who had undergone SNL biopsy. The preoperative diagnosis was obtained by physical examination, mammography, ultrasonography and fine needle aspiration (FNA) cytology and/or core (hystology) confirmation of malignity.

Preoperatively, all patients were administered dual contrast media (radiotracer + blue dye). Radiotracer was antimony sulfide marked with Tc99m, and the blue dye was Patentblau V (Byk Gulden, Atlanta, USA). Both types of contrasts were administered subcutaneously above the primary tumor and in some cases paraareolarly (localization of primary tumor near the axilla, multifocal or multicentric tumors) with thin needles (25 G). Radiotracer was administered 2-16 h preoperatively, and blue dye 15 min before surgery. Radioactivity of the injected radiotracer was 0.3 mCi (11.1 MBq). For the detection of the accumulated radioactivity in the SNL, we used intraoperative handheld gamma counter to identify nodes with the greatest numerical and sound activity, by probe of 10 mm in diameter. The color was visually identified (figures 1, 2, 3).

Firstly, we performed extirpation of SNL, and then all patients underwent breast-conserving surgery or mastectomy with or without complete axillary lymph node dissection (cALND) of level I and II, depending on SNL status.

Immediately after the extirpation, SLNs were sent for intraoperative frozen section evaluation. Ten sections of SLNs were obtained from each block of tissue and stained with haematoxylin and eosin (H&E) or immunostained for epithelial membrane antigen (EMA). The remaining SLN tissue was fixed in formalin and embedded in paraffin.
and the embedded tissue blocks were stained with H&E or immunostained for EMA; these preparations were compared with frozen section results.

### Statistical Analysis

All data were grouped, statistically analyzed (median, average value, percentage) and presented as Tables and Figures. The Statistical Package for the Social Sciences (SPSS) V1.6 program was used for statistical analysis.

### Results

Four hundred and thirty one (54.48%) patients were pre-menopausal and 360 (45.52%) postmenopausal women, their average age being 57 years (ranging from 25 to 84) (Figure 1).

Breast-conserving surgery was performed in 726 patients and subcucaneous mastectomy with immediate reconstruction was carried out in 65 patients.

Solitary tumor was present in 722 (91.2%) cases, multifocal tumors in 36 (4.57%), multicentric in 28 (3.55%) and bilateral in 5 (0.68%) patients.

Ductal carcinoma was encountered in 63.79% of the cases, lobular in 28.43%, medullary in 1.18%, and other histological types in 1.35% cases. In 42 (5.25%) patients, ductal carcinoma in situ (DCIS) was identified, and SLN biopsy was performed because of the large size of the DCIS field, or suspected high-grade forms.

SLN biopsy was negative in 543 (68.7%) patients. In this group most of the patients (n=280; 51.5%) had T1c tumor stage. SLN biopsy was positive in 248 (31.3%) patients. The most frequent tumor stage in this group was T1c (n=127; 51.08%) (Table 1).

The mean number of extirpated SLNs in both groups (SLN positive and SLN negative) was 1.84 (median 1, range 1-6). The mean number of dissected axillary lymph nodes in the group with positive SLNs on paraffin embedded tissue sections was 18.49 (median 17, range 8-28 after cALND). The mean number of dissected axillary lymph nodes with metastases in SLN-positive patients was 6.59

### Table 1. Tumor (T) classification in groups with positive and negative SLN

<table>
<thead>
<tr>
<th>Tumor stage (cm)</th>
<th>Negative SN/Negativan SN</th>
<th>Positive SN/Pozitivan SN</th>
<th>Total/Ukupno</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients, n/Pacijenti, n</td>
<td>%</td>
<td>Patients, n/Pacijenti, n</td>
<td>%</td>
</tr>
<tr>
<td>T1a: 0.1 - 0.5</td>
<td>38</td>
<td>4.57</td>
<td>8</td>
</tr>
<tr>
<td>T1b: 0.5 - 1.0</td>
<td>112</td>
<td>14.21</td>
<td>23</td>
</tr>
<tr>
<td>T1c: 1.0 - 2.0</td>
<td>278</td>
<td>35.19</td>
<td>129</td>
</tr>
<tr>
<td>T2: 2.0 - 3.0</td>
<td>98</td>
<td>12.52</td>
<td>71</td>
</tr>
<tr>
<td>T2: 3.0 - 4.0</td>
<td>17</td>
<td>2.20</td>
<td>17</td>
</tr>
<tr>
<td>Total/Ukupno</td>
<td>543</td>
<td>68.70</td>
<td>248</td>
</tr>
</tbody>
</table>
Table 2. Distant metastases according to SLN status

<table>
<thead>
<tr>
<th>Metastases/Organ</th>
<th>Positive SN/Pozitivan SN</th>
<th>Negative SN/Negativan SN</th>
<th>Total/Ukupno</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bones/Kosti</td>
<td>Patients, n/Pacijenti, n</td>
<td>14, 39.13</td>
<td>2, 4.35</td>
</tr>
<tr>
<td>Liver/Jeta</td>
<td>Patients, n/Pacijenti, n</td>
<td>8, 21.74</td>
<td>2, 4.35</td>
</tr>
<tr>
<td>Lungs/Pluća</td>
<td>Patients, n/Pacijenti, n</td>
<td>4, 13.04</td>
<td>0, 0</td>
</tr>
<tr>
<td>Brain/Mozak</td>
<td>Patients, n/Pacijenti, n</td>
<td>2, 4.35</td>
<td>0, 0</td>
</tr>
<tr>
<td>Death/Smrt</td>
<td>Patients, n/Pacijenti, n</td>
<td>4, 13.04</td>
<td>0, 0</td>
</tr>
<tr>
<td>Total/Ukupno</td>
<td>Patients, n/Pacijenti, n</td>
<td>32, 91.30</td>
<td>4, 8.70</td>
</tr>
</tbody>
</table>

(paraffin embedded tissue preparations) and the mean number of dissected axillary lymph nodes without metastases in the same group was 11.8 (paraffin embedded tissue sections) (Table 1).

In 67 (27.03%) patients SLN was the only metastatic lymph node in the axilla after cALND (paraffin embedded tissue). In 44 (17.84%) cases SLN contained micrometastases. The mean duration of follow-up was 60.59 months (median 65, range 12-132).

Systemic metastases in SLN-positive patients developed mostly in bones (39.13%), liver (21.74%), lungs (13.04%) and brain (4.35%). Four (13.04%) patients died due to distant metastases. In the patients with negative SLN biopsy there were 4 cases with distant metastases (2 in the liver and 2 in the bones) (Table 2).

The overall diagnostic accuracy of SN biopsy was 96%.

Discussion

For more than 2 decades, SLN biopsy has been used in breast cancer patients to predict axillary lymph node status avoiding cALND if possible [1-8].

In this study SLN biopsy was performed mostly in solitary tumors sized up to 3 cm, from which it follows that breast-conserving surgery was by far the most frequent operation performed (n=726 patients). Tumors > 3 cm in size had the same percentage of positive and negative SLNs, although the clinical, ultrasonographic and mammographic evaluation was negative.

After the histological analysis of primary cancer in all patients, ductal carcinoma was encountered in 63.79% of the cases, lobular in 28.43%, 1.18% in medullary, and other histological types in 1.35% cases, very close to the global distribution of histological types of breast cancer [1-14]. In 42 (5.25%) patients DCIS was identified, and SLN biopsy was performed because of the large size of the DCIS field, or suspected high-grade forms.

Breast carcinoma was mostly found in T1c stage (304 patients; 51.44%), which is in accordance with data of other authors [1-8].

In 67 (27.03%) patients SLN was the only axillary lymph node with metastasis after cALND. When considering the need for dissection of other axillary nodes in the presence of micrometastatic SLN, one should take into account the fact that for all positive SLN (micro+macrometastases) the SLN is the only positive axillary node in 28-40% of the cases (and even more) depending on the stage of disease [9-14]. The available evidence suggests that micrometastases and isolated tumor cells in SLNs have no prognostic value. If SLN biopsy reveals no additional disease, the patients’ survival with isolated tumor cells or micrometastases is the same as in those with node-negative disease. All patients with SLN micrometastases should have minor surgical treatment with adjuvant radiotherapy, chemotherapy and hormonal therapy [13-24].

So far, the present study has shown that in patients with SLN macrometastases, systemic metastases developed mostly in bones (39.13%), liver (21.74%), lungs (13.04%) and brain (4.35%). Distant metastases resulted in fatal outcome in four cases (13.04%). In patients with negative SLN biopsy there were two cases with metastasis in the liver and two in bones.

The overall accuracy of detection of SN in this study is completely satisfactory (97%), and the results arising from it can be incorporated into prognostic parameters, which correspond to the literature data [23].

Conclusion

Sentinel node biopsy must be performed with double-contrast (Radiotracer + color) and the intraoperative handheld gamma counter must be used in order to maintain the required level of accuracy of the method and avoid false negative results.

It is better to perform first sentinel node biopsy and then proceed with surgery on the breast (conservative or mastectomy).

Axillary sentinel nodes can serve as a reliable predictor of negativity of other ipsilateral axillary nodes, breast cancer size of less than 3 cm in diameter.

It has been confirmed that in the absence of metastases in the axillary sentinel nodes, dissection of other lymphnodes has no justification and should be omitted to avoid unnecessary post-operative complications associated with complete axillary dissection (extended development of a seroma, numbness and pain in the region, contracture, the need for intensive physical treatment, lymphedema ...).
Axillary sentinel nodes in breast cancer, as expected, can be accurately identified and analyzed histopathologically with exceptional accuracy, which may eliminate the possibility of false-negative findings in them with statistical significance.

If the sentinel node on serial sections of fast frozen histological examination does not contain any metastases, we should certainly perform an immunohistochemical examination.

Micrometastases in the sentinel nodes (real micrometastases or groups of cells) are not an indication for dissection of other axillary nodes.

References