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Sentinel Lymph Node Biopsy In Breast Cancer: Validation Study And Comparison Of Lymphatic Mapping Techniques

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ABSTRACT

Introduction: Sentinel lymph node biopsy is a standard staging procedure in patients with early breast cancer. Aim of the study is a validation procedure of sentinel lymph node biopsy (SLNB) in our institution and comparison between two mapping techniques - isotope mapping and methylene blue dye for lymphatic mapping.

Material and methods: The study comprised 75 women with breast cancer of clinical stage T1-2N0M0. We analyzed patients from June, 2010 to March, 2013. In 39 patients, (Group A) lymphatic mapping technique was performed by using the peritumoral injection of 37MBq activity isotope (99m Technetium NANOCIS),and in 36 patients (Group B) mapping technique was performed by using the periareolar injection of 2-4 ml blue dye (Methylene blue 1%). Axillary dissection was performed in both groups after SLNB.

Results: Out of 75 patients, sentinel lymph node was identified in 68 (90.7%). Identification rate was similar between the groups - 89.7% (Group A), 91.7% (Group B). Accuracy rate was 97% between the groups, that is, Group A 97.1% and Group B 96.9%. In relation to the Group A (90.6%), sensitivity rate was slightly higher in the Group B - 91.6%,. False negative rate of SLNB was higher in the Group A (9.1%) in relation to the Group B (8.3%). The average number of sentinel nodes detected in both groups was 1.2.

Conclusion: The results of the study confirmed and validated both methods of lymphatic mapping techniques in SLNB. There were no significant statistical differences ($p>0.05$) in accuracy, sensitivity and false negative rate between these two groups.

Keywords: breast cancer, sentinel lymph node biopsy, isotope, blue dye

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Introduction

On the basis of numerous clinical studies carried out over many years, the procedure of sentinel lymph node biopsy (SLNB) was taken as a valid procedure in diagnosing lymph node axillary metastasis in invasive breast cancer.[1-3]

In clinical manuals, the following methods of marking, that is, mapping of sentinel lymph node (SLN), are recommended: isotope mapping method, blue dye mapping method and a combined mapping method with blue dye and isotope.[4,5] Before SLNB introduction, validation studies were conducted with the aim to determine predictive values of sentinel lymph node in relation to the status of other lymph nodes in the axilla, and, at the same time, to practice surgical teams in the procedure conducting.[6-9] Practical importance of SLNB procedure can be seen in significant decreasing of postoperative comorbidity (lymphedema, parenthesis, pain, etc.) in relation to the patients who underwent axillary lymphadenectomy.

The study conducted in our institution had an aim to determine procedure validity and compare the methods of SLN blue dye mapping (methylene blue) and isotope (Technetium, 99Tc).

Materials and methods

The study was conducted in Clinical Center Banja Luka in the period from June, 2010 to March, 2013. It was approved by the Ethic Council of Clinical Center Banja Luka. 75 patients who fulfilled the criteria for participating in study were analyzed in this period. Sentinel biopsy procedure was first introduced to the patients and they gave a written consent to participate in the study. The patients fulfilled the following criteria to enter the study: female patients, 30-year-olds and more, histologically verified primary invasive breast cancer, unifocal tumor in a breast, clinical axillary area without dubious palpable lymph nodes, ultrasound check up without visualization of dubious infiltrated lymph nodes, clinic stage T1/2NoMo, that in the past, lymph node sentinel biopsy in axillary area was not performed, that axillary area was not treated by rays and/or operated, that a patient was not pregnant, and that a patient previously did not receive neoadjuvant chemotherapy.

The patients with histologically verified invasive breast cancer were separated in two groups: patients in which sentinel lymph node mapping was performed by isotope application (Group A), and in which sentinel lymph node mapping was performed by blue dye (Group B).

In Department of Nuclear Medicine of Clinical Center Banja Luka, radioisotope technetium-nano-sulphur colloid used in sentinel lymph node mapping procedure was obtained from pharmaceutics nano-sulphur colloid (Cis Bio international Paris, France) and technetium pertechnetate (Tc99m). Preoperatively, in the case of a palpable tumor, radioisotope was applied subcutaneously peritumoral. In a case of a non-palpable tumor, radioisotope was applied periareolar, usually four puncture spots in the amount of 0.2ml per puncture spot in a dose of 0.25mCi (9.25MBq), that is in total, 0.8ml in radioactivity dose 1mCi (37MBq). The procedure was conducted 1 to 4 hours prior to an operation. Sentinel lymph node was intra-operatively detected by mobile gamma camera. Mobile gamma camera "Europrobe" (Lyon, France) was used for detection. While detecting, one or more sentinel lymph nodes were identified.

Figure 1. Mobile „gamma" probe

All identified sentinel nodes were analyzed histopathologically intra-operatively ("ex tempore") on frozen sections, and afterwards, on permanent paraffin molds, depending on size and number of samples, by standard method of dyeing hematoxylin-eosine (HE).

During the operation, mobile gamma camera detected a place of greatest radiation, and after extirpation, radiation level of an extracted sentinel node was detected on a counter. As a proper parameter, a radiation detection 10 times bigger in relation to surrounding tissue was taken.[2,3] After performed sentinel lymph node biopsy, axillary lymphadenectomy was performed in all patients in the group. Total number of analyzed patients in Group A was 39 women.

In the other group (Group B), sentinel lymph node mapping was performed by method of dyeing with blue dye (Methylene blue 1%), which is in our conditions available because of its economic acceptability. Methylene blue has smaller molecular weight in relation to patent blue and isosulphan blue. Immediately after giving anesthetic to the patient, blue dye (1% Methylene blue) was applied subcutaneously periareolary to a breast quadrant where a tumor was localized in amount of 2 to 4ml. After blue dye application, a gentle massage of a breast was done for 2-3 minutes in order to stimulate lymph drainage. In interval

from 15 to 20 minutes from dye application, incision and exploration of axillary area and visual identification of sentinel lymph node were performed. After identification and extirpation of sentinel lymph node, axillary lymphadenectomy was performed in this group of patients as well. 36 women were analyzed in Group B.

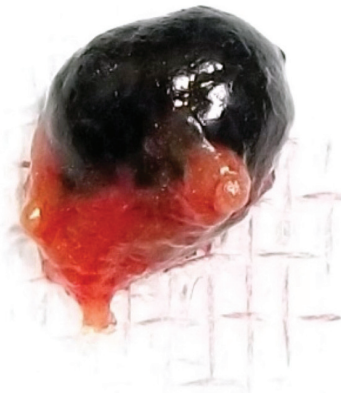

Figure 2. Sentinel lymph node mapped by blue dye

χ^2 test, Fisher's exact test, Yates correction for continuity, Mann-Whitney's Test and Kolmogorov–Smirnov test were used in the analysis. Analytical statistical tool SPSS – version 20 was used in statistical data processing.

Results

In statistical analysis of the patients, the following characteristics of examined groups were processed: age, tumor size, histological grade of a tumor, histological type of a tumor, lymph-vascular and perineural invasion of a tumor, immune-histochemical determined hormone status of a tumor and expression of HER2 gene. In the examined groups, model of an applied surgical treatment was analyzed.

Iin the attached statistical data analysis, except for the type of operation, there is no proved statistically significant difference between examined Groups A and B, according to their general characteristics.

In data related to sentinel biopsy, the following are processed: identification rate, accuracy rate, sentinel biopsy sensitivity rate, false negative results rate, average number of extracted sentinel lymph nodes and presence of micrometastasis in a sentinel lymph node and their correlation with other lymph nodes in dissection of axillary lymphatics.

In Group A, where mapping was performed by isotope, identification rate in the study was 89.7%, while in group B, where mapping was performed by blue dye, the rate was 91.7 %. In Group A, accuracy rate was 97.1% and in group B 96.9%. Our results showed 90.9% sensitivity rate in Group A and 91.6% in Group B. False negative results rate in Group A was 9.1% and in group B 8.3%. Statistically significant difference between examined groups was not determined by using Fisher's test (p=1.000).

Table 1. Characteristics of examined patients and tumors

Characteristics	Group A (Radiotracer 99mTc) n=39	Group B (Methylene blue) n=36	P
Median age (years)	58.6	59.9	0.983*
Median tumor size (mm)	20.5	21.7	0.644*
Histological type			
Invasive ductal carcinoma (NOS)	26 (66.7%)	30 (83.3%)	
Invasive lobular carcinoma	7 (17.9%)	1 (2.8%)	
Hystological grade of tumor			0.068**
Grade 1	9 (23.1%)	2 (5.6%)	
Grade 2	18 (46.1%)	24 (66.7%)	
Grade 3	12 (30.8%)	10 (27.7%)	
ER/PR positive	35 (89.7%)	28 (77.8%)	
ER/PR negative	4 (10.3%)	8 (22.2%)	
HER2 positive	3 (7.7%)	9 (25.0%)	
HER2 negative	36 (92.3%)	27 (75.0%)	
Type of surgery			0.007**
Modified radical mastectomy	7 (17.9%)	18 (50.0%)	
Breast conserving surgery	24 (61.5%)	16 (44.4%)	
Skin sparing mastectomy	8 (20.6%)	2 (5.6%)	
Side of tumor			0.076**
Right breast	17 (43.6%)	24 (66.7%)	
Left breast	22 (56.4%)	12 (33.3%)	
Localization of tumor			
Outer upper quadrant	12 (30.8%)	10 (27.8%)	
Junction of upper quadrants	9 (23.1%)	5 (13.9%)	
Upper inner quadrant	16 (41.0%)	6 (16.6%)	
Others	16 (41.0%)	15 (41.7%)	

* - Mann Whitney test, **- c-square test

Table 2. Sentinel biopsy results

	Group A (Radiotracer 99mTc) n=39	Group B (Methylene blue 1%) n=36	P
Identification rate	35/39 (89.7%)	33/36 (91.7%)	1.000*
Accuracy rate	34/35 (97.1%)	32/33 (96.9%)	1.000*
Sensitivity rate	10/11 (90.9%)	11/12 (91.6%)	1.000*
Positive predictive value	100%	100%	
Negative predictive value	96.0%	95.4%	
False negative rate	1/11 (9.1%)	1/12 (8.3%)	
Mean number of SLNs	1.2	1.2	

* - Fisher's exact test

Discussion

So far, many conducted comparative studies showed that a percentage of sentinel lymph node identification by usage of double method was bigger in relation to mapping using only blue dye or isotope. In comparison of sentinel lymph node mapping methods with blue dye and mapping with isotope, there was no statistically significant difference related to accuracy rate, sensitivity rate and false negative results rate of a sentinel node.[10-12] Dilemma whether to use just one reagent or both in the sentinel biopsy procedure is still without consensus and for now, there are only recommendations.

Because of its acceptable price, methylene blue is a dye which is available for all the health institutions. In the case of dye validity, methylene blue dye in a sentinel biopsy procedure, in relation to the other two (patent blue, isosulphane), previously conducted studies did not confirm superiority of patent blue and isosulphane in relation to methylene blue dye. The results of these studies showed that methylene blue dye is valid in sentinel biopsy procedure. There was no statistically significant difference in efficiency of sentinel biopsy procedure in relation to the method of dyeing with methylene and isosulphane or patent blue dye.[13-15] Disadvantage of the studies dealing with methylene blue dye used in sentinel biopsy procedure was in a number of analyzed patients. Those were usually single institution studies involving a relatively small number of patients. Vital methylene blue dye related to patent and isosulphane dyes has certain advantages, such as lower price and low allergy potential, but it also has some disadvantages which reflect in lower resorption in lymph flow, in relation to the other two dyes. In our study, we applied methylene blue dye in 36 patients. In all examined patients who underwent sentinel biopsy procedure with methylene blue dye, we did not record any kind of allergic reactions. As for side effects, only mention temporary pigmentation of skin in the place where dye was injected and temporary urine discoloration is worth mentioning.

Nowadays, there is still no clear consensus and attitude about optimal spot for application of isotope and blue dye. There are two basic localizations for marker application. One technique is to apply isotope or blue dye in the tumor area, that is peritumoral, and the other one is based on applying the marker in the area of areolar complex, that is periareolar. The other dilemma concerns the depth of marker application; one option recommends superficial, subcutaneous application, and the other one recommends deeper, that is parenchyma marker application.

British study (The New Start) and French study (FRANSENODE) note that optimal spot for dye application is periareolar localization towards a breast quadrant of the tumor location, so as subcutaneous dye injection.[7,16] We practiced methylene blue dye application in periareolar area subcutaneously towards a breast quadrant where the tumor change was localized. This type of application is also more practical at non-palpable lesions.

In more extensive studies, identification rate was from 80% - 99%.[1-3,6] On the basis of the results of the studies done so far, in most cases ,double method of sentinel node mapping has the biggest identification rate. Validity and success of SLNB procedure is valued on the basis of accuracy rate. SLNB accuracy rate in more extensive studies was from 95-99%.[2,3,9] Sensitivity rate in study NSABP B-32 in mapping SLN by blue dye was 87.8%, while isotope mapping was more successful with 92.2%.[3] In some studies, sensitivity was greater in patients who underwent SLN mapping by blue dye.[17] Many studies indicated bigger sensitivity rate in SLN mapping by double method.[2,9] One of the first validation studies done at the area of former Yugoslavia showed blue dye sensitivity rate at 82% and double method at 95%.[18] SLN false negative results rate in the studies varied from 2-22%.[19-21] In the studies involving greater number of examined patients, false negative results rate was from 6.7%, 8.2% to 11.4%.[9,22,23] Results of validation study conducted in our institution pass all criteria set by most of training programs and recommendations of oncology associations dealing with introduction of SLNB procedure in standard use.

In present micro-metastasis in SLN, without any official confirmation in the form of clinical manuals, the attitude which is becoming more and more common is not doing the axillary lymphadenectomy. On the basis of obtained results of the study IBCSG 23-01 there was no statistically significant difference in five years period without disease (DFS, Disease free survival) between a group of patients who underwent lymphadenectomy and a group of patients who did not undergo lymphadenectomy after verified

metastasis in SLN.[24] In our study, micrometastatic deposits in SLN were verified in four patients, and observing the state of other lymph nodes in lymphadenectomy preparation, there were no verified metastatic deposits.

Recent studies (ACOSOG Z0011 trial) have given the results which are still discussed by experts, and they are related to an attitude that axillary lymphadenectomy in early invasive breast cancer should not be done, not even if macrometastasis of breast cancer are histologically verified in sentinel lymph node.[25] In such cases, axillary area would undergo radiotherapy. The results of the American study Z0011 showed that there were no statistically significant difference between examined groups of patients regarding the overall survival (OS, Overall Survival) and a period without disease (DFS) in women who underwent axillary lymphadenectomy and those who underwent radiotherapy of axillary area after histologically verified macro-metastasis in SLN.[25] A study of European Oncology Institute in Milan (SOUND trial) went even further, stating that in the case of early invasive breast cancer with clinically negative axillary area, nothing more than an observation should be done.[26] An attitude of experts about this is not unanimous.[27] German, Austrian and Swiss Senologic Society still withhold their attitude towards this subject.[28] Their recommendation is to avoid lymphadenectomy in positive SLN only in groups of patient with a low risk for disease return and clinically and ultrasonographicly negative axillary area.

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Sentinel biopsija limfnog čvora kod karcinoma dojke: Validaciona studija i komparacija metoda obeležavanja sentinel čvora

SAŽETAK

Cilj: Sentinel biopsija limfnog čvora je standard u tretmanu pacijenata oboljelih od ranog invazivnog karcinoma dojke. Cilj istraživanja je standardizacija procedure sentinel biopsije u našoj ustanovi i poređenje metode obilježavanja sentinel limfnog čvora između tehnike obilježavanja radiofarmakom i tehnike obilježavanja tkivnom bojom.

Materijal i metode: U istraživanju je učestvovalo 75 žena oboljelih od karcinoma dojke sa kliničkim stadijumom T1/2N0M0. Ispitanice su analizirane u periodu od juna 2010. godine do marta 2013. godine. Kod 39 ispitanica (Grupa A), za obilježavanje sentinel čvora korišćen je radiofarmak Tehnecijum aplikovan peritumorski u aktivnosti od 37MBq. Kod 36 ispitanica (Grupa B), za obeležavanje je korišćena 1% tkivna boja metilen plavo koja je aplikovana periareolarno u volumenu od 2-4ml. Disekcija aksilarnih limfatika sprovedena je kod svih pacijentkinja nakon procedure sentinel biopsije.

Rezultati: Od ukupno 75 analiziranih ispitanica, sentinel limfni čvor je identifikovan kod njih 68 (90,7%). Stopa identifikacije bila je slična između poređenih grupa - u grupi A iznosila je 89,7% , a u grupi B 91,7%. Stopa preciznosti iznosila je 97%, između poređenih grupa 97,1% (Grupa A) i 96,9% (Grupa B). Stopa senzitivnosti je bila nešto veća u grupi B (91,6%) u odnosu na grupu A (90,9%). Stopa lažno negativnih nalaza sentinel limfnog čvora bila je veća u grupi A (9,1%) u odnosu na grupu B (8,3%). Prosečan broj izvađenih sentinel čvorova iznosio je 1,2.

Zaključak: Rezultati istraživanja potvrdili su validnost obe metode obilježavanja kao i samu proceduru sentinel biopsije. Između poređenih grupa nije bilo značajne statističke razlike (p>0,05) u odnosu na stopu identifikacije, preciznosti, senzitivnosti i lažno negativnih nalaza.

Ključne riječi: karcinom dojke, sentinel biopsija, radiofarmak, tkivna boja