Feasibility of lymphoscintigraphy for sentinel node identification after neo-adjuvant therapy

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AIM: *To assess the sentinel-node identification rate at lymphoscintigraphy and its technical feasibility after neo-adjuvant treatments.*
MATERIAL OF STUDY: *Between 2000 and 2013, 444 consecutive patients affected by primary locally advanced breast cancer were enrolled in this study. All individuals were candidate for neo-adjuvant treatments and for lymphoscintigraphy before surgery.*
RESULTS: *The median age was 44 years at onset; almost one sentinel node was identified during lymphoscintigraphy in 430 cases. The detection rate at lymphoscintigraphy was 96.9% (95% CI, 94.8-98.1%). Considering the correlation between specific treatments and sentinel node identification rate, we verified that the detection rate did not vary significantly (p=0.53) according to the type of neo-adjuvant therapies administered to the patients.*
CONCLUSIONS: *Our results demonstrated that lymphoscintigraphy for sentinel node identification is a safe and feasible procedure after neo-adjuvant therapies, independently of treatment types.*

KEY WORDS: Breast Cancer, Neo-Adjuvant Treatment, Sentinel lymphnode biopsy, Lymphoscintigraphy

Introduction

Neo-Adjuvant Treatment (NAT) is a consolidated approach for the care of locally advanced Breast Cancer (BC). The main objective of NAT is to obtain a tumour down-staging [1] with a cytoreductive surgery that may comprise the sentinel lymph-node biopsy (SNB).
To date, the role of SNB in patients receiving NAT still remains controversial. The American Society of Clinical Oncology (ASCO) in 2014 defined specific guidelines for SNB indication; in general, NAT is not a contraindication for SNB and clinicians may offer SNB for women who have operable BC (2). However, this procedure seems less accurate after NAT, as there are currently discussions about two main issues, and in particular the false negative and the identification rates.
It has been theorized that systemic chemotherapy as local radiotherapy are responsible to alter lymphatic drainage causing a false negative rate in the SN detection during lymphoscintigraphy. In fact, some institutes discourage the SNB after NAT, due to the high failure of SN identification rate [3-6].
The aim of this study was to assess the SN identification rate at lymphoscintigraphy and its technical feasibility after NAT. We investigated a series of 444 consecutive patients affected by primary BC and candidate to NAT. All patients were observed retrospectively in a single-institution study.

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Methods

Patients' Characteristics

Four hundred forty-four patients affected by primary locally advanced BC were enrolled in this study (clinical staging cT1-4 cN0 or cN+ or who became cN0 after NAT). All individuals were eligible for NAT, including hormone therapy alone, chemotherapy alone, or chemotherapy plus hormone therapy. Patients were observed consecutively between 2000 and 2013 and treated at the European Institute of Oncology (IEO). NATs were performed either at the Institute or elsewhere. Clinical and biological data were prospectively collected in the IEO Breast Cancer database.
All patients gave informed consent and use of anonymized data was approved by the Institute's Review Board.

Lymphoscintigraphy

A subdermal injection of the radiotracer, ^{99m}Tc-labeled human albumin colloid particles (Nanoalbumon - Radiopharmacy laboratory Ltd., Budaors, Hungary - or Nanocoll - GE Healthcare S.r.l., Milan, Italy - at least 95% particle size ≤80 nm for both), was performed 2-20 hours before surgery in correspondence of the skin projection of the tumour. The radiotracer was injected in a volume of 0.2 ml of isotonic sodium chloride solution. The average injected activity was 12-20 MBq.
Planar scintigraphic images of involved breast and axillary regions were acquired 15–30 min post-injection (p.i.) by a gamma camera (Millenium MPR GE Medical Systems, Milwaukee, WI, USA) equipped with a low-energy, high-resolution collimator (LEHR). Static left/right 40° anterior-oblique (LAO/RAO) and anterior views were performed (128x128 matrix, zoom 1.4) collecting 400 Kcounts. When the sentinel node did not appear after the standard wait, delayed images even up to 3 hours p.i. were acquired and patients were asked to perform a light massage on the injection site to favour the lymphatic drainage. In few cases, a second injection of the radiopharmaceutical was carried out in order to get the identification of the sentinel node.
The images showed a single area or, less frequently, two or multiple hot spots, corresponding to the SNs (Fig. 1). After the acquisition of the last scan, the skin projection of these hot spots was marked with a suitable pen.
During surgery the SN was identified by gamma ray detection probe (Neoprobe 2000; Ethicon, Somerville, NJ, USA). This method allows the surgeon to remove the sentinel node and to send it for histopathological examination.

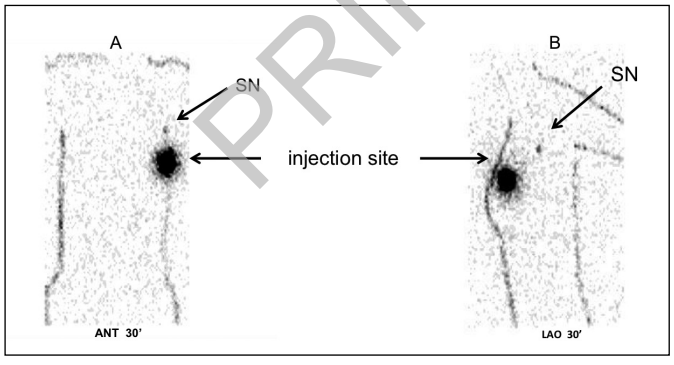

Fig. 1: Anterior (A) and left anterior oblique static views (B) acquired 30 minutes after the injection of 99mTc-nanocolloid in the left breast. A single left axillary lymphnode is visualized. The images allow the exclusion of radiotracer uptake by internal mammary chain lymph nodes.

Statistical Analysis

Contingency table was used to display the frequency distribution of LN identification at lymphoscintigraphy against lymphnodal staging at surgery. 95% confidence intervals (CI) for the detection rate at lymphoscintigraphy were obtained according to Newcombe [7]. Association between lymphoscintigraphy results and type of neo-adjuvant therapy was tested using the Fisher's exact test. Statistical analysis was performed with SAS, version 9.2 software (Cary, NC). All test were two-sided. $P<0.05$ was considered statistically significant.

Results

A total of 444 consecutive BC patients were enrolled for this study with a median age of 44 years at diagnosis (range between 18 and 84 years at onset); SN was identified during lymphoscintigraphy in 430 cases (Table I). The detection rate at lymphoscintigraphy was 96.9% (95% CI, 94.8-98.1%).
For the subgroup without SN identification at lymphoscintigraphy (14 patients, 3.2%), 11 cases underwent directly axillary dissection (pathologic examination revealed respectively 1 pN0 and 10 pN+) and in three

Table I - *Number of lymphnodes identified at lymphoscintigraphy in breast cancer patients after neo-adjuvant treatments.*

Axillary SN identified	Patient number (%)	Total (%)	IMC SN identified
0	14*	14 (3.1)	435 (98)
1	305 (68.7)		7 (1.6)
2	95 (21.4)	430 (96.9)	1 (0.2)
> 2	30 (6.8)		1 (0.2)

*Three SNs were identified with probe during surgical axillary exploration.

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TABLE II - *Number of lymphnodes identified at lymphoscintigraphy in accordance to different type of neo-adjuvant therapies*

Neoadjuvant Treatment	Total	No SN identified	SN identified (%)	P value*
All	444	13	430	
Antracyclin plus taxane	122	5	117 (95.9%)	
Antracyclin containing regimen without taxane	118	6	112 (94.9%)	
Trastuzumab containing regimen	52	1	51 (95.9%)	
Infusional (no Antracyclin)	28	1	27 (96.4%)	
Other	48	0	48 (100%)	
Hormonotherapy only	76	1	75 (98.7%)	0.53

*Fisher Exact test

cases, SN was identified during the operatory time with the probe [2 with pN0(sn) and 1 with pN+]. A mean of 2 SN were removed during surgery (range 1-6). In details, in the majority of patients only one SN was identified at lymphoscintigraphy (68.7%, Table I). In some cases, SNs belonging to the Internal Mammary Chain (IMC) were also identified (about 2%, Table I), however these SNs were not removed during surgical procedures.

Considering the correlation between specific treatments and SN identification rate, we verified that the detection rate did not vary significantly (p=0.53) according to the type of NAT administered to the patients (Table II).

Discussion

Treatment of invasive BC is by now well-assessed in clinical routine; classically the SN identification before surgery requires a correct approach using specific carriers as for example the ^{99m}Tc-labeled colloid particles of human albumin during lymphoscintigraphy procedure. In high volume center for BC treatment, the identification rate of SN is more than 98% (8). The accuracy of lymphoscintigraphy was confirmed with the identification-number of SNs during surgical time, in 67% of patients only one SN was found by probe [9].

The treatment of locally advanced BC care is now challenging. The introduction of NAT opens a new possibility in the management of these cases, considered in the past as unfavourable prognosis. However, frequently axillary dissection is the standard procedure in patients after NAT, also in cases with cN0 staging.

In the common opinion, SNB was not considered a safe procedure after NAT, since the identification rate and the false negative rate are extremely variable, with respectively low and high values [3-6].

Dalu et al. [4] considered a series of 61 patients with a SN identification rate of 86% vs. 100% than in those not receiving NAT; Nason et al. [10] similarly enrolled only 15 women with 86.7% of identification rate. Moreover, Lee et al. [6] reported a large series of 238 patients in which the identification rate was significantly lower in patients receiving chemotherapy (77.6% *vs.* 97%), although the accuracy did not significantly differ between the two groups. In these groups preoperative chemotherapy was associated with unacceptable low identification rate.

The largest meta-analysis reported in the literature [11] collected a series of 24 trials comprising 1,799 patients affected by BC all eligible for NAT. It was estimated that the successful identification and the false negative rates were respectively 90% (range 63-100%) and 8%, and data about the identification rates were heterogeneous. Similar observations were more recently described in a second meta-analysis comprising 21 studies and 1,273 BC patients [12]. In 2009, Hunt et al. analyzed a series of 575 patients underwent SNB surgery after chemotherapy with an identification rate of 97.4% [13].

In accordance with these results, the recent ASCO and St. Gallen guidelines defined that clinicians may offer SNB for women who have operable BC after preoperative/ neo-adjuvant systemic therapy [2,14]. Moreover, recently it has been verified that SNB is acceptable in cN+ patients who become cN0 after NAT [15].

In the present study, we confirmed that lymphoscintigraphy is a safe and feasible procedure also in patients with locally advanced BC after NAT, as the identification rate is about 97% (with a mean of two SN identified with probe during surgery). This is a single study that contrasts results reported by other single centres, mostly with small populations. We hypothesize that the contrasting results about IR of SN after neo-adjuvant treatments could be explained by different reasons such as number of BC patients enrolled, clinicians experience, lymphoscintigraphy technique, etc.

In our Institution, this technique has been used since 1995, with nearly 35,000 lymphoscintigraphy performed till now (25,000 in the last 10 years). The experience accumulated over these years had definitely a great impact on the IR of SN, both in patients not submitted to therapies and in the post-neoadjuvant setting. Therefore, we recommend performing this procedure in specialized centre with high flow of BC patients. Moreover, the abovementioned studies considered as neo-adjuvant only chemotherapy. On the contrary, we enrolled patients that were submitted to systemic chemotherapy, HER2-targeted therapy, hormonal therapy or the combination of these treatments. We didn't find any significant difference between these groups (p=0.53) (Table I). With this observation we can conclude that neo-adjuvant chemotherapy is not a contraindication for lymphoscintigraphy, and damage of the lymphatic system is limited since the re-organization of drainage is possible.

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The on-going treatment of breast conservative surgery seems consider the SNB as the only surgical approach for axillary staging for which is planned adjuvant treatments [16]; in case of NATs, axillary dissection is still indicated in presence of SNB positivity. Axillary dissection in negative axilla is considered an overtreatment also after NATs [17,18]. In conclusion, our results demonstrated that lymphoscintigraphy for SN identification is a safe and feasible procedure after NAT, independently of treatment types.

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Riassunto

Lo scopo dello studio è quello di valutare la fattibilità della linfoscintigrafia dopo trattamento neoadiuvante nelle pazienti affette da carcinoma mammario localmente avanzato. Sono state selezionate 444 pazienti dal 2000 al 2013 con neoplasia mammaria e candidate al trattamento neoadiuvante e alla linfoscintigrafia prima dell'intervento chirurgico. L'età media era di 44 anni alla diagnosi. In 430 casi almeno un linfonodo sentinella era stato identificato alla linfoscintigrafia. L'*identification rate* complessivo era del 96.9% (95% CI, 94.8-98.1%). Non abbiamo notato una correlazione statistica tra l'*identification rate* e il tipo di trattamento neoadiuvante eseguito (p=0.53). I nostri risultati hanno dimostrato che la linfoscintigrafia per l'identificazione del linfonodo sentinella è una procedura fattibile dopo trattamento neoadiuvante, indipendentemente dal tipo di farmaco utilizzato.

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