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Sentinel Lymph Node Biopsy after Neoadjuvant Treatment for Breast Cancer. The Validation Protocol

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Rezumat

Protocol de validare a identificării și biopsiei ganglionului santinelă la pacientele cu neoplasm mamar și chimioterapie neoadjuvantă

Introducere: Identificarea şi biopsia ganglionului santinelă (SLNB) la pacientele cu cancer mamar ce necesită tratament citostatic neoadjuvant (NAC), cu ganglioni limfatici clinic negativi în urma tratamentului, poate reprezenta o metodă eficientă de de-escaladare a intervențiilor chirurgicale axilare.
Material şi Metodă: Este un studiu prospectiv care cuprinde 47 de cazuri de cancer mamar stadiul IIB-IIIA, cu tratament NAC şi răspuns clinic şi imagistic axilar complet, operate la Institutul Oncologic „Prof. Dr. Alexandru Trestioreanu" din Bucureşti (IOB) de către aceiaşi echipă, la care a fost practicată SLNB folosind metoda cu trasor radioactiv. Tehnica SLNB cu trasor radioactiv Tc99 presupune: - injectarea trasorului radioactiv şi limfoscintigrafie pre-operatorie, - identificarea intraoperatorie a ganglionului/ganglionilor santinelă şi biopsia excizională a acesora, - examenul histopatologic intraoperator, la parafină şi imunohistochimic al ganglionului santinelă (SLN).
Rezultate: SLN a fost identificat în 46 din 47 de cazuri. În 19 cazuri SLN a fost pozitiv, iar în 2 cazuri am înregistrat rezultate fals negative. Toate pacientele au beneficiat de limfadenectomie axilară standard (Back-up lymphadenectomy). Corelația dintre examenul histopatologic intraoperator şi la parafină al SLN cu examenul la parafină şi imunohistochimic al restului ganglionilor axilari (N-SLN), au condus la următoarele rezultate ale metodei: sensibilitate 91% (19/21), specificitate 100% (25/25), valoarea predictivă pozitivă 100% (19/19), valoarea predictivă negativă 94% (25/27). Acuratețea metodei a fost de 96% (44/46). Invazia SLN a fost mai frecventă la

pacientele cu tumoră reziduală > 2 cm (vs T ≤ 2 cm) (p = 0.01), ganglioni N-SLN pozitivi (vs N-SLN neinvadați) (p=0.003). N-SLN au fost mai frecvent invadați atunci când a existat invazie limfocitară peritumorală (vs fără invazie) (p=0.01).
Concluzii: SLNB la pacientele cu neoplasm mamar ce necesită NAC, cu ganglioni limfatici clinic şi imagistic negativi în urma tratamentului, prezintă o rată mare de specificitate şi un număr acceptabil de rezultate fals negative. Invazia ganglionară este mai frecventă la pacientele cu tumori reziduale > 2 cm, cu invazie limfovasculară prezentă sau cu boală multicentrică/multifocală.

Cuvinte cheie: neoplasm mamar, ganglion santinelă, tratament neoadjuvant

Abstract
Introduction: The identification and biopsy of the sentinel lymph node (SLNB) in breast cancer patients requiring neoadjuvant cytostatic treatment (NAC), with clinically negative lymph nodes following treatment, may be an effective method of de-escalation of axillary surgery.
Materials and methods: This prospective study includes 47 cases of breast cancer stage IIB-IIIA, with NAC treatment and complete axillary clinical and imaging response, surgeries performed at Prof. Dr. Alexandru Trestioreanu Oncological Institute in Bucharest (IOB) by the same team. In all the cases, SLNB was employed using the radioactive tracer method. The SLNB technique with Tc99 radioactive tracer involves: - injection of the radioactive tracer and preoperative lymphoscintigraphy, - intraoperative identification of the sentinel node/ lymph nodes and their excisional biopsy, - intraoperative histopathological examination, in paraffin blocks, and immunohistochemistry of the lymph node (SLN).
Results: SLN was identified in 46 of 47 cases. In 19 cases SLN was positive, and in 2 cases we recorded false negative results. All patients underwent standard axillary lymphadenectomy (back-up lymphadenectomy). The correlation between the intraoperative and paraffin histopathological examination of SLN with the paraffin and immunohistochemical examination of the rest of the axillary nodes (N-SLN) led to the following results: sensitivity 91% (19/ 21), specificity 100% (25/ 25), positive predictive value 100% (19/ 19), negative predictive value 93% (25/ 27). The accuracy of the method was 96% (44/ 46). SLN invasion was more common in patients with residual tumor > 2 cm (vs T ≤2 cm) (p = 0.01), positive N-SLN (vs non-invaded N-SLN) (p = 0.003). N-SLNs were more frequently invaded when there was peritumoral lymphocyte invasion (vs. no invasion) (p = 0.01).
Conclusion: SLNB in patients with breast cancer who require NAC, with clinically and imaging negative lymph nodes following treatment, has a high rate of specificity and an acceptable number of false negative results. Node invasion is more common in patients with residual tumors > 2 cm, with lymphovascular invasion or with multicenter/ multifocal disease.

Key words: breast cancer, sentinel lymph node, neoadjuvant treatment

Introduction

The incidence and mortality due to breast cancer in Romania are constantly increasing (1). Unfortunately, because of the lack of a breast cancer screening program, more than half of the newly diagnosed cases are in stages III and IV of the disease.

Locally advanced stages of breast cancer benefit from neoadjuvant chemotherapy (NAC), with the goal of increasing resectability and conservative treatment rate, increasing survival, and assessing the *in vivo* response of the tumor to the systemic treatment (2,3). Knowing the status of the regional lymph nodes is essential because it is one of the

most important prognostic factors and contributes to the contouring of the oncological treatment plan (4,5).

The clinical assessment of the axillary lymph nodes is not always reliable, with high percentages of false positive and false negative estimates, thus, low sensitivity and specificity. The concept of sentinel node (SLN) is based on the theory of sequential dissemination of cancers via the lymphatic pathways. The invasion initially occurs in a first node that drains the lymph from the tumor. The identification and excisional biopsy of the sentinel lymph node (SLNB), its histopathological and immunohistochemical examination are allowing the assessment of the status of the regional lymph nodes and the establishment of the indication for regional lymphadenectomy. Although in the less advanced stages of the disease SLNB has proven its effectiveness, the role of this biopsy after NAC still raises many debates, mainly due to important variations in terms of identification rate and false negative results (5-10).

Axillary lymphadenectomy remains, unfortunately, the most used method in patients with breast cancer treated with NAC, both in terms of local control of the disease and in obtaining prognostic information and subsequent oncological therapeutic indication. The deviation from this routine has been the subject of several published studies on NAC followed by SLNB, with the intention to avoid the morbidity associated with axillary lymphadenectomy after NAC (10,11).

The aim of our prospective study was to assess the accuracy of SLNB after NAC, as well as to establish the clinical and pathological factors that correlate with SLN invasion.

Materials and Methods

This prospective study includes 47 consecutive cases of stage IIB-IIIA breast cancer, with NAC treatment and complete clinical and imagistical axillary response, operated at Prof. Dr. Alexandru Trestioreanu Oncological Institute in Bucharest by the same team during 2011-2013, surgeries performed with SLNB using the radioactive tracer method.

Malignancy diagnosis was confirmed by breast tumor core biopsy with histopathological and immunohistochemical examination preoperatively. The disease was staged according to the American Joint Commission 6th Edition, TNM 2012 (12). All patients underwent mammography and ultrasound examination both on diagnosis and preoperatively, after completion of NAC (*Figs. 1,2,3*). The study was approved by the Ethics committee, and informed consent was obtained from each patient enrolled in the study.

The patients benefited from NAC according to the following therapeutic protocol (FAC): 6 series of treatment with 5-Fluorouracil 500 mg/m^2, Adriamycin 50 mg/ m^2, Cyclophosphamide 500 mg/ m^2.

After completion of chemotherapy, clinical evaluation and local imaging considered a complete axillary clinical response in patients

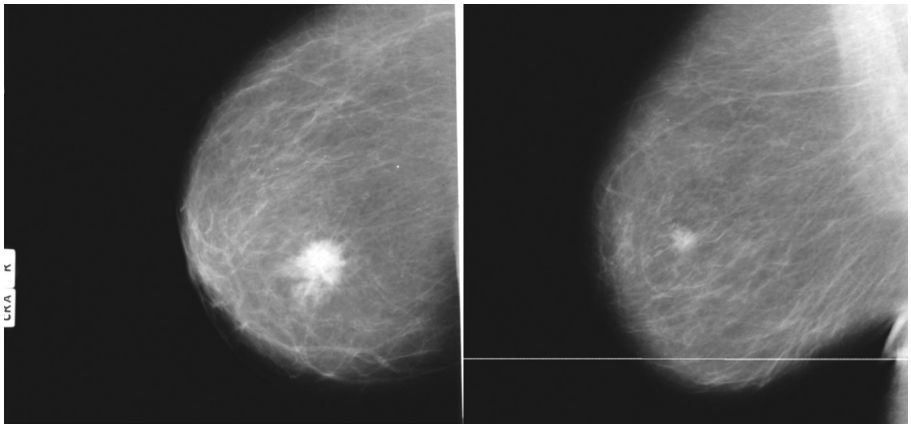

Figure 1. Breast cancer: Mammographic examination before and after NAC

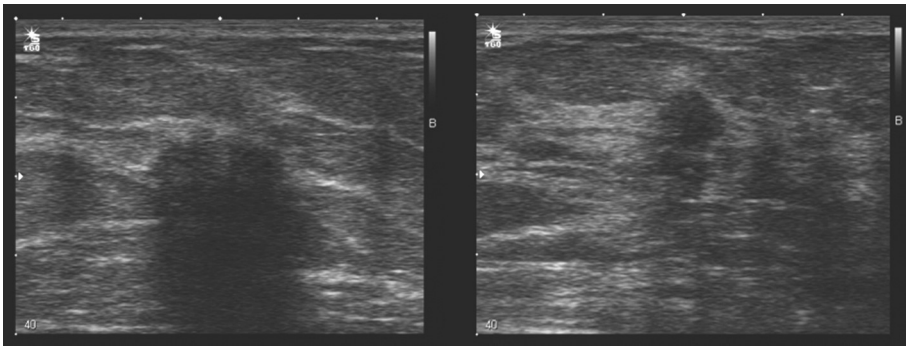

Figure 2. Breast cancer: pre- and post-NAC ultrasound examination

without palpable suspicious lymph nodes, and from an imagistical point of view the absence of ultrasound-suspicious ipsilateral axillary lymph nodes (*Fig. 2*).

We performed SLNB in 47 patients using the Technetium-99 (Tc99) radioactive tracer method (13). The injection of the radioactive tracer was performed peritumorally, with a minimum of 6 hours and a maximum of 24 hours preoperatively (*Fig. 7*). If the tumor was non-palpable after NAC, preoperative localization of the breast lesion was performed by imagistical methods (14) (*Figs. 4, 5, 6*). Intraoperative detection of the sentinel node was performed using a portable gamma probe by detecting the radioactive tracer in the sentinel node, the so-called "hot node" – "hot spot", which was sent first for frozen sections examination, and, subsequently, for paraffin embedded sections and for immunohistochemistry (*Fig. 9*). Standard axillary lymphadenectomy (back-up lymphadenectomy) was then performed on all patients. Regarding the surgical treatment of the primary breast

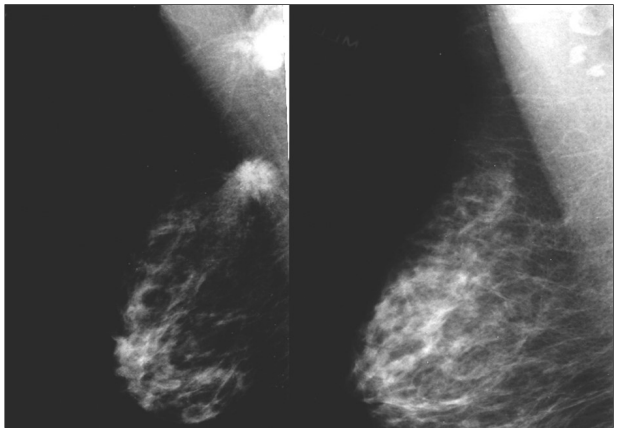

Figure 3. Mammographic appearance of primary tumor and axillary lymph nodes before and after NAC

tumor, patients received conservative treatment with/ without oncoplastic surgery (n = 19) or mastectomy with/without immediate reconstruction (n = 28), according to the initially established surgical therapeutic plan (15-17).

The intraoperative histopathological examination of the sentinel node was performed by frozen sectioning without prior fixation of the

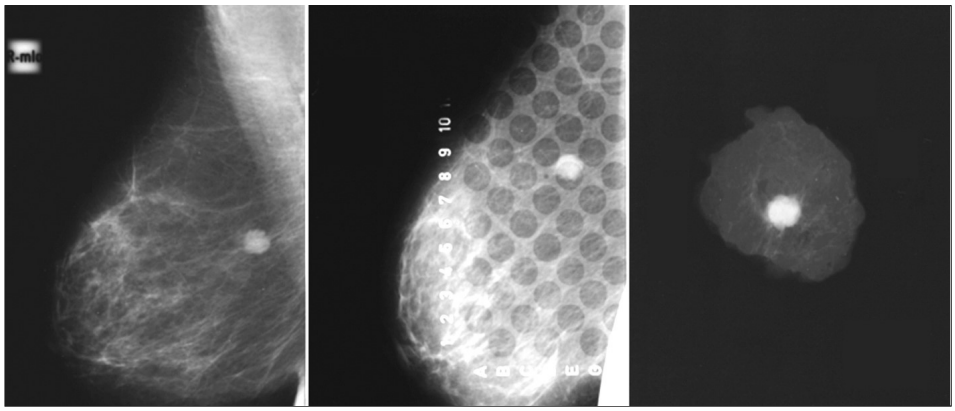

Figure 4. Preoperative mammographic localization of the breast tumor with complete clinical response after NAC and radiography of the specimen after tumor excision

Figure 5. Intraoperative ultrasound localization of the breast tumor with complete clinical response after NAC

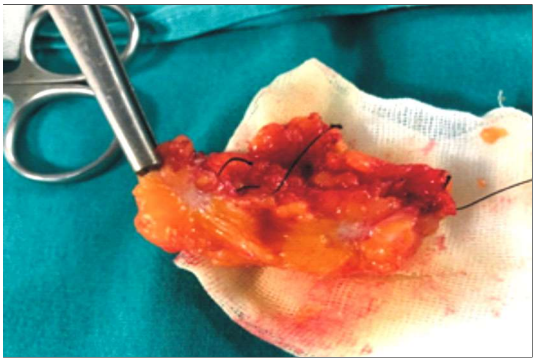

Figure 6. Macroscopic appearance of the breast tumor shrink after NAC

piece, or at the freezing microtome after prefixation by boiling in 10% formalin (minimum 2 sections). For a rapid staining, toluidine blue was used, the slides were read under an optical microscope. The remaining fragment, as well as the additional fragments necessary to evaluate the tumor extension, were included in serially sectioned paraffins. Staining of paraffin sections required preliminary deparaffinization steps in 3 successive baths of toluene solvent, then hydration of the sections by successive ethyl alcohol baths in progressively decreasing concentrations. The histological sections (performed at 2 mm) were assessed microscopically with hematoxylin-eosin (HE) and using special staining techniques to identify various tumor components (18).

For immunohistochemical (IHC) detection of tissue antigens we used the indirect three stage Avidin-Biotin-Peroxidase (ABC) method.

Figure 7. Peritumoral injection of the radioactive tracer

Statistical Analysis

Statistical analysisof the data was performed using the EPI-INFO version 7.1 software, developed and distributed by the Center for Disease Control and Prevention, Atlanta, USA, the World Health Organization, Geneva,

Figure 8. Preoperative lymphoscintigraphy

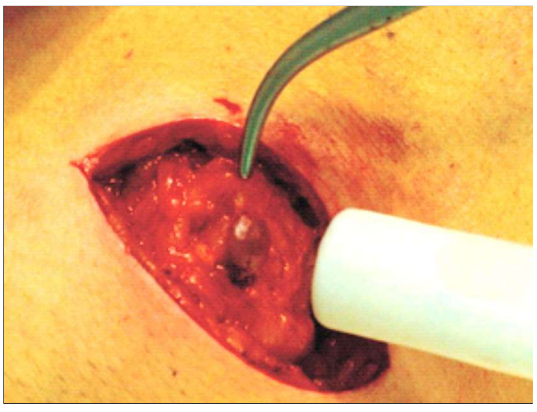

Figure 9. Intraoperative appearance of sentinel node identification and biopsy

Switzerland (WHO), and NCSS Statistical Software, developed and distributed by NCSS, Utah, USA. The 2x2 tables used allowed the calculation of sensitivity, specificity, negative, and positive predictive value. When the histopathological examination of the sentinel node was negative and metastatic disease was found in other lymph nodes on the lymphadenectomy (back-up lymphadenectomy) specimen, we considered the result to be false negative. Relative risks and confidence intervals such as statistical significance were obtained by the Chi-square Testt for each comparison. Independent of these 2 parameters, the real value of the p-index was also calculated to assess the statistical significance of the relative risk values and the confidence interval. A "p" value <0.05 was considered statistically significant.

Results

The onset form of the disease with the highest frequency was represented by the appearance of a breast tumor, a situation found in 83% (39 of 47 patients) of the cases that the studied group comprised.

Breast tumor was detected in 66% (31 patients) of cases by the patient by self-examination, in 17.03% (8 patients) by the physician's clinical examination, in 13% (6 patients) of cases by mammographic examination, and in 4% (2 patients) of cases the tumor was discovered by medical examination performed for other conditions.

The study group included patients aged between 31 and 69 years, with a mean age of 53.21 years. Two age subgroups were highlighted by a higher number of cases: 41-50 years and 51-60 years, accounting for 30% (14 patients) and 36% (17 patients) of the patients studied.

Approximately 2/3 of the patients resided in urban areas, 30 patients (64%), and only 17 patients in rural areas (36%).

The distribution of patients according to hormonal status revealed a higher percentage of menopausal (60% - 28 patients) than premenopausal patients (40% - 19 patients)

The analysis of the breast tumor localizations in the studied group revealed the balanced distribution of the lesions located in the external quadrants (÷ 50%) compared with those located internally (÷ 35%) and centrally (÷ 15%).

The mean tumor diameter was 38 mm (on diagnosis), the tumor size varying between 6 and 62 mm. The correlation with tumor diameter by NAC is shown in *Table 1*.

The most common histopathological tumor type was invasive ductal carcinoma encountered in 76% of cases. The degree of tumor differentiation (G, Scarf-Bloom-Richardson) had the following distribution in the studied group: G1 – 21% (10 patients), G2 – 30% (14 patients), G3 – 49% (23 patients).

Peritumoral tissue invasion was observed on histopathological examination in 27 cases (57%), whereas 30 tumors (63%) had a peritumoral lymphocytic infiltrate.

In 60% of patients (28 cases) estrogen receptors (ER), and in 55% (26 cases) progesterone receptors (PGR) were positive. Ki-67 (cut-off value <14%) was positive in 16 patients (34%) from the studied group. The c-erbB-2 oncogene (Her-2/ neu) was overexpressed in 13 cases (28%).

The injection of the radioactive tracer was performed in 47 patients who had previously undergone NAC, patients who met the selection criteria. In 20 cases, in which the tumor was smaller than 10 mm, the injection was guided under imagistical techniques. Lymphoscintigraphy was performed after injection of the radioactive tracer and showed drainage of the ipsilateral axillary tracer (*Fig. 8*). The radioactive tracer did not migrate

Table 1. Tumor and lymph node features before and after NAC

n=47	Before NAC, cT, cN	After NAC, pT, pN
Mean tumor diameter	38 mm (limits 6-65 mm)	25 mm (limits 0-51 mm)
T0	0	5
T1	7	27
T2	34	13
T3	6	2
N0	6	26
N1	41	21

in one case, making SLN detection impossible.

In the 46 successful SLNB procedures, 27 patients were found with 1 SLN, 11 patients with 2 SLNs, 5 patients with 3 SLNs, 2 patients with 4 SLNs, and 1 patient with 5 SLNs (77 SLNs identified, with a mean of 1.67SLN/ case). All identified SLNs were located in the ipsilateral axilla. Metastatic invasion of SLN was recorded intraoperatively in 19 cases (40%) of all patients included in the group. In 2 cases (4%) we recorded false negative results (negative intraoperative SLN and positive N-SLN on microscopic examination after paraffin embedding). The correlation between intraoperative histopathological examination and the paraffin block of SLN with the assessment of the paraffin blocks and immunohistochemistry of the rest of the axillary nodes (N-SLN) led to the following results of the method: sensitivity 91% (19/21), specificity 100% (25/25), positive predictive value 100% (19/19), negative predictive value 93% (25/27). The accuracy of the method was 96% (44/46) (*Table 2*).

In 19 cases we found 26 SLNs with metastatic disease distributed as follows: in 13 cases a single invaded node was discovered, in 5 cases 2 invaded nodes, and in one case 3 invaded nodes were identified. The histopathological examination of the axillary resection specimen embedded in paraffin revealed other neoplasia invasion of the axillary nodes in 9 patients. In 12 cases, SLN was the only one invaded, with no positive lymph nodes discovered on axillary lymphadenectomy specimen.

We recorded 2 false negative results, in which, although SLN was free of the disease on the intraoperative histopathological examination and on the paraffin blocks, the examination of the axillary lymphadenectomy piece showed neoplasia invasion of N-SLNs.

Table 2. Histopathological results of axillary lymph nodes, SLN, and N-SLN

n=46	Back-up lymphadenectomy		
	+	-	Total
SLNB			
+	19	0	19
-	2	25	27
Total	21	25	46

The identification rate of SLN was statistically significantly higher in patients with tumors under 2 cm in diameter (vs. T ≤2 cm) (p = 0.04). The identification rate was not influenced by the patient's age, breast tumor location, degree of differentiation, or immunohistochemical type.

Node invasion was more common in patients with residual tumor > 2 cm (vs. T ≤2 cm) (p = 0.01), positive N-SLN lymph nodes (vs. non-invaded N-SLN) (p = 0.003). N-SLNs were more frequently invaded when there was peritoneal lymphocyte invasion (vs. no invasion) (p = 0.01).

Discussions

Axillary surgery is still an essential part of breast cancer treatment and has a diagnostic and curative purpose (19,20). The morbidity frequently associated with complete axillary dissection is mainly represented by lymphedema of the arm, while in the case of conservative treatment by lymphedema of the breast (20).

The first studies in the literature, related to the intraoperative identification rate of the sentinel node in breast cancer in patients with NAC, showed an identification rate that ranged between 66% and 100% (21). In our study group, we recorded a sentinel node identification rate of 97.8%, similar to data from the literature cited even for SLNB surgery in the absence of NAC.

In cases in which neoadjuvant systemic treatment has been performed, the identification and biopsy of the sentinel node is still a topic of discussion given the increased rate of false negative results (22, 23). The rate of false negative results recorded in this study is 4.25%, which is in the range of 4-6% accepted and published in the MD Anderson study (22).

Advances in NAC in recent decades have led to complete clinical and histopathological response rates of over 50% of cases in breast tumor and axillary lymph nodes (9, 10, 11, 22, 23). In this protocol for validating SLNB after NAC, a number of 25 patients (48.2%) with

clinical cN1and preoperative imaging had a complete histopathological response after NAC (pN-).

For the improvement of the technique after neoadjuvant treatment and the decrease of the number of false negative results, the pre-therapeutic marking of the invaded nodes, the dual detection (radioactive tracer and blue dye), and the excision of at least 3 axillary nodes are useful.

Axillary lymphadenectomy after neoadjuvant treatment can be avoided if no lymph node invasion is identified. Axillary lymphadenectomy is required after neoadjuvant treatment if lymph node invasion is found, even if it is limited to isolated cells or micrometastases (4, 24).

Conclusion

SLNB in patients with breast cancer requiring NAC, with clinical and imagistical negative lymph nodes following treatment, has a high rate of specificity and an acceptable number of false negative results and can be used safely in current practice. Node invasion is statistically significantly more common in patients with tumors > 2 cm remaining after NAC, in the presence of peritumoral lymphocyte invasion or with multicenter/ multifocal disease.

Conflict of Interest

The authors declare no conflicts of interests.

Ethics Approval

All procedures involving human participants were in accordance with the ethical standards of the 1964 Helsinki Declaration and its later amendments.

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