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Original research

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