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Original Research

Feasibility, accuracy and prognosis of sentinel lymph node biopsy before neoadjuvant therapy in breast cancer. A prospective study

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HIGHLIGHTS

- All 123 patients undergoing NAT had their SLN successfully identified on technetium mapping before treatment.
- SLNB before NAT reduced the number of patients undergoing axillary lymph node clearance by nearly three quarters (72.4%)
- Sentinel lymph node involvement did not affect survival during follow-up for a median of 40 months.
- Disease Free Survival was associated with molecular-like subtypes and response to NAT.

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ABSTRACT

Background and objective: It remains controversial whether sentinel lymph node biopsy (SLNB) should be performed before or after neoadjuvant therapy (NAT). We aimed to evaluate the feasibility and accuracy of SLNB before NAT at a single institution, and to determine its relation to patient prognosis.
Methods: A prospective study of T1c-T2-T3 N0 breast cancer patients, after ultrasound examination, who underwent SLNB prior to NAT. Overall, disease-specific and disease-free survival were calculated by Kaplan–Meier curves.
Results: SLNB before NAT was performed in 123 patients from December 2006 to May 2014. The identification rate was 100%. SLNB was positive in 42.3% of cases (27.6% macrometastases). NAT was chemotherapy in 88.6% of cases and endocrine-therapy in 11.4%. Lymphadenectomy was avoided in 72.4% of cases. Median follow-up was 40 months (range 8–100). Overall and disease-free survival was 90.2% and 88.6% respectively.SLN involvement was not related to patient outcome (p 0.72); however there were significant differences in survival according to molecular-like subtypes ($p < 0.025$) and NAT response ($p < 0.0001$).
Conclusions: SLNB prior to NAT is an accurate method of axillary staging associated with a high identification rate. It avoided lymphadenectomy in more than 70% of patients. SLN involvement did not worsen the prognosis in our cohort.

1. Introduction

Over recent years, neoadjuvant therapies (NAT) such as chemotherapy and endocrine therapy have begun to play an important role in breast cancer treatment, even in women with

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operable tumors [1–7]. NAT has been shown to produce survival rates equivalent to those of adjuvant therapy, and offers a series of advantages such as facilitating conservative breast surgery, acting as an in vivo test of chemosensitivity, and adding prognostic information to axillary staging [5–8].

Axillary lymph node (ALN) status is one of the most important prognostic factors in breast cancer. Several studies are currently underway in order to improve its diagnosis. Ultrasound and radiological techniques such as strain elastography [9], magnetic resonance [10], and positron emission tomography/computed tomography [11] are being investigated to predict axillary status, although none so far has shown significant diagnostic value for ALN. Moreover, new trials are ongoing to compare sentinel lymph node biopsy (SLNB) against simple observation by physical exam and ultrasounds (i.e., wait-and-see) in the presence of negative axillary nodes [12]. Until new evidence becomes available, SLNB must remain the standard approach for predicting axillary status in these cases. However, its timing in the context of NAT is controversial: NAT can modify lymphatic drainage patterns due to fibrosis and downstage the axilla in breast cancer tumors, lowering the identification rate to around 84.3%–94.1%, with false negative rates that vary between 7% and 18.4% from study to study [13–17]. In contrast, SLNB before NAT seems to minimize the risk of false negative results and may improve the accuracy of initial staging, providing identification rates of 99.1%–100%, even if it entails the need for two different surgical procedures [18–20].

Against this background, in this study we decided to perform SLNB before NAT in order to evaluate the feasibility and accuracy of this approach at our institution, and also to clarify the associated prognosis.

2. Materials and methods

A prospective study of SLNB prior to NAT in breast cancer tumors was conducted at the Multidisciplinary Breast Cancer Unit of Hospital Universitari Bellvitge - Institut Catala d'Oncologia in Barcelona, Spain, from December 2006 to May 2014. All procedures were approved by a multidisciplinary committee who agreed that NAT was beneficial for each patient. In total, 123 patients met the inclusion and exclusion criteria. The study was approved by the ethics committee of our hospital (ref 247/06).

2.1. Inclusion & exclusion criteria

Patients were required to meet all of the following eligibility criteria: 1) age 18–80 years old; 2) palpable breast tumors with a diameter greater than 1.5 cm, as measured by ultrasound; 3) negative axillary nodes, as measured by ultrasound; 4) core-biopsy of infiltrating breast carcinoma; 5) and provision of written informed consent. The following patients were excluded: those who were ALN-positive, as identified only by fine needle aspiration if there was a suspicion on pre-NAT ultrasound; those >80 years old, because the latest international guides [21] do not recommend SLNB in the elderly; breast tumors measuring less than 1.5 cm; stage T4 tumors; a personal history of ipsilateral breast cancer; and refusal to participate.

3. Methods

Peri-tumor injection of 3 mCi (mCi)/ml of 99 m-technetium radiocolloid was administered for lymphatic mapping 24 h before the SLNB. Radioactivity was detected with an intraoperative gamma probe (Europrobe; Britec; Sheffield; UK). The SLNs were processed by either hematoxylin & eosin and immunohistochemistry (HE/IHC) of 2-mm sections between 2006 and 2011 according to international recommendations [22] or by one step nucleic acid amplification (OSNA) since 2011 [23]. Micrometastasis was defined as a small cluster of cells measuring 0.2–2 mm by HE/IHC or 251–5000 copies by OSNA. Macrometastasis was defined for values greater than either 2 mm by HE/IHC or 5000 copies by OSNA.

NAT was started as soon as the patient had recovered from the SLNB (2–3 days). Endocrine therapy or chemotherapy was chosen according to the tumor's molecular subtype. Endocrine NAT consisted of letrozole at a dose of 2.5 mg per day for 6–12 months. Chemotherapy consisted of a regimen that included anthracyclines followed by taxanes for 6 months, plus trastuzumab if Her2 positive.

Breast surgery (either conservative or radical) was performed 6–12 months after the start of endocrine treatment or 4 weeks after the completion of neoadjuvant chemotherapy. The choice of conservative or radical surgery was made according to the response to NAT, the size of the breast in relation to tumor volume, radiological characteristics of the tumor and predictable esthetic results. During surgery, complete ALN dissection was performed only when macrometastases were identified in the SLNB performed before NAT. Patients with negative SLN or micrometastasis [24] did not undergo further treatment of the axilla. Adjuvant radiotherapy for the breast was indicated after conservative surgery and after mastectomy in T3 tumors. Cases with positive SLNB also received radiotherapy in the supraclavicular and level III lymph nodes. The doses administered were 50 Gy with a daily fraction of 2Gy.

Pathological complete response (pCR) was considered when the pathologist observed no invasive carcinoma in either breast or axillary lymph nodes, and pathological partial response when the pathologist observed infiltrating carcinoma and fibrosis >30%. No response was considered when the pathologist observed infiltrating carcinoma and fibrosis <30%.

Clinical and pathological parameters were recorded, including age, tumor size assessed by ultrasound before and after NAT, histological type, Nottingham histological grade, estrogen and progesterone receptors, Her2 amplification, proliferative index Ki-67, lymphovascular invasion (LVI), SLN identification rate, SLN involvement, and extranodal extension. Immunohistological staining of the tumor samples, based on receptor status, were classified into five surrogate molecular subtypes [25,26]: Luminal A-like, Luminal B-like Her2 negative, Luminal B-like Her2 positive, Her2 positive, and Triple Negative (Table 1 shows the definitions of the subtypes and the baseline patient characteristics in our sample).

Patients were followed by clinical exploration every six months and radiological every year for five years and annually thereafter. Recurrence was defined as local when present in the ipsilateral breast or lymph nodes, and systemic when other organs or the contralateral lymph nodes were involved.

3.1. Statistical analyses

We performed a descriptive analysis of the clinical and pathological parameters of the patients and tumors. Overall survival (OS) was calculated from the date of diagnosis to the date of last follow-up or death. Disease-specific survival (DSS) was calculated from the date of diagnosis to the date of last follow-up or death due to breast cancer progression. Disease-free survival (DFS) was calculated from the date of diagnosis to the date of recurrence or death. Kaplan–Meier survival curves were calculated in both cases. SPSS statistical software (version 17.0 for Windows; SPSS Institute Inc., Chicago, IL, USA) was used for all analyses.