Diagnostic Accuracy of Sentinel Lymph Node Biopsy in Axillary Lymph Nodes at the Early Stages of Breast Cancer

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1. INTRODUCTION

For almost 100 years, standard procedure for evaluation of axillary lymph node status has been axillary nodes dissection (ALDN)—dissection of 1st, 2nd or possible 3rd level of axilla. Use of less invasive evaluation methods of axillary node pathologically (PH) status of non-invasive breast carcinoma has been started before about 30 year and that new method has been named sentinel lymph node biopsy (SLNB). Objective: Primary objective of study is to establish specificity, sensitivity, positive and negative predictive value of SLNB method comparing to presents of malignant changes of axillary sentinel lymph node and to establish true indication for ALDN. Patients: Study included 50 female patients, aged between 18-75, at Clinic for Glandular and Oncological Surgery, Clinical Center University of Sarajevo (CCUS), with non-invasive breast carcinoma, in the period from January 2008-January 2011, which fulfill established criteria. Material and methods: The study is of retrospective-prospective, clinical-manipulative and descriptive-analytic character. Sample consisted of patients of Clinic for Glandular and Oncological Surgery with diagnosed breast carcinoma, at T1 and T2 stage, with adequate preoperative preparation. Preoperative imaging with injection of radioactive isotope Tc99m albumin-colloid is done at the Clinic for Nuclear Medicine CCUS. Intraoperative PH examination of SLN node (or nodes) by frozen-section and hematoxylin-eosin staining and postoperative PH examination of lymph nodes after ALND was done at the Institute for Clinical Pathology and Cytology CCUS. Intraoperative identification of SLN is done with manual gamma probe. After the SLNB, all the patients underwent immediately appropriate breast carcinoma surgeries followed with dissection of 1st and 2nd level of axilla on the Clinic for oncology and glandular surgery of CCUS. Results: Statistic data evaluation was done by statistical program MedCalc for Windows, version 12.2.1.0 (MedCalc Software Mariakerke, Belgium). In the part of descriptive statistics all results are shown in table manner: mean, 95% CI for average value, standard deviation, median values, 95% CI for median value, maximal value, 25-75 percentiles, evaluation of normal distribution by D’Agostino-Pearson test, Chi square test for evaluation of differences in frequencies between subgroups. For evaluations of specificity and sensitivity of results were applied 2x2 tables and following equations: sensitivity=TP/TP+LN, specificity=TN/P+TN, overall accuracy = TP+TN/N, positive predictive value= TP/TP+LP, negative predictive value = TN/LN+TN. Defined significance level was p<0.05. Conclusions: Results of sensitivity (68%), specificity (98%), positive (67%) and negative predictive value (96%) and overall accuracy of method (98%) are comparable and compatible with results from oncological breast cancer centers and allow introducing of SLNB in routine surgical practice in our clinical practice as the alternative for ALND for T1 and T2 breast carcinoma. It also contributes to better co-ordination between specialist of nuclear medicine, surgeon and pathologist. Key words: breast carcinoma, radioactive isotope, sentinel lymph node biopsy

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or dye and c) that it can be successfully identified.

Kreigh et al. (1993) were the first to present data on successful application of unfiltered Tc99 in breast cancer and identification of sentinel lymph nodes in 18 of 22 patients using a manual gamma probe that was followed by numerous other studies (Giliano et al., Albertini and al., Veronesi et al., Imoto et al., Motomura et al.) that used either dye or radioactive isotope labeling as a means for marking axillary SLN which had a percentage of identifying over 90% with the percentage of false-negative results below 10% (3).

However, SLN biopsy is a relatively new method that has not yet been standardized and that requires clearly defined and precise collaboration between nuclear medicine specialists, pathologists and surgeon.

Therefore, all the authors in the beginning of application of SLN biopsy validate the results with complete axillary lymph node dissection (or axillary backup). Until now are made 69 clinical studies as well as five multicenter study in which the results of SLN biopsy were evaluated with ALND (4). According to estimates American Cancer Society in the 2011/2012 year, at the United States discovered 230480 new cases of invasive breast cancer with an additional 57650 women who had been diagnosed with breast cancer „in situ” (5).

Although all present radiological techniques can define the parameter T and M parameter in patients with newly diagnosed breast cancer, their diagnostic value is unacceptably low and too expensive for the prediction of the parameter N in patients with negative clinical finding. Mammography „screening” procedure has resulted in the detection of breast cancer at early stage where the probability of the presence of axillary metastases is between 20-40% (T1a-c) and ALND is routinely carried out in these patients as part of the staging, regardless of clinically negative axilla (6).

ALND is associated with a high incidence of early and late postoperative complications so that raises the question of justification for routine axillary lymph node dissection in all patients with breast cancer (7). Detailed histological evaluation of 15 to 20 lymph nodes is practically impossible during standard pathological analysis. On other hand, focusing on only one or a few sentinel lymph nodes in the course of extensive histological analysis improves the accuracy of the histopathological axillary lymph nodes staging (8).

Randomized clinical trials have confirmed that avoiding axillary dissection in breast cancer with negative sentinel lymph nodes can maintain the current parameters for locoregional recurrence and overall survival, while reducing the percentage of postoperative morbidity (9,10,11). Therefore, the radioactive guided biopsy of sentinel lymph node can be considered a new, minimally invasive standard axillary surgery in patients with early-stage breast cancer.

2. GOAL

The goal was to establish specificity, sensitivity, positive and negative predictive value of SNLB method in relation to the presence of malignant changes in axillary sentinel lymph node and to determine the actual need for implementation of ALND.

3. PATIENTS AND METHODS

3.1. Patients

The study included 50 female patients at the Clinic of Glandular and Oncological surgery CCU Sarajevo, with an initial breast cancer, aged 18-75 years in the period from January 2008 to January 2011, and which fulfilled the predefined criteria.

3.2. Methods

The study was of retrospective-prospective clinical informative and descriptive-analytical character. The sample consisted of patients who were admitted to the Clinic of Oncology and Glandular surgery with a diagnosis of breast cancer, at stage T1 and T2, which have been subjected to appropriate preoperative preparation. Preoperative injection of radioactive isotope Tc99 m albumin-nanocolloid was carried out at the Clinic of Nuclear Medicine CCUS, multiple, subcutaneous, above tumor at a dose of 0.2 mL 640 microCi. Intraoperative SLN identification is done using manual gamma probe with appropriate types of surgical breast cancer surgery and dissection of 1st and 2nd level of axillary lymph nodes performed at the Clinic of Oncology and Glandular Surgery CCUS. PH treatment of intraoperative dissected SLN was carried out at the Institute of Clinical Pathology and Cytology CCUS according the corresponding protocol.

Statistical analyzes were performed in the statistical program MedCalc for Windows, version 12.2.1.0. (MedCalc Software, Mariakerke, Belgium). In the part relating to the descriptive statistics all of the results are presented in tables by: the mean value (arithmetic mean), 95% CI for the mean, standard deviation, median, 95% CI for the median value, minimum value, maximum value, 25-75 percentiles, estimate of normal distribution by D’Agostino-Pearson test, chi-square test, 2x2 tables and formulas for evaluation of the sensitivity, specificity, PPV, NPV, and accuracy. Values that is obtained with the value of p <0.05 was accepted as statistically significant. The results of all analyzes performed are presented in tables and charts.

4. RESULTS

The study included 50 patients who met criteria for inclusion in the study, the average age of the patient’s was 51.32±10.5 years, with the youngest at age of 30 and the oldest at the age of 74 years. Analysis of tumor size showed that the patients had an average tumor size of 1.78±0.84 cm, with a 95% confidence interval (95% CI) of 1.482 to 2.079 cm.

Most tumors were larger than 1.5 cm in a total of 24 (48%). The largest recorded tumor size in the study was 4.0 cm. The average tumor size was 1.906 was the average number of lymph nodes after complete ALND.

**Figure 1. Measuring of tumor size (in cm)**
cm and the smallest 0.2 cm. Intraoperative identification of SLN (one or more) by gamma probe was performed in all patients as a condition for inclusion of the patients into the study.

Most of the patients had undergone quadrantectomy (n=21, 42%), and hemi mastectomy (n=14, 28%), mastectomy (n=7, 14%), and finally bisectionectomy (n=4, 8%) and segmentectomy (n=4, 8%).

The histopathological analysis revealed that the most common cancers were ductal (n=27, 54%, p=0.0184), and lobular (n=12, 24%) followed by other types (n=11, 22%). Under group of other group most cancer was of tubulo-lobular (n=4), and tubular (n=3) with one apocrine, mucinous, neuroendocrine and papillary (Table 1).

<table>
<thead>
<tr>
<th>Cancer type</th>
<th>n</th>
<th>%</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ductal</td>
<td>27</td>
<td>54</td>
<td>0.0184</td>
</tr>
<tr>
<td>Lobular</td>
<td>12</td>
<td>24</td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>11</td>
<td>22</td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>50</td>
<td>100</td>
<td></td>
</tr>
</tbody>
</table>

Table 1. Histological types of the cancer

All patients (n=50) underwent histopathological analysis of sentinel lymph nodes and axillary lymph node involvement. On average was sent to analysis 1.98 ± 0.742 sentinel lymph nodes, and 8.86 ± 1.906 was the average number of lymph nodes after complete ALND.

<table>
<thead>
<tr>
<th>N</th>
<th>Mean</th>
<th>95% CI</th>
<th>SD</th>
<th>Median</th>
<th>95% CI</th>
<th>Minimum</th>
<th>Maximum</th>
</tr>
</thead>
<tbody>
<tr>
<td>SLN</td>
<td>50</td>
<td>1.980 ± 0.7</td>
<td>1.9601</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>50</td>
<td>9.000 ± 1.9800</td>
<td></td>
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Table 2. Lymph nodes analysis

"TNM" (TNM Classification of Malignant tumor) classification showed that most patients with either with cancer in stage T1 (n=31, 62%, p=0.0339), and somewhat less in stage T2 (n=11, 22%) and the least number at the stage Tcis (n=8, 16%). "AJCC" (American Joint Committee of Cancer) classification showed that most patients with any stage of cancer was in stage T1 (n=26, 52%, p=0.0661), in stage Ib (n=15, 30%) and in the stage 0 (n=5, 10%) with the least number in the stage IIa (n=4, 8%).

Figure 2 shows that the average number of SLN in the total sample was approximately 2 (1.98±0.7) and ranged from 1-4. In patients with subsequent positive PH findings the number of SLN was slightly higher and ranged from 2-3, as compared to those with negative PH findings and ranged from 1-4.

The analysis of method sensitivity and specificity was done based on the following data, positive or negative results of analysis of sentinel lymph nodes and on the basis of positive or negative findings of axillary lymph nodes at the same patient. In 46 patients there was a negative result in sentinel lymph node as well as in the axillary lymph nodes and these findings were classified as true negative (TN), in two patients there was a positive finding in the sentinel lymph node and positive findings in lymph node and these was classified as a true positive (TP), in one patient there was a positive finding of sentinel lymph nodes while the axillary lymph node was negative so it is classified as a false positive result (FP), and finally in one patient the sentinel lymph nodes were negative, while axillary lymph nodes were found positive so this finding is classified as a false negative (FN) findings. (Table 3)

Based on the above analysis we obtained sensitivity of 67%, specificity 98%, PPV of 67%, NPV of 96% and diagnostic accuracy of 98%.

5. DISCUSSION

The hypothesis that one or more sentinel lymph node receives most lymphatic drainage from the primary breast tumor and axillary lymph node dissection can be avoided if the sentinel lymph node is negative is logical, intuitive and represents a new standard in the treatment of early-stage breast cancer.

However, SLN biopsy is a relatively new surgical technique that has its own learning curve, which is a highly multidisciplinary and which has not yet been standardized. The biggest dilemma regarding the use of SLN biopsy method is the impact on overall survival of patients and the percentage of local axillary recurrence compared to ALND. Results of several randomized controlled trials in clinically negative patients showed no difference in overall survival and local recurrence in patients who underwent SLNB method only and those patients who underwent simultaneous and SLNB and ALND (9, 10, 11, 12, 13).

Different types of radioactive colloids are used when performing SLN biopsy, different particle carriers size. Using radio colloid particle size between 100 and 200 nm is a compromise between fast lymphatic drainage and optimum retention in the sentinel lymph node.

The percentage of sentinel lymph node identification of 90-95% and the percentage of false-negative results of no more than 5-10% should be the target during the validation of the method (9, 14, 15).

The average number of SLN per patient was two lymph nodes, while biopsy of more than 4 lymph nodes is not recommended due to the risk of develop-
ing additional morbidity without additional benefits for the patient.

Recommendation of the American Cancer Society Organization (ASCO) is 20–30 procedures per surgeon to check the results of SLN biopsy with ALND, although some papers indicate that a smaller number of cases may be sufficient (9).

After the “ex tempore” analysis (FS) is negative sentinel lymph node (or nodes) are routinely further examined by hematoxylin & eosin technique (H&E) as a control “ex tempore” analysis which is the standard practice of all involved in SLNB. If the H&E technique found negative nodes, remaining sentinel lymph node can be further analyzed by immuno-histochemical methods for cytokeratin (IHC), which is not yet standard practice of all centers that deal with the treatment of breast cancer.

Results of studies of PH SLN analysis shows that in about 10–20% of cases when IHC is used for cytokeratin are found micro metastases that are not registered in the examination of sentinel lymph nodes by H&E technique (16).

In connection with the above is the issue of treatment of micro metastases (<0.2 mm), their classification and determination of appropriate stages of breast cancer and the impact on the recurrence and overall patient survival. Primary non-detected metastases are having prognostic and statistical significance associated with 10-15% of the deterioration in terms of overall survival (17).

In general, monitoring of patients after SLN biopsy was done during the whole life. Clinical studies have multi-year follow-up of patients after SLNB and showed that the percentage of overall survival and disease-free period was high (90.3 to 94.8% for overall survival and 81.5 to 87.6% for disease-free period) and was not significantly different compared to ALND (13, 15).

6. CONCLUSION

The obtained values of sensitivity, specificity, PPV, NPV, and accuracy of the this method are compatible and comparable with the results of the leading cancer centers that deal with breast cancer surgery and allow the introduction of SLN biopsy method in everyday surgical application at the Clinic of Oncology and glandular surgery CCU Sarajevo as a substitute for ALND in case of T1 and T2 stage breast cancer, with better co-ordination of multidisciplinary team of CCUS consisting of surgeon, pathologist and nuclear medicine specialists.

REFERENCES