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ORIGINAL PAPER

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Local-Regional Metastases and Mortality After Sentinel Biopsy and Complete Dissection of Axillary Lymph Nodes in Patients with Early Invasive Breast Cancer

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ABSTRACT

Introduction: Current, standard procedure for evaluation of axillary lymph node pathological (PH) status has been sentinel lymph node biopsy (SLNB). To demonstrate the long-term validity of sentinel lymph node biopsy (SLNB) using the radioactive isotope only Technetium 99m albumin-colloid (Tc99m) we compared the loco-regional recurrence and mortality of breast cancer patients with negative SLNB without axillary lymph node dissection (ALND) (SLNB group) to that of lymph node-positive patients undergoing ALND (ALND group). **Aim:** The aim of our study is to evaluate the results of long-term monitoring of patients with early invasive breast cancer in which the radio-actively guided axillary SLN biopsy and complete ALND were studied, with special emphasis on local-regional recurrence and mortality. **Patients and methods:** We studied a total of 63 patients with T1-2early invasive breast cancer diagnosed at Clinic for general and abdominal surgery, Clinical Center University of Sarajevo (CCUS) between 2004 and 2007, with follow-up till 2013, retrospectively, who met the criteria for inclusion. Preoperative peritumorous injection of radioactive isotope (Tc99m albumin-colloid) is done on the Clinic for Endocrine and Nuclear Medicine-CCUS. Intra and postoperative pathohistological (PH)examination of SLN node (or nodes) and PH examination of lymph nodes after complete ALND was done at the Clinic for Clinical Pathology and Cytology-CCUS. Statistical evaluation was done by statistical program MedCalc Statistical Software, version 18.10. Depending on the given variables were used: mean, standard deviation, median values, 95% CI for median value, Chi-square test, D'Agostino-Pearson test,

Kaplan-Maier curve of survival. Defined level of significance was $p < 0,05$. **Results:** The SLNB group consisted of 33 SLN-negative women and ALND group consisted of 30 axillary lymph node-positive women. The sentinel node identification rate was 100%. In the SLNB group no patients has developed axillary recurrence during the follow-up. The mortality rate in the SLNB group was equivalent to that in the ALND group. **Conclusions:** The SLN biopsy conducted with only a radioactive isotope TC 99m have the same results as loco-regional recurrence and mortality as well as the complete ALND method and may be the method of choice for the treatment of axillary in breast cancer patients and the clinically negative axillary lymph node (or nodules) with the notion that patients should be micro metastases given special attention during long-term monitoring.

Keywords: breast cancer; sentinel lymph node biopsy.

1. INTRODUCTION

The standard procedure for assessing the condition of axillary lymph nodes in breast cancer for nearly 100 years was complete dissection of the axillary lymph nodes (CALND), which implies the dissection of the I, II (eventually III level) axillary lymph nodes on the basis of which pathohistological (PH) analysis determines the exact tumor status of the axilla (1).

The use of less invasive methods of determining the PH status of the axillary lymph nodes in case of breast cancer began thirty years ago as a sentinel lymph node biopsy (SLNB) biopsy. Terminological sentinel (the guard) is the first

lymph node located in the lymph drainage pathway in the primary tumor area (2).

The radioactive isotope or dye (methyl-blau, indocyanin-green and similar) is used as a means of identifying, or marking the sentinel lymph node, with the possibility of using both agents at the same time, and with the percent of the sentinel lymph node of identification which is additionally increasing (3-5).

Meta-analysis performed by the Early breast cancer Trialists collaborative group (EBCTCG) as well as many other clinical studies have shown that the overall survival rate (OS) and disease-free period (DFS) after SLNB was high and correlated with OS and DFS after complete ALND (6-10).

Regardless of the aforementioned change in axillary surgical treatment, it also caused a number of dilemmas to be addressed in the future (question of treatment of micro metastases and isolated tumor cells, surgical vs. radiotherapeutic treatment of positive SLN biopsies etc.).

2. AIM

The aim of our study is to evaluate the results of long-term monitoring of patients with early invasive breast cancer in which the radio-actively guided axillary SLN biopsy and complete ALND were studied, with special emphasis on local-regional recurrence and mortality.

3. PATIENTS AND METHODS

3.1. Patients

The study was retrospective, clinically-manipulative and descriptive-analytic, and included 63 female patients of the Clinic for General and Abdominal Surgery of the Clinical Center of the University of Sarajevo (CCUS), radiologically (echography and mammography, mandatory magnetic resonance imaging) and pathohistological (CORE-biopsy) verified early invasive breast cancer, at age of 18 and older, surgically treated at the Clinic in the period January 2004–January 2007, which meet the defined criteria.

Patients who participated in the study were divided into two groups: a) 33 patients with cytologic and pathohistological negative SLNs who did not undergo CALND; and b) 30 patients with positive SLN who underwent CALND after SLNB.

2.2. Methods

Surgical treatment was performed at the CCUS General and Abdominal Surgery Clinic in the form of radical modified mastectomy (RM) or partial mastectomy (PM) with SLN biopsy or complete dissection (I and II level) of axillary lymph nodes (CALND).

Preoperative injection of radioactive isotope Technetium 99m, albumin nanocolide („Mo99/Tc99m generator, elution with sodium chloride 0.9% -Manufactured and released by: Mallinckrodt Medical BV, The Netherlands, NANOCOLL-Manufactured by GIPHARMA Srl, Italy“) was performed at the Clinic for Endocrinology and Nuclear Medicine of CCUS, repeatedly, subcutaneously, peritumorally in a dose of 0.2-0.3 ml, radioactivity 0.2-0.5 mCi. Intraoperative identification of the sentinel lymph node marked with the radioactive isotope was performed by a manual gamma-probe (Europrobe, manufactured by Euromedical Instruments, France).

Pathohistological analysis of the intraoperatively dis-

sected lymph node (or nodule) sentinel was performed at the Department of Clinical Pathology and Cytology of CCUS. The cut-off surfaces of each half of the lymph node were „ex tempore“ made by imprint-cytology, followed by staining with hematoxylin-eosin (H&E) technique. Regardless of the outcome of the intraoperative biopsy, each half of the lymph node was analyzed by immunohistochemical technique according to the accepted protocol of the Clinic for Pathology and Cytology where each half of the lymph node continued to be cut into equal slices, thicknesses of 2-3 mm, with the first three slices analyzed by the H&E method, then the fourth were submitted as a check for IHH test, after which the same procedure was repeated until complete PH lymph node analysis. The axillary tissue of lymph nodes of the I and II level, obtained from complete ALND, was postoperatively analyzed by standardized immuno-histophysiological (IHH) method at the Clinical Cytology and Pathology Clinic of CCUS.

All patients underwent oncological therapies (endocrine, chemotherapy and radiotherapy) at the Clinic of Oncology and Radiotherapy of CCUS after oncological protocols for adjuvant therapy. Postoperatively all patients were followed out clinically at the Clinic for General and Abdominal Surgery of CCUS according to the current protocols.

The study is conducted in accordance with the basic principles of the Helsinki Declaration last revision of 2008 on the rights of patients involved in biomedical research. During the implementation of this study the identity and all personal data of the patients will be permanently protected in accordance with the protection regulations on the identification data. The confidentiality of personal data will be guaranteed by the researcher, author of this work. Patients did not have any financial or any other interest in participating in the research.

2.3. Statistical analysis

The data were processed using MedCalc Statistical Software, version 18.10. by descriptive and inferential statistical methods. In the section related to descriptive statistics for all results, the following results were analyzed: average value (mean), 95% CI for mean value, standard deviation, median, 95% CI for median value, minimum value, maximal value, 25-75 percentile, estimate the normality of the D'Agostino-Pearson test distribution. The following section of the section relating to inferential statistics was performed: Chi square test to estimate the differences in frequencies between subgroups and the Kaplan-Meier survival curve. Values for which $p < 0.05$ were accepted as statistically significant. The results of the individual analyze are presented in form of tables and charts.

4. RESULTS

As can be seen from Table 1, the average age in our sample ($n=63$) was 52.1 years (± 10 years), ranging from 29 to 74 years ($p=0.5944$). In both examined groups, almost 80% were women in the postmenopausal age, or over 45 years of age.

Pathohistological tumor analysis showed that most tumors belong to invasive ductal cancer as the most common pathohistological type of breast cancer ($n=41/63.65\%$) followed by lobular ($n=13/63.20\%$) and other types of carcinoma ($63/9.14\%$).

		SLN + (30)	SLN -(33)	P-value
Age	Median (min-max) (year)	52 (31-74)	51 (29-73)	0.5944
Histology	Ductal	20	21	0.7095
	Lobular	5	8	
	Others	5	4	
Tumor size	<2cm	21	25	0.61
	2-5cm	9	8	
Molecular sub-type of breast carcinoma	Basal like	3	2	0.0412
	HER2-overexpression	6	1	
	Luminal A	18	19	
	Luminal B	3	11	
Tumor treatment	Spare	21	30	0.0363
	Radical	9	3	
Number of days treatment	<7 days	15	29	0.0012
	>7 days	15	4	
Metastasis	Negative	28	31	0.9221
	Positive	2	2	
Death	Positive	4	3	RR-1.4667 P=0.5952
	Negative	26	30	

Table 1. Characteristics of patients of both groups (SLNB positive versus SLNB negative)

By analyzing the molecular subtypes of the breast, we found that in the examined sample both groups were dominated by Luminal A submolecular subtype (n = 37/63, 59%) with significant significance (P = 0.0412) followed by Luminal B (n = 14/63, 22% and HER2- “over expression” (= 7/63, 11%) and “Basal Like” (n = 5 / 63.8%).

With regard to the type of surgery (PM vs. RM), in both analyzed groups there are dominant partial types of breast surgery (n=51/63, 81%) in relation to radical surgical interventions on the breast (n=12/63, 19%) with significant difference p=0.0363.

Postoperative stay at the hospital up to 7 days was significantly higher in the group of patients with only SLNB (n=29/63.46%) compared to the group with CALND (n=15/63.23%), with significant difference p=0.0012.

In other analyzed study variables (age, type of cancer, TNM classification, mortality, regional metastatic changes, false-positive and false-negative SLNBs) we did not find significant differences among compared groups.

5. DISCUSSION

The biopsy of the guard or sentinel lymph node currently represents a standard procedure during axillary surgery in the treatment of early invasive breast cancer.

However, SLN biopsy is a multidisciplinary, minimal-invasive surgical technique whose complications (as opposed to other purely surgical techniques) are detected only a few years and even decades after the end of the surgical treatment and is therefore a very important multi-year evaluation of patients undergoing SLNB.

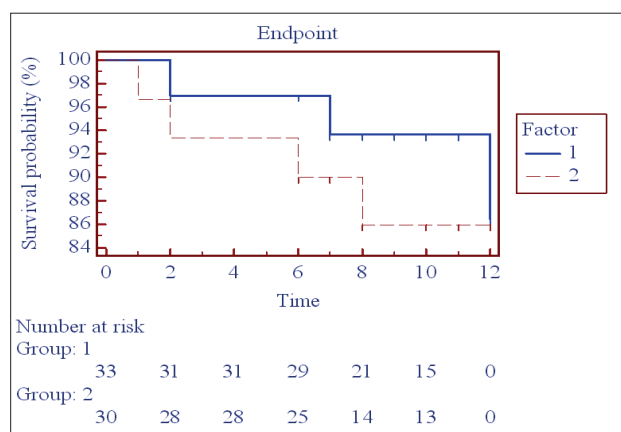


Figure 1. The survival curve of patients of both groups (SLNB positive vs SLNB negative)

The biggest dilemma associated with the use of SLN biopsies is overall survival of patients and local-regional recurrence in relation to complete ALND and the question of treatment of micrometastases (<0.2 mm) and isolated tumor cells (ITC) in positive SLN.

In this respect, several clinical trials were conducted to analyze the overall survival and percentage of local-regional recurrence in the SLN biopsies method such as „National Surgical Adjuvant Breast and Bowel Project (NSABP) B-04“, a study which showed that the multi-year follow-up course had 1 axillary recursion for every 2.2 patients without the use of systemic therapy and irradiation. However, studies „NSABP B-32“ and „International Breast Cancer Study Group 23-01“ (IBCSG) reduced the occurrence of 1 axillary relapse in every 13 to 14 patients with metastasis in lymph nodes but both studies used chemo and radiotherapy in over 70% of patients examined. A further reduction of the reported 1 recurrence ratio to every 30 patients with positive lymph nodes was recorded by the „ACOSOG Z0011“ clinical trial, but there was also a higher percentage of patients who were referred for postoperative adjuvant therapy (11-15).

The questions of micrometastases (<0.2mm) in treatment of early invasive breast cancer were evaluated by the aforementioned „IBCSG 23-01“ study whose results showed that the DFS was similar (87.8% vs. 84.4%, p=0.16) between SLNB and CALND (16).

The multicentric clinical study „AATRM 048/13/2000“ has been divided into two groups of patients with early invasive cancer (T<3.5 cm, clinical N0, M0) and SLN micrometastases in axilla—one group was subjected to CALND and the other only for clinical observation. The results of the 5-year follow-up study showed that patients with CALND had 13% additional positive nodes and that there was no significant difference in DFS (p=0.33) between patients undergoing complete ALND and observation (17).

The current dilemma in the treatment of axillary lymph nodes is the question of the use of axillary surgery or radiotherapy in patients with positive SLN nodes. The clinical study „AMAROS“ divided and compared the patients in two groups with regard to the treatment of axilla (a) CALND and b) radiotherapy (RT) after positive SLN biopsy. The study showed that there was no additional benefit from the complete ALND versus RT in the DFS (86.9% in the CALND

group vs. 82.7% in the RT group, $p=0.18$) (18).

Although local-regional recurrence usually occurs within the first two years of follow-up, in our work according to available medical documentation of patients, we did not record any case of axillary recurrence (AR) during the long-term monitoring of patients in our study where only SLNB was performed (19, 20).

Regarding the treatment duration (postoperative stay up to 7 days) between the two study groups, statistically significant shorter postoperative hospitalization ($p=0.0012$) was observed in patients from the group with only SLN biopsy expected as CALND followed a much higher percentage of postoperative complications compared to SLN biopsy (21, 22).

Unfortunately, we were not able to include and compare the data on postoperative long-term morbidity (lymphedema, mobility, pain, paresthesia, etc.) in the study of patients with only SLN biopsy versus CALND.

In our study, we also observed statistical significance ($p=0.0412$) regarding the incidence of „Luminal A“ submolecular breast cancer type corresponding to the data available from the relevant data that Luminal A represents 50-60% of all molecular breast cancer subtypes (23).

Regarding the type of surgical interventions in the breast, in our study dominated partial types of surgery in both groups, in over 80% ($n=51/63$, $p=0.0363$), which goes in favor of the fact that the relationship between tumor size and breast size plays an important role in determining the type of breast treatment.

Also, we had one case of false positive SLN on the definitive pathohistological (PH) finding of lymph node axilla which represents a significantly less dangerous complication of PH evaluation of the axillary lymph node than the false negative SLN biopsies found in two patients in our study the consequences of which can occur years after surgical treatment.

During the long-term evaluation of patients with SLN biopsy and complete ALND we had 9 lethal outcomes (Table 2). Out of the total number of deaths, three cases are a direct or indirect consequence of the occurrence of regional metastatic changes (lung, bone). Of the three cases mentioned above, it should be noted that in two cases, in the „ex tempore“ of dissected SLNBs micrometastases were found.

Such findings may indicate that patients with metastatic presence in SLNB should pay special attention during postoperative long-term evaluation although the results of randomized clinical trial „The ACOSOG Z0011 phase 3“ indicate that in patients with T1 and T1 stage breast cancer without palpable axillary lymphadenopathy case 1 or 2 positive SLN, 10-year overall survival (OS) of patients treated with SLNB alone is not less than 10-year OS in patients treated with complete ALND (24).

The remaining six cases with a lethal outcome that we had during the long-term follow-up of patients were the result of other pathological conditions (cardiovascular, neurological, etc.) that are not directly related to primary oncological disease.

Generally, patient follow-up after SLN biopsies is life-long, as well as in all patients treated for breast cancer, regardless of the type of surgical method.

6. CONCLUSION

Regardless of the relatively small sample in our study, our research has shown that during the long-term monitoring of patients with only SLNBs, the percentage of local-regional relapse and mortality is without significant difference compared to the complete ALND, while significantly reducing postoperative duration of treatment.

- **Author's contribution:** S.P. gave substantial contribution to the conception or design of the work and in the acquisition, analysis and interpretation of data for the work. S.P. had role in drafting the work and revising it critically for important intellectual content. Each author gave final approval of the version to be published and they are agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.
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- **Conflicts of interest:** There are no conflicts of interest.

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