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Original article

The Neoadjuvant Net: A patient- and surgeon-friendly device to facilitate safe breast-conserving surgery in patients who underwent neoadjuvant treatment

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ABSTRACT

The primary goal of the study was to describe an innovative and helpful tool in defining the minimal surgical margins necessary during breast-conserving surgery (BCS) after neoadjuvant treatment: the Neoadjuvant Net (NN). The secondary endpoint was to assess its usefulness in achieving postoperative disease-free margins and reducing Ipsilateral Breast Tumor Recurrences (IBRTs). The breast-conserving surgical technique together with the use of the Neoadjuvant Net is herein reported. Age, stage at diagnosis, clinical and pathological response, lymph node status, type of surgery, margin status, and incidence of local and distant recurrence were retrospectively analyzed. Seventy-five patients underwent BCS following medical treatment from 2000 to 2011. The majority of the patients had significant size reduction (63/75, 84%). Twenty-two had a complete clinical response but only 11 (11/75, 14.7%) showed a complete pathological response. Two patients (2/75, 2.67%) had infiltrated surgical margins. After a mean follow-up of seventy months, 3 patients (3/75, 4%) had IBRTs and 4 women had distant metastases (4/75, 5.34%). The NN is an easy-to-use, non-invasive instrument designed with the purpose of facilitating the surgeon's task of reducing infiltrated margins and IBTRs.

Introduction

Neoadjuvant treatment has been established as the standard of care for operable, locally advanced breast cancer.[1] The introduction of neoadjuvant chemotherapy (nCT) has dramatically improved results in cases of inflammatory breast cancer, although the mortality rate continues to be elevated. In non-inflammatory cancer patients, remarkable benefits have been seen in terms of survival (both disease free and overall) in those 10–30% of patients in whom a complete pathological response was achieved after neoadjuvant treatment.[2,3]

For the other 80%, the beneficial effect of this strategy is mostly related to the opportunity of an "in vivo" chemosensitivity test and, above all, to obtaining reduction of the tumor size with the consequent possibility of undergoing breast-conserving surgery.

The possibility of achieving reduced tumor size amenable for gland sparing surgery has helped patients to accept the amount of time "spent" before the removal of the primary tumor, and the surgical oncologist to implement less invasive strategies in order to perform oncologically radical surgery under hostile conditions.[4]

As we know, about 80% of patients experience tumor shrinkage; unfortunately, the cancer regression does not happen uniformly but instead usually involves random loci of tissue in a "polka-dot" fashion. For this reason, removing the entire pre-treatment tumor bed is mandatory in order to obtain satisfactory local treatment with a low local recurrence rate (LRR).

The *Neoadjuvant Net* is a simple, easy-to-use device which allows the surgeon to take a bidimensional picture of the size of the neoplasia before treatment and to transfer this shape over the skin, after the nCT, defining the minimal surgical margins necessary during breast-conserving surgery.

The primary goal of the study was to describe and standardize this innovative and extremely helpful tool. The secondary endpoint was to assess its usefulness in achieving postoperative disease-free margins, thereby improving surgical technique and reducing Ipsilateral Breast Tumor Recurrence (IBTR).

Materials and methods

The *Neoadjuvant Net* technique originated with Dr Margolese[5] of McGill University who reported the usefulness of a metal web for topographically localizing breast cancer margins. In the last 10 years, the number of patients requiring neoadjuvant treatment and

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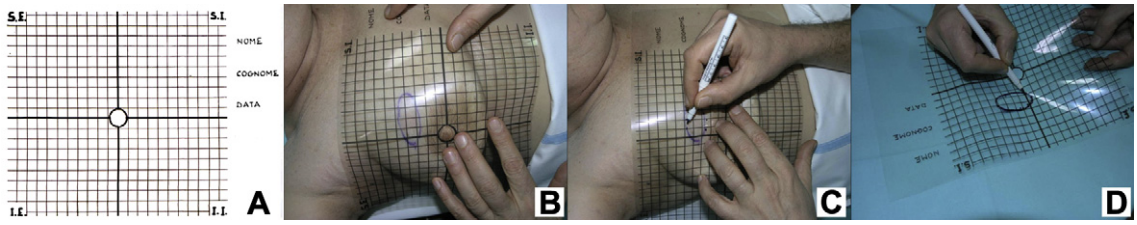

Fig. 1. (A) The *Neoadjuvant Net* is a PVC soft film; a 1 cm square grid is printed on the surface. The net is divided into 4 quadrants; the nipple needs to be placed at the center of the main *x* and *y* axes. (B) The main *y* axis must be pointed toward the shoulder. The epidermal projection of the lesion is marked on the patient's skin. (C) The film is modeled according to the breast shape and the surgeon can copy the skin projection of the neoplasia onto the film. (D) The neoadjuvant net is then stored and put away until after the nCT.

dedicated breast-conserving surgery has increased; thus, we re-assessed the original idea.

The *Neoadjuvant Net* is a polyvinyl chloride (PVC) soft film; on this surface, a 1 cm square grid is printed. It is divided into 4 quadrants; at the center of the main *x* and *y* axes, a hole is made in which to place the nipple (Fig. 1). The main *y* axis must be pointed toward the acromion process of the shoulder. The procedure starts by marking the epidermal projection of the palpable lesion on the patient's skin.

The film is then modeled according to the shape of the breast, and the surgeon traces the skin projection of the neoplasia onto the PVC film. Before surgery, the neoadjuvant net is oriented and re-applied onto the skin (Fig. 2); at that moment, a new drawing of the skin projection of the neoplasia is traced onto the device. At the same time, the pre-nCT tumor shape is re-drawn on the patient's skin. This will allow the surgeon to identify the eventual amount of cancer shrinkage but only the pre-treatment tumor margin (re-marked on the skin) needs to be followed for a "safe" quadrantectomy.

The specimen is removed and oriented for pathological evaluation of the margins.[6] We do not perform an intraoperative evaluation of the margins due to the lack of information regarding the in situ component which surrounds the invasive cancer.[7] In our center, breast reconstruction with a sliding flap of gland is performed at the same time as a quadrantectomy, following the "level one" Clough reconstructive technique.[8] All patients, operated on after neoadjuvant chemotherapy, undergo axillary lymph node radical dissection. All patients who underwent neoadjuvant treatment followed by BSC also undergo whole breast radiation therapy.

The general indications for neoadjuvant treatment in our Unit are a grade T2 tumor (greater than 3 cm in size), locally advanced breast cancer (grades T3–T4) and/or diffuse nodal involvement (N2); nCT is also performed in cases of inflammatory breast cancer (grade T4d). In addition, we try to match these "classic" indications with the data resulting from the analysis of the biopathological parameters (Ki-67, Estrogenic, Progestinic and Her-2 receptor status).[9]

Because of the extended period of time of this study, the neoadjuvant chemotherapy schemes varied substantially from patient to patient depending on the prevailing guidelines.

Further description of the chemotherapy protocols is not reported because the aim of the study was not to assess the outcome of perioperative chemotherapy, but to evaluate the results of a novel surgical technique.

We recorded every patient who underwent neoadjuvant treatment in a specifically designed database. Age, stage at diagnosis, clinical and pathological response, postoperative lymph node status, pathological response according to Miller and Payne,[10] type of surgery, margin status, and incidence of local and distant recurrence were retrospectively analyzed. Clinical response was classified into 3 groups: less than 50% of tumor size shrinkage, more than 50% of tumor size shrinkage and complete clinical response.

Results

One hundred and ninety-eight patients underwent neoadjuvant treatment for breast cancer from January 2000 to February 2011. Fifty-one patents were treated for inflammatory breast cancer and underwent a radical mastectomy. Seventy-two patients underwent a mastectomy due to the tumor preoperative characteristics (multifocal, central or retroareolar) while seventy-five patients benefited from BCS.

The demographic data of the study population are shown in Table 1.

Preoperative clinical response to the neoadjuvant treatment was recorded, and the results are reported in Table 2. The vast majority of our patients had significant size reduction, at least 50%, and, in 22 cases, a complete clinical response (cCR) was recorded (63/75, 84%). Unfortunately, of the 22 patients with a complete clinical response, only 11 (11/75, 14.7%) showed a complete pathological response (cPR).

When BCS was performed with the correct use of the *Neoadjuvant Net*, only 2 out of 75 patients (2.67%) had infiltrated surgical margins. In one case, the consequent treatment was limited to postoperative radiation therapy because only focal involvement of the margin was found while one patient required completion surgery. Two additional patients had a final pathology report showing cancer cells close to the surgical margin (<1 mm) but no further intervention was required.

After a mean follow-up of seventy months, only 3 patients (3/75, 4%) showed IBTRs. Our data, as compared to the data reported in the literature, is consistently lower regarding IBTRs.[4,6,11,12]

In this subgroup of patients, only 4 women had distant metastases (4/75, 5.34%).

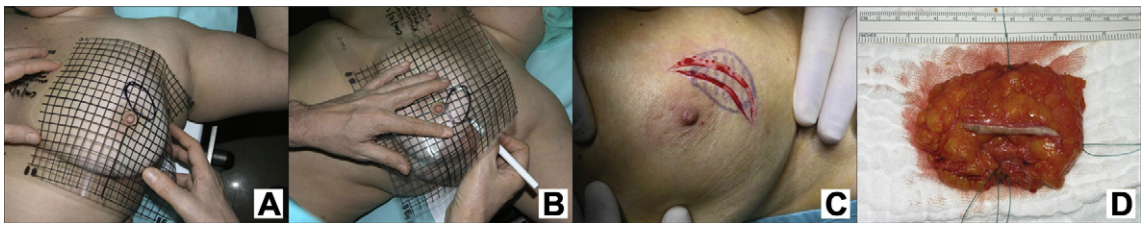

Fig. 2. (A) The film is oriented and re-applied onto the skin. (B) The pre-nCT tumor shape is re-drawn on the patients skin. (C) The pre-treatment tumor edge (re-marked on the skin) will be completely removed for a "safe" quadrantectomy. (D) The specimen is removed and oriented for pathological evaluation.

Table 1
Demographic data.

Number of patients	198
Age: mean (range)	51 (28–78)
Surgical procedure	
Mastectomy	123
Breast-conserving surgery – "quadrantectomy"	75
Tumor stage[a]	
cT2 (>3 cm)	79
cT3	38
cT4 a-b-c	30
cT4 d	51
Tumor stage[a] for BCS patients	
cT2 (>3 cm)	58
cT3	16
cT4	1

[a] Tumor stage was defined before the neoadjuvant treatment.

Discussion

Neoadjuvant chemotherapy was initially designed for advanced breast cancer converting "inoperable" cases into "operable" cases.[13–15] Because of the unexpected success of this treatment, in the mid-90s, neoadjuvant chemotherapy also became the goal standard for locally advanced operable breast cancer, above all for patients with an elevated cell proliferation index.[16–19]

Over the course of years, despite the lack of evidence of any advances in terms of disease-free or overall survival, except for patients with complete clinical response,[1,3,20,21] neoadjuvant treatment had considerable success in reducing tumor size, promoting the chance of conservative surgical treatment.

The role of breast-conserving surgery (BCS) has been widely debated and there have been concerns about its appropriateness after primary chemotherapy. Several studies have questioned the safety of breast-conserving surgery (BCS) which showed a higher LRR as compared to a mastectomy.[22] Many of these studies were unfortunately affected by major bias (e.g. the conservative treatment was confined to radiation therapy only). Eventually, in 2009, a Cochrane review by van der Hage reported that, when optimal surgical treatment was performed, the LRR was the same in cases treated by BCS or mastectomy.[1]

Despite the uncertain definition of clear, close or negative margins, it has been shown that IBTR is proportionally related to surgically infiltrated margins.[23] Regardless of the appeal of less invasive surgery for advanced disease, the decreased survival rates in cases of local recurrence resonated in every breast surgeon's ear.[24] Recurrence rates after breast-conserving surgery in patients who underwent neoadjuvant treatment range from 7 to 26% internationally, depending on the T stage and the response to perioperative chemotherapy.[3,4,25] Neoadjuvant treatment is absolutely effective in downsizing the primary tumor. Unfortunately, the cancer does not shrink uniformly but like a honeycomb with isolated islets of neoplastic cells trapped in a fibro-necrotic cage which is the consequence of the effect of the chemotherapy on the cancer. For this reason, in our Institution we strongly believe that removing all the pre-neoadjuvant tumor burden is mandatory during breast-conserving treatment. Not considering this standard could lead to an unjustified elevated number of positive margins, and IBRTs requiring multiple surgeries.[26] Radical BCS can be extremely complex because the necrotic tissue which replaces the tumor cells is always softer and, consequently, less palpable, above all, in cases of a complete clinical response. Several techniques to map the post-nCT tumor size have been proposed and validated. Above all, tumor clip marking and tattooing have widely been described as being effective in achieving free resection margins with titanium clip placement, leading to less extensive resections.[27]

Our study describes a novel yet simple device for helping the breast surgeon in this process: the *Neoadjuvant Net*.

The Neoadjuvant Net is easy and non-invasive as compared to other mapping techniques, and is extremely well accepted by patients who are reluctant to tattoo the cancer shape on their skin or undertake an adjunctive procedure for clip placement.

Our results demonstrate both a low number of infiltrated surgical margins and a reduced number of IBTRs as compared to the results published in the scientific literature. Despite the inappropriateness of comparing a single center population with other data, regardless of case mix, we are enthusiastic about this tool in that it facilitates the surgeon's task and reduces both infiltrated margins and IBTRs (2.67% and 4%, respectively). A second bias of our study is possibly represented by the multiplicity of neoadjuvant and adjuvant chemotherapy programs which extended over a long period of time and may have affected our results.

Table 2
Clinical response to neoadjuvant chemotherapy.

Type of response	No	%
No response	2/75	2.67
<50% of tumor size reduction	10/75	13.33
>50% of tumor size reduction	41/75	54.67
100% of tumor size reduction	22/75	29.33

Conclusion

Randomized Control Trials and multicentric studies might be necessary to compare the results obtained with and without this tool; however, the *Neoadjuvant Net* is clearly the first, easy-to-use, non-invasive instrument designed with the specific purpose of facilitating the surgeon's task of reducing infiltrated margins and IBTRs.

Conflict of interest statement

None declared.

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There was no sponsorship for this study.

Ethical approval

No ethical approval was required for this study.

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