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Intraoperative ultrasound in conservative surgery for non-palpable breast cancer after neoadjuvant chemotherapy

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ABSTRACT

Aims: A complete clinical response after neoadjuvant chemotherapy (NACT) in breast cancer patients hinders the localization of the residual lesion and the removal of a minimum amount of breast tissue. The aim of the present work is to report our single-centre experience with intraoperative ultrasound-guided (IOUS) excision performed by surgeons in these patients.

Patients and methods: From January 2008 to December 2012, IOUS excisions were performed on 58 patients with a previous intralesional ultrasound-detectable metallic marker and non-palpable breast cancer after NACT. The specimen margins were estimated by ultrasonography and macroscopic pathologic examination. Successful lesion removal, specimen weight, and analysis of the results as regards margins were evaluated, and the need for breast-conserving re-excision and mastectomy was considered.

Results: After NACT the average ultrasound/mammography and MRI diameters were 11.7 mm (0–30) and 9.1 mm (0–40) respectively. In all cases, the residual lesion or tissue around the marker was removed. The average weight of the specimens was 26.4 g (6–84), being lower in cases of complete response according to ultrasound ($p < 0.05$). In 4 patients (6.8%), breast-conserving re-excision was carried out, and in 3 patients (5.2%) a secondary mastectomy was performed, two of which had invasive lobular carcinoma.

Conclusions: The emplacement of a readily echodetectable metal marker before NACT makes IOUS excision feasible in an increasing number of complete clinical responses, with the excision of small amounts of breast tissue and a high percentage of conservative breast surgery. This technique requires surgeons to be trained, but has the advantage of a reduced use of other hospital services, better planning of operating theatres, and less discomfort for patients, which means that it is attractive and indeed recommendable.

1. Introduction

Neoadjuvant chemotherapy (NACT) allows conservative surgery to be performed on the breasts of women who are potential candidates for a mastectomy owing to the size of their tumours. The complete and partial response rates for NACT are high according to published works [1,2] indicating that a relatively high proportion of these patients can benefit from conservative surgery. However, even though the clinical response is complete, surgery is always mandatory [3] since there may be residual cells in 70% of patients [4]. Additionally, imaging studies only indicate the response of the tumour to NACT but do not define the real surgical margins. Thus a non-palpable tumour after NACT is a challenge for surgeons because they must localize a non-palpable residual lesion intraoperatively and, also, they must excise the minimum amount of tissue to achieve tumour-free margins and be able to perform conservative surgery with the best aesthetic result possible. In light of these problems, it is crucial to mark the location of the tumour before NACT [5] with metal clips or skin tattoos in case a complete clinical response occurs later on. In these cases, after NACT and prior to surgery it is necessary to localize the residual lesion or the marking clip, but there is no standardized method for preoperative

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localization or for defining the amount of breast tissue to be removed. The wire-guided localization technique (WGL) is the standard procedure but is a time-consuming procedure because it requires the expertise of an experienced radiologist and it is uncomfortable and usually stressful for the patient. Moreover it may be associated with a high number of positive margins, increases in local recurrences and a poor cosmetic result [6].

In view of the good results obtained with intraoperative ultrasound excision (IOUS) in suspicious lesions [7,8] and non-palpable breast cancers [9,10], our aim here is to report our experience with IOUS as an alternative to WGL in patients with breast cancer treated previously with NACT in which the tumour or residual lesion was non-palpable.

We analyse the surgical efficiency of IOUS excision using the following parameters: the weight of the specimens excised, the number of excisions with tumour-free margins and the proportion of second operative procedures or mastectomies in patients who were candidates for conservative surgery.

2. Material and methods

Using a prospective clinical database compiled at our Breast Surgery Unit, between January 2008 and December 2012 we identified patients diagnosed with a core breast biopsy as suffering from invasive breast carcinoma who had been treated with NACT in order to reduce the size of the tumour and perform conservative surgery. The patients underwent diagnostic imaging studies with ultrasound, mammography and MRI. After the NACT had been completed, a multidisciplinary team decided on conservative breast surgery after assessing the tumour response by physical exploration and imaging studies.

The NACT protocol used at the discretion of the treating medical oncologist was based on CAF (cyclophosphamide (600 mg/m^2)/epirubicin (90 mg/m^2)/5-fluorouracil (600 mg/m^2) q 3 weekly $\times$ 4 cycles, followed by docetaxel (100 mg/m^2) $\times$ 4 cycles or paclitaxel (100 mg/m^2) q weekly $\times$ 8 weeks, depending on the patient's age and the characteristics of the tumour. If the tumour was also Her2-positive, trastuzumab (2 mg/kg) q weekly was added throughout the treatment period.

According to our protocol, before the patients were subjected to NACT they received, under ultrasound control, a metal marker, locating this as close to the tumour centre as possible. Although IOUS has been applied gradually since 2007, in our study we only analysed patients who had been fitted with a non-ferromagnetic clip. Such clips are readily localizable with ultrasound, owing to their shape and size and they are also compatible with the MRI exploration (MReye Breast Localization Coil, Cook Incorporated. Bloomington, IN 47404, USA). We began to use these devices as of January 2008. Later, the correct positioning of the clip was checked by imaging studies, mammography and ultrasound.

A complete clinical response (cCR) was defined by the absence of clinical evidence on palpation at the time of surgery [4]. Moreover, the response to NACT was assessed by radiologists belonging to the Multidisciplinary Breast Unit of our University Hospital, who localized the marker and the size of the tumour (the greatest diameter in mm) if it was measurable with mammography, ultrasound or MRI before the surgical intervention. A complete radiological response (rCR) was defined when there was no evidence of lesions from the radiologic imaging studies, and tumour size was defined as the largest measurement obtained with any of the techniques employed.

In these patients conservative surgery was indicated and IOUS excision of the residual tumour was performed as an alternative to other means used for preoperative localization. Cases in which a WGL excision had been made and those in which the residual lesion or the marker were difficult to detect by ultrasound were excluded from the study. We also excluded all those cases who had undergone reducing oncoplastic techniques with or without contralateral symmetrization, where the volume excised is much larger than in classic lumpectomy.

Surgical resection with IOUS consisted of a residual tumorectomy next to the marker or removal of breast tissue from around the marker when no tumour was detected with pre and intraoperative ultrasound. The idea was not to remove the pre-NACT tumour volume but to eliminate the ultrasound-detectable residual tumour with negative margins in the pathological examination. The ultrasound-guided excision technique has been described by us previously [9]. The IOUS-excised specimen was oriented appropriately and marked three-dimensionally with sutures and the margins were inked in. Then, the main tumour specimen was weighed and additional cavity margins were included in these measurements. Because the surgical specimen is not a sphere but an ellipsoid, we believe that the most objective way of assessing the excised breast tissue should be based on weight.

In all cases, using ultrasound and intraoperative gross study of the specimen we checked the removal of the marker in the cases of complete ultrasound response and in the cases of partial response we checked the removal of the marker and the tumour. In these latter cases, the resection margins were assessed using ultrasound and gross macroscopic pathologic examination jointly. Where the presence of affected or close margins ($<$3 mm) was suspected, a re-excision of the suspicious margin(s) was performed. No radiography of the surgical specimens was carried out.

Complete pathological response in the breast (pCr) was defined when the surgical specimen did not contain invasive tumour cells. When there were only clusters or dispersed cells remaining ($>$90% loss), the case was considered as minimum residual disease (MRD). When there was a measurable tumour, a 30–90% reduction in tumour cells was considered a partial response (pPR). These three classifications (pCR, MRD and pPR) coincide with scores 5, 4 and 3 of the tumour regression grade of Miller and Payne's criteria, respectively [11].

In cases of pPR or MRD, the margins of the specimen were examined. The margin was considered histologically positive or very close to the lesion if the carcinoma, invasive or "in situ", was localized at the margin or within an area $<$2 mm from the inked border in the final pathological examination [12]. In these cases, a reoperation was performed, either re-excision of margins or a mastectomy if a poor aesthetic result was foreseen. Margin status was classified as negative if it was $\geq$2 mm.

Sentinel node biopsy was performed after NACT in those patients whose axilla was clinically negative by ultrasound or by fine-needle aspiration before and after NACT. In those with biopsy-confirmed axillary lymph node involvement before or after NACT, full axillary lymph node dissection was performed. The combined technique (blue dye plus isotope) was used for node staging by subareolar intradermal injection.

Loco-regional recurrence (LRR) was defined as recurrent disease in the ipsilateral breast or in the axillary, supraclavicular, infraclavicular, or internal mammary lymph nodes. The time to LRR was defined as the time from initial tumour diagnosis to the time of the last follow-up or development of LRR [13].

The study was observational and non-randomized, and was based on prospective acquisition of data from a clinical database compiled at our clinic. The clinico-pathological data, successful lesion removal, specimen weight, and analysis of the results as regards margins were evaluated, and the need for re-excision on the same (synchronous) or on a different day (metachronous) was considered. For the purposes of this study, the database holding these patients was updated to include the clinical and radiological

responses and the pathological results of the surgery performed on the axilla and on the breast. The outcome endpoints examined were LRR and overall survival.

Statistical analyses. Descriptive data analysis was performed and continuous variables between groups were tested using the *t*-test for unpaired data. Data analysis was performed with the Statistical Package for the Social Sciences (SPSS statistical software, Version 15.0; SPSS, Inc., Chicago, IL, USA).

3. Results

From January 2008 to December 2012, 122 breast cancer patients were treated at our breast surgical unit with neoadjuvant chemotherapy for primarily operable breast carcinoma. In all cases, prior to NACT a marker (MReye Breast Localization Coil) was placed in the correct position in the lesion under ultrasound guidance, as confirmed by mammography. None of the radiologists encountered difficulties in placing a marker and no complications occurred.

In 85 (69.7%) of these patients breast-conserving surgery was indicated at the interdisciplinary meeting after NACT. In 27 of the 85 patients in which breast-conserving surgery was attempted, the tumour was still palpable or an excision was performed via WGL or using any of several different oncoplastic reduction methods. In the remaining 58 (47.5%) patients a complete clinical response (cCR) was considered to have occurred and a local excision was performed with the use of the IOUS technique exclusively by surgeons and these patients were included in the study.

The patient and tumour characteristics are summarized in Table 1. The patients' mean age was 48.57 ± 9.6 years (31–77 years). The radiological response was determined by mammography and/or ultrasound in all cases and with MRI in 52 patients. According to ultrasound/mammography and MRI the median tumour size pre-NACT was 28.3 mm (11–53) and 33.1 mm respectively (15–60). The majority of patients (79.3%) presented with T2 tumours.

After NACT, the diameter decreased to 11.7 mm (0–30) and 9.1 mm (0–40) in the imaging tests conducted with ultrasound/mammography and MRI respectively. A complete radiological response (rCR) was seen in 23 of 58 (39.7%) patients, while the rest of the patients showed a partial or nearly complete radiological response. 18 of the 58 patients (31%) achieved a pCR after NACT but in the patients with an rCR, the cases of pCR increased to 52.2% (Table 2).

In all cases, the metal marker (with or without residual lesion) was removed, and successful excision of the metal marker and residual lesion was confirmed by ultrasound with/without macroscopic intraoperative evaluation of the specimen, and with no need for a mammogram. After intraoperative assessment of the margins of the surgical specimen, compromised margins were deemed to be present in 29 cases (50%) and the patient underwent intraoperative re-excision of the margin(s) in question, with a total of 35 margins (Table 3). In 9 cases residual invasive tumour was observed in re-excision margins and 4 of these patients underwent reoperation for inadequate microscopic margins. In another 5 cases (8.6%, 5/58), the intraoperative ultrasound and macroscopic assessment and appropriate directed re-excision achieved clear margins, circumventing a second procedure. Of the 29 cases with sufficient intraoperative ultrasound and macroscopic margins, 3 were subjected to a second operative procedure for the microscopic margins involved. Overall, 7 patients underwent second interventions for unclear margins; in 4 patients (6.8%) breast-conserving re-excision was performed, and in 3 patients (5.2%) a mastectomy was performed. In two of the latter patients the histologic diagnosis was invasive lobular carcinoma (Table 4).

The average weight of the specimens studied here was 26.4 g (6–84). On analysing the weight of the surgical specimens with respect to the responses in the imaging studies and the pathologic responses, we observed that the weights of the specimens were significantly lower ($p < 0.05$) in the complete responses observed with ultrasound, there being no significant differences in the MRI and pathologic results (Table 5).

The median follow-up was 35 months (p25–75: 21–49 months); two patients (3.4%) developed LRR at 16 and 37 months. One of these patients had LRR in the ipsilateral breast close to the primary tumour site. Her initial IOUS specimen weighed 6 g and had a pCR in its initial excision. The other patient developed

Table 1
Pre-NACT patients and tumour characteristics.

	$n = 58$ cases
Age in years (mean ± sd) (range)	48.57 ± 9.6 (31–77)
Clinical tumour size. Median (range) mm	
By MRI ($n = 52$)	33.1 (15–60)
By US/mammogram ($n = 58$)	28.3 (11–53)
Clinical tumour stage	
T1	8 (13.8%)
T2	46 (79.3%)
T2 (≤3 cm)	18
T2 (>3 cm)	28
T3	4 (6.9%)
T4	0
Clinical nodal stage	
N0	41
N+ (FNA+)	17
UICC stage	
I	6
IIA	27 (46.6%)
IIB	20 (34.5%)
III A	3
Histology	
Invasive ductal carcinoma	54 (93.1%)
Invasive lobular carcinoma	3 (5.2%)
Others	1 (1.7%)
Grade	
Highly differentiated	8
Moderately differentiated	20
Poorly differentiated	30
Unknown	5
Receptor-based subtype	
ER-/PR-/HER2-	16
ER + o PR+	28
HER2+	11

Table 2
Treatment outcome.

Radiological response after chemotherapy	
Partial response (rPR)	35
Complete response (rCR)	23 (39.5%)
Clinical tumour size. Median (range) mm	
By MRI ($n = 52$)	9.1 (0–40)
By US/mammogram ($n = 58$)	11.7 (0–30)
Pathological response after systemic treatment	
Partial response (pPR)	31 (18.7 6–55)
Minimal residual disease (MRD)	9
Complete response (pCR)	18 (31.0%)
Axillary lymphadenectomy	42
Sentinel node biopsy	16
Lymph node metastasis	13 (22.4%)
Weight of resected specimen (g), median (range)	26.4 (6–84)
Breast-conserving surgery	96.5%
Positive margins at the first resection	7
Breast-conserving re-excisions	4 (6.8%)
Subsequent mastectomy	3 (5.2%)
Follow-up mediana (p25–75) (months)	35 (21–49)
LRR	1
LRR + metastasis distant	1
Metastasis distant (death)	2 (1)

Table 3
Results of intraoperative margins and their relationship with the definitive histological margins.

Sonography ± gross-pathologic intraoperative margins		Definitive histological margins	
		Positive	Negative
Suspected[a]	29 (50%)	9[b]	20
Negative	29	3[c]	26
Total	58	12	46

[a] Intraoperative re-excision margins.
[b] 5 patients with tumour in re-excised specimens (invasive or in situ) but with clear margins, and 4 second therapeutic operations for non- clear margins (2 breast conservative re-excisions and 2 mastectomies).
[c] 3 patients with second therapeutic operations (2 breast conservative re-excisions and 1 mastectomie).

concomitant distant metastasis and her LRR was in a different quadrant, with a weight of 26 g and pCR in its initial excision. Another two patients also developed distant metastases and one of them died (Table 2).

4. Discussion

It is unquestionable that surgical intervention in cases of breast tumours after NACT is a challenge for breast surgeons, above all if the tumour or the residual lesion is not palpable. The main aim of administering NACT is to perform conservative surgery with acceptable aesthetic results by removing the minimum amount of breast tissue possible, although such an intervention must be sufficient to remove all the residual foci of echo-mammographically evident disease and obtain negative histologic margins. Thus, predicting the size of the residual tumour is crucial for planning the type of intervention to be performed and the volume of breast tissue to be removed.

Although marking tumour margins prior to NACT has been received well, the results are controversial [1,14,15] and the only agreed method for orienting the surgeon when excising residual tumours after NACT is to place a metal marker inside the tumour at the start of NACT [5]; this serves as a guide for different methods of post-NACT localization when the tumour is not palpable.

With a non-palpable tumour after NACT it is difficult to locate tumours or residual lesions and it is hard to determine the amount of parenchyma around them to be excised. Accordingly, different methods have been used for localization as alternatives to the standard procedure by means of a wire guide [15–17]. Currently, as far as we know, and after a Pubmed search (with terms non-palpable breast cancer, intraoperative breast ultrasound, IOUS breast, neoadjuvant chemotherapy, primary systemic therapy), the present work is the only one to report on IOUS as a method for the localization and excision of tumours or residual non-palpable lesions post-NACT.

At present, no reliable imaging methods are available for predicting a pCR, and MRI is the most accurate imaging technique to assess tumour response after NACT [18], although with a negative predictive value close to 65%. The ultrasound study, although with a lower negative predictive value, is still a valid option for the assessment of tumour size and the surgical strategy to be used [19–23]. IOUS is the only method that excises the residual lesion together with the ultrasound-detectable clip by means of images taken intraoperatively, avoiding excess removal of breast tissue, which is incompatible with the aesthetic aspect of conservative surgery. IOUS excision achieves this aim since the surgeon is better able to plan the surgical technique to be used and the volume to be excised because with images acquired in real time it is possible to localize the residual tumour and the marker in their exact spatial position during the operation. It is important that the marker be readily echodetectable and compatible with MRI because the objective of IOUS is to localize it and excise it together with the residual lesion close to it. This is different from other techniques (ROLL and WGL), where the marker is used to "highlight" the localization of the lesion by injecting a radiotracer or by placing a metal guide wire.

Table 5
Weight of the intraoperative specimen and its relationship with ultrasound, RMI and pathologic complete/partial response.

(n° patients)	Specimen weight (g) (n° patients)	
	Complete response	Partial response
MRI (52)	28.2 (23)	23.6 (29)[a]
Ultrasound (58)	16.4 (11)	28.8 (47)[b]
Pathologic (58)	24.4 (27)	27.4 (31)[c]

Significant p-values: [a]$p = 0.35$, [b]$p = 0.04$, [c]$p = 0.52$.

The most determinant factor with respect to affected margins and cosmetic outcome [24] is the amount of breast tissue removed around the residual lesion. The greater the volume removed, the fewer the affected margins, but the poorer the aesthetic results. According to the work of Loibl et al. [25], re-excisions were more frequent after segmentectomy than after quadrantectomy (24.1% vs. 19.3%). In non-palpable lesions after neoadjuvant chemotherapy, Van Riet et al. [16], using radioactive 125 Iodine seed, and Donker et al. [26], comparing radioactive seed localization versus ROLL, reported a mean specimen weight of 39 and 48–53 g respectively. In our patients, with IOUS excision, mean specimen weight was considerably lower (26.4 g). We believe that this lower specimen weight in IOUS would be due to the fact that the surgeon, with information about the preoperative ultrasound images post-NACT, mainly performed an excision of the residual lesion and/or the marker with adequate margins. In support of this hypothesis is the lower ultrasound specimen weight ($p < 0.05$) when it was only necessary to excise the marker because no ultrasound residual tumour lesion was detected (Table 5).

In our patients conservative surgery was performed in 94.8% of cases, similar or higher to what has been reported in other series: 96.3% [16], 94% [26], and 82.7% [25]. In the meta-analysis

Table 4
Second therapeutic operations for nonclear margins. Ultrasound and pathological characteristics and definitive surgery.

# Patient	Tumour diameter (mm)					
	Ultrasound Pre-NACT	Ultrasound post-NACT	Pathological	Specimen weight (g)	Invasive histology	Definitive surgery
1	40	15	10	40	Ductal	BCS
2	23	13	10	22	Ductal	BCS
3	26	18	22	52	Ductal	BCS
4	30	RC	55	27	Lobular	Mastectomy
5	15	7	13	7	Ductal	BCS
6	34	21	50	75	Lobular	Mastectomy
7	30	12	12	10	Ductal	Mastectomy

performed by Loibl et al. [25] on patients with a complete clinical response, the percentage of re-excisions performed because of affected margins was 19.6%. Accordingly in our serie, in 6.6% patients it was necessary to carry out a second breast-conserving re-excision and in 8.6% a second procedure was avoided with an appropriate re-excision directed by ultrasound and macroscopic intraoperative evaluation, obtaining clear margins. Although they excised twice the breast volume, Donker et al. [26] reported 13% of affected margins for the two localization methods employed (radioactive seed localization versus ROLL), but those authors only performed 7 and 8% of re-excisions. Van Riet et al. [16], using a radioactive seed, observed similar numbers of affected margins (6.4%), but differed from our series in that the tumours were grouped as palpable and non-palpable and in that those authors removed a greater weight of breast tissue. Espinosa-Bravo et al. [15], analysing two localization techniques in patients in which conservative surgery had been performed, found 5.9% and 3.2% of affected margins, but we believe that these findings cannot be compared with our own because those authors analysed patients with palpable and non-palpable residual tumours and, also, because of the greater volume of breast tissue removed. On comparing IOUS excision in non-palpable breast cancers without NACT, the percentage of affected margins was lower (4%) [9]. This could be because in tumours not treated with NACT a more precise assessment of the margins can be gained with ultrasound [27] and intraoperative macroscopic studies [9].

Upon analysing the seven re-excisions according to histologic types (Table 4), 5 were found to be ductal and 2 were lobular carcinomas, representing 11% and 66% of the ductal and lobular carcinomas treated with NACT respectively. These data are consistent with those reported in the GEPARDUO trial [25], in which re-excisions and mastectomies were seen to be more frequent in lobular carcinomas and conservative breast surgery was less frequent in patients with a partial clinical response. Like other authors [28] we believe that this would be due to the smaller and non-concentric pathological pattern response and the difficulty involved in determining the post-NACT extent of lobular carcinomas by imaging techniques.

Just as in non-palpable cancers [9], it should be taken into account that this technique does not interfere in sentinel node biopsy, because in our cases we injected dye and radiotracer under the areola. Neither is it necessary to use the radiology service preoperatively, with less discomfort for the patient, nor to take a radiograph of the operation specimen, since the marker and the residual lesion, if indeed present, are checked with IOUS. Accordingly, IOUS excision is less complex than other methods, which saves time and money [29] owing to a reduction in the use of radiology and nuclear medicine and decreases the number of second interventions.

One of the limitations of this study is that the follow-up period for assessing the LRR was very short, since according to most authors [13,30] the follow-up period is longer and the mean interval between local relapses in other studies is longer than our follow-up period. Accordingly, we should have used a longer follow-up to detect possible cases of LRR. Although the amount of breast tissue to be removed is not defined, if LRR were to remain at acceptable levels after a longer follow-up period it could be proposed that with small excision volumes it would be possible to achieve excellent local control.

5. Conclusions

Although the technique takes surgeons some time to master, with IOUS is it possible to perform the excision of a small amount of breast tissue in non-palpable tumour after NACT, the first factor to be considered for conservative surgery with good aesthetic results. Moreover, with this technique it is also possible to achieve a low number of breast-conserving re-excisions due to affected margins, which would afford cost-savings and good local control. We believe that this is because with IOUS it is possible to focus the residual lesion or marker in the surgical specimen, allowing a smaller volume of tissue to be excised and greater possibilities of free margins. These advantages, together with a reduced use of other hospital services, better planning of operating theatre schedules and the reduced discomfort for patients make IOUS excision an attractive and recommendable practice as an alternative to other excision techniques in patients with complete clinical responses after NACT.

Ethical approval

Not applicable.

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None.

Author contribution

Manuel Ramos: study design, data collections, data analysis and writing.
Juan Carlos Díaz: study design, data collections.
Teresa Ramos: data collections, data analysis and writing.
Ricardo Ruano: data analysis and writing.
Magdalena Sancho: data collections.
José María González-Orús: data collections.

Conflicts of interest

None of the authors have any conflicts of interest to disclose.

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