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Intraoperative Ultrasound and Oncoplastic combined approach: an additional tool for the oncoplastic surgeon to obtain free margins in breast conservative surgery. A two years, single centre, prospective study.

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Title:

Intraoperative Ultrasound and Oncoplastic combined approach: an additional tool for the oncoplastic surgeon to obtain free margins in breast conservative surgery. A two years, single centre, prospective study.

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MicroAbstract

In case of breast postoncologic reconstructive surgery when an oncoplastic approach is adopted and volume replacement with glandular flap mobilization are performed, tumour positive margins may create a significant problem. We present our experience with intraoperative ultrasound as an adjunctive tool to guide breast surgeons to improve “margin free” management of neoplastic breast lesions in patients undergoing oncoplastic surgery.

Abstract

Background: The main goal of oncoplastic breast conservative surgery (OBCS) is to obtain tumour free resections margins (TFM) after cancer excision, with satisfactory cosmetic results. Positive tumour margins are associated to high rates of tumour recurrence requiring reoperation. The aim of this prospective clinical trial is to demonstrate the reliability of intraoperative ultrasound (IOUS) to obtain TFM in OBCS.

Materials and methods: Between December 2016 and March 2018, 130 patients affected by T1-T2 breast cancer, either invasive or in situ, submitted to OBCS were prospectively collected for the study. The oncoplastic surgeon performed IOUS in the theatre to localize the lesion and mark its skin projection. Then specimens were examined to assess the presence of the lesion and margins' adequacy. The definitive histological reports were reviewed, focusing on margins' status.

Results: All patients experienced oncoplastic approaches and lesions were always found on the specimen at the histological report. In 126 cases (97%) margins were considered adequate. In 17 cases (13%) IOUS showed positive margins and resection was contextually enlarged. In 12 of these (9%) the pathological report confirmed the need for enlarged resection.

Discussion: This study shows that IOUS guided surgery can obtain a high percentage of TFM in OPBS without scheduling conflicts between radiology, nuclear, and surgery department. Full cooperation between radiologists and oncoplastic surgeons is mandatory to achieve high standard oncological and reconstructive outcomes.

Conclusions: IOUS represent an additional tool for the breast surgeon to improve "margin free" management of neoplastic lesions, preventing reoperations in patients undergoing oncoplastic surgery.

Keywords: Oncoplastic breast conservative surgery (OBCS), Tumour free margins (TFM), Intraoperative Ultrasound (IOUS).

Introduction

The primary goal of breast conserving surgery is to obtain tumour free resections margins after an excision for cancer either invasive or in situ. Positive tumour margins are associated to two-fold rates of ipsi-lateral tumour recurrence¹⁻² and in this event it is required re-excision or even mastectomy to obtain definitive clear margins.³ The secondary goal of conservative surgery is to offer to the patients a satisfactory cosmetic result after surgery. During the last decades the trend of conservative surgery has been to shift from quadrantectomy, to large excision, to lumpectomy with the intent to minimize the excision volume in order to reduce breast shape deformities, asymmetry, length of the scars. Oncoplastic breast surgery, on the contrary represents a group of techniques that integrates oncological principles and plastic surgical approach.⁴⁻⁶

When an oncoplastic approach is adopted and volume replacement techniques along with glandular flap displacement are performed, tumour-positive margins may arise a significant problem. Most reconstructive techniques involve some manipulation of the partial mastectomy cavity that become difficult for the surgeon to identify during re-excision of the margins. In these cases reoperation will represent a challenge because margins may be shifted. Therefore precise preoperative lesion localization and intraoperative margins assessment are mandatory to obtaining clear margins. Several techniques have been described for this purpose in standard conservative breast surgery such as radio-occult lesion localization (ROLL), needle wire localization, intraoperative ultrasound (IOUS). Full communication among different specialists involved in the multidisciplinary approach is always recommended, and cooperation between radiologists and surgeons is fundamental in order to achieve high standard oncological and reconstructive outcomes.⁷⁻⁸

Nevertheless there is a variable set of circumstances, especially in the setting of low-resource areas or poorly equipped hospitals, in which a surgeon finds oneself dealing with potentially difficult conditions. Cases of accidental wire mobilization, preoperative marking deletion as

well as unexpected situations in which the Radiologist may be operated or not always immediately available in the operating room, turn to be very challenging for the surgeon forced to work “freehand” with high risk of inadequate resections. We present our experience in performing IOUS in the operative room to localize the lesion and mark its skin projection. The aim of this paper is to describe the feasibility and accuracy of perioperative IOUS as an adjunctive tool for the breast surgeon to improve the management of neoplastic breast lesions in patients undergoing oncoplastic surgery.

Materials and Methods

After the approval of Institutional review Board 130 patients submitted to oncoplastic breast conservative surgery were prospectively collected for the study between December 2016 and March 2018. Patients' inclusion criteria were a diagnosis of early breast cancer, and indication for conservative surgery. Both invasive and in situ lesions were included. All patients had received a preoperative digital mammography, ultrasonography and a histologic diagnosis by core biopsy. Patients informed consent was obtained. An ultrasonography intraoperative localization was conducted using a linear probe L12-4 MHz (Affiniti 50 G.). The US scan was adopted for the localization of both palpable and not palpable lesions. Lesions not detectable by US, such as micro-calcifications, were previously localized with a tissue marker US-visible (Mammostar 8-10 G; Devicor Medical) applied during the vacuum-assisted stereotactic breast biopsy (VAB) before the surgical intervention. Then, intraoperatively, ultrasonography was used to identify the marker inside the hole produced by the procedure. The same surgeon performed the exam in the operative room before the anaesthesia induction. The lesion was localized in supine position and its cutaneous projection was marked on the skin surface with a surgical pen. Pre-, intra- and post-operative pictures were taken to all patients undergoing oncoplastic surgery. Surgical planning was drawn with patient in upright position. An onco-

plastic surgical approach was proposed in all cases. The procedure was performed both for the resection and for the reconstruction step by the same surgeon. Factors considered before surgery were volume of tissue to be excised, tumour location, breast size, shape and glandular density, and some patients related risk factors such as: smoke, diabetes and previous surgery. The oncoplastic patterns used were: Wise pattern, Benelli pattern, vertical scare, J pattern, previously described in literature. ^{5,9,10,11}

After the removal of the specimen IOUS was performed again in order to assess the presence of the lesion and margins adequacy (5 mm). A specimen Rx was performed whenever a tissue marker was applied before surgery with the intent to check the marker and the residual microcalcifications. All the definitive histological report were reviewed in particular regarding whether the main component was in situ, invasive, or both, the evidence of clear or positive margins, and if they matched to the IOUS results.

Results

Between December 2016 and May 2018, 130 consecutive patients were recruited for the study. The mean age was 60.6 years (range 42-90 yrs). The patients were divided into two groups: the ones with palpable and the ones without palpable lesions. In the first group there were 66 patients and in the second 64 patients. Data regarding number of lesions, mean dimension, and histology grouped according to palpable or non-palpable lesions, were collected and are shown in table 1. **(Tab 1)**

Oncoplastic procedures were performed in all cases. The patterns we used are shown by figure 1. **(Fig. 1)**

Lesions were always found on the specimen at the histological report. In 126 cases (97%) the margins were considered adequate. In the remaining 4 cases the preoperative ultrasonogra-

phy study revealed not to be effective (Fig.2). In one patient we found a positive margin infiltrated by a focal ductal carcinoma in situ (DCIS) in the parenchyma surrounding the main lesion, which was a 19 mm palpable invasive ductal carcinoma. In the second case the positive margin was again for DCIS, both in the medial and in the lateral margin of the specimen with a pathological report of multiple invasive and in situ ductal carcinoma (greatest dimension 9 mm) in the parenchyma surrounding the main lesion. In the third case the US scan which localized the lesion preoperatively failed to reveal it in the specimen (a 5 mm invasive lobular carcinoma), so an intraoperative frozen section was requested which confirmed the presence of the lesion. In a fourth patient with a not palpable, 7 mm mucinous invasive carcinoma, the closest margin was initially considered free from tumour at the intraoperative ultrasonography check. Nevertheless, at the final histological report, it resulted to be not adequate, measuring only 0.07 mm from the closest margin. In the three cases with positive margins, a second surgical procedure was performed to broaden the margins. In one case a mastectomy was deemed necessary. In the not palpable lesions group in one case the clip applied during the VAB procedure and revealed by the US scans preoperatively was not found on the specimen at the X-ray control performed in the operative room. The lesion was, however, present with adequate margins. Surgical manoeuvres might have been responsible for accidental removal of the clip from the surgical field. In 17 cases the US scan conducted on the specimen showed inadequate margins and the extent of the resection was contextually enlarged, in one case followed by the removal of the nipple-areolar complex. In 12 of these cases, the pathological report confirmed the need for the enlarged resection. In the other 5 cases (at the very beginning of our experience) the resection would have been adequate even without any enlargement.

Discussion

Oncoplastic breast surgery have become more and more accepted and adopted in the clinical routine in the last decade.¹² A recent study demonstrated that OBCS had a four-fold increase in the percentage of all breast surgery between 2007 and 2014, raising from 4 to 15%. In 2014 OBCS represented about 33% of all conservative breast surgery procedures.¹³ This approach allows the removal of the neoplastic lesion with adequate margins and at the same time the immediate reconstruction of the defect maintaining a natural breast mound and improving cosmetic results. Literature reports as indications for OBCS: anticipated poor cosmetic outcomes, large tumours in large breasts, the need to reduce large breast to prevent complications related to post-operative radiotherapy.¹⁴ In our series we did not register restriction criteria, and OBCS was proposed to all women undergoing conservative breast surgery; furthermore a contralateral immediate procedure was performed if necessary, in order to obtain good breast symmetry. The main goal of OBCS is to obtain free surgical margins. A positive margin is associated with a significant increase in local recurrence risk and warrants consideration for additional surgery. The margin issue was clarified at the San Gallen Consensus conference of 2017,¹⁵ as 'no ink on tumor' for primary surgery of invasive tumors, and for 2 mm margins in DCIS. The panel again clarified that margins should not depend on tumor biology. Involved surgical margins occur in 20-40 % of the cases of standard breast conservative operations and 20% of these patients undergo reoperation including re-excision or completion mastectomy. When a re-operation is requested, a delay of adjuvant treatment might occur as well as additional surgical complications with poorer cosmetic outcomes. Moreover, extra surgeries represent a cause of stress and discomfort to patients and their families. Several preoperative localization studies have been proposed: wire guided excision (WGE), radio

occult lesion localization (ROLL). WGE has been probably the most commonly adopted pre-operative localization study for not palpable lesions in the last years.¹⁶

After WGE 10-43% of positive margins are reported and up to 40% of patients experience re-excision.¹⁷⁻¹⁸ Several disadvantages are reported in relation to this procedure.

WGE needs to be accurately scheduled with radiologists before acceding to the theatre but sometimes surgeries may be cancelled or postponed. The resulting discomfort and pain might prove to be difficult for patients to tolerate. Moreover, the wire can displace during the transportation procedures or mobilization of these patients to the surgical theatre. Most importantly, this technique does not allow checking on the specimen to evaluate whether an adequate amount of tissue has been removed. The ROLL, technique described elsewhere,¹⁸ shows percentages of free margins between 73-96% with a re-excision rate of 4.6-27%.¹⁹⁻²⁰

Main disadvantages are represented by the fact that the borders of the tumour are not visible during surgery and the gamma probe only guides the excision following the radiotracer diffusion area.

Furthermore, ROLL has to be programmed before surgery, involving multiple professionals such as radiologists and nuclear physicians to localize the lesion and to inject the radiotracer. Nowadays a multidisciplinary approach is always desirable; nevertheless, scheduling conflicts among departments can arise, especially in very crowded centers with high demand and few resources. Intraoperative ultrasound, in traditional conservative breast surgery, shows for palpable lesions, high rates of clear margins (95%), increasing the surgical accuracy of the cancer excision when compared to palpation guided procedure. Moreover US guided conventional breast surgery allowed to remove smaller specimen volume, avoiding resecting greater portions of healthy tissue, improving the cosmetic result as well as patient satisfaction.²¹ In non-palpable lesions the ultrasound-guided surgery has shown consistent benefits with a percentage of 81-97% negative margins even with DCIS, when an appropriate marker was adopted.²²⁻²⁴ After reviewing the literature, as far as we know, this is the first study focusing on ul-

trasound guided breast surgery in association with oncoplastic techniques. The oncoplastic approach requires an even more accurate lesion localization than conventional conservative breast surgery. In fact, while CBS consists in removing the specimen directly through a skin incision overlying the tumor, in case of oncoplastic techniques, the skin and or the nipple areolar complex are undermined and the full glandular thickness is resected; then volume displacement is performed and dermoglandular flaps are used to fill the defects. Intraoperative US guided surgery allows precise localization of the lesion, avoiding unnecessary wide excisions, with the final result of a specimen containing the cancer in the central part. Another advantage of intraoperative US is the represented by possibility of direct measuring the distance from tumour to the skin. This info is of main importance in guiding during the decision-making process especially in “border line” cases, to orienting the surgeon whether to remove the skin overlying the neoplasia or to maintain it. Once removed, the specimen can be checked again with US. It is possible to verify the presence of the lesion, and margins adequacy. If they appear to be not free surgical radicalization can be performed during the same procedure. In our series the tumour was always found within the specimen removed. This is particularly significant in case of not palpable lesions, mostly in the ones of small size found in patients with large breasts. In the 97% of cases the margin adequacy was confirmed by the histological report. This percentage is similar to data reported in literature for US guided standard conservative breast surgery.

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Currently to our knowledge, our study is the only one in literature reporting data about the combination of intraoperative US and OBCS. In 4 cases (3%) the procedure failed. In the first of these cases a margin was focally infiltrated by DCIS. The main lesion was correctly localized and removed, through a “wise pattern” approach with adequate margins, but it was surrounded by a multifocal DCIS that was neither visible at the pre-operative studies nor at the specimen US check. Patient was submitted to a second operation with an enlargement of the infiltrated margin creating great technical difficulty due to the residual volume replacement.

The second surgical specimen was negative for neoplasia either invasive or DCIS at the histological report. In the second case again a multifocal DCIS component was diagnosed at the histological report and it infiltrated the medial and the lateral margin of the removed specimen. The lesion diagnosed preoperatively was again removed with free margins but US was not able to localize the surrounding DCIS component. In this case due to the extensive intraductal component that affected almost completely a specimen measuring 13 x 8.5 x 6 cm, we deemed it necessary to submit the patient to a skin-reducing mastectomy with immediate heterologous reconstruction. The final histological report showed the presence of DCIS in the residual parenchyma indicating a multicentric disease. In the third patient the histological report was mucinous carcinoma. In this tumour the lesion can be isoechoic relative to the fat surrounding the breast tissue on ultrasound, which can make diagnosis difficult.²⁵⁻²⁶ In the fourth case the margin was actually adequate (0.07 mm) but due to the patient's young age, the report of triple negative ductal carcinoma a tissue enlargement was preferred. In our series of 12 patients with invasive ductal carcinoma with extensive intraductal component associated, 2 cases showed inadequate margins of excision (16.6%). This proportion of tumour-free margins even in women with additional in-situ carcinoma demonstrates the improvements in surgical accuracy obtained with perioperative ultrasound-guided surgery.²¹ Multicentric DCIS is uncommon, but DCIS within one quadrant may be extensive, with 46% of the lesions measuring > 3 cm.²⁷⁻²⁸ DCIS is mostly located in or around the invasive tumour, and although surgeons are generally unaware of the presence of a tumour-associated intraductal component—since it is non-palpable and mostly invisible with ultrasonography—the accuracy of ultrasound-guided surgery in localization of the central point of the cancer allowed additional and complete resection of DCIS. In 17 cases the US changed the surgical strategy. In 12 cases the margins were deemed not adequate and they were enlarged intraoperatively. The histological report found the lesion on the margin indicated by the US scan confirming the necessity to enlarge the resection. In this way 12 reoperations were saved. In the remaining 5 cases the en-

larged resection was proved to be not useful. This can be attributed to a prudent attitude we had at the beginning of our experience. The results of our preliminary experience clearly show that US guided surgery allows obtaining a high percentage of free margins in OPBS. This is independent from the oncoplastic pattern adopted. The time spent for the intraoperative US exam does not prolong significantly the entire surgical procedure.²⁹⁻³⁰ Moreover, the learning curve is acceptable, and we consider not very hard to reach an average and reliable level of confidence for a dedicated surgeon in order to gain enough experience to safely and adequately perform this procedure. A limit of this article is represented by the absence of a comparative study. Nevertheless, the outcomes are comparable to the ones published for intraoperative ultrasonography study in conventional conservative breast surgery.²¹

Conclusion

Full cooperation between radiologists and oncoplastic surgeons is mandatory to achieve high standard oncological and reconstructive outcomes. The procedure of tumor localization performed by an experienced dedicated radiologist is an indispensable step in planning the proper breast cancer surgical treatment and cannot be replaced. Nevertheless, an ideal technique that can guarantee an 100% free margins does not exist, and there is a variable set of circumstances in which a surgeon finds oneself dealing with potential difficult conditions and forced to work “freehand” with high risk of inadequate resections. Intraoperative IOUS definitely represents an additional cheap tool for the breast surgeon to improve the management of neoplastic breast lesions especially in patients undergoing oncoplastic surgery.

Conflict of interest

The authors declare that there is no conflict of interest.

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Figure Legend

Oncoplastic patterns adopted in this series of patients.

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Tables

	Total Lesions	Palpable lesions	Unpalpable lesions
Number	130	66	64
Mean dimension	12 mm (range 4-40 mm)	16 mm (range 11-40 mm)	7.8 mm (4-11 mm)
T staging	T1: 105 (80.7%) T2: 25 (19.3%)	T1: 41 (62.2%) T2: 25 (37.8%)	T1: 64 (100%)
Free Margins	126/130 (96.9%) Mean: 5.1 mm	64/66 (96.9%) Mean: 4.2 mm	62/64 (96.8%) Mean: 6 mm
IDC	90	48	42
DCIS	13	3	10
ILC	11	9	2
IDC + DCIS	12	5	7

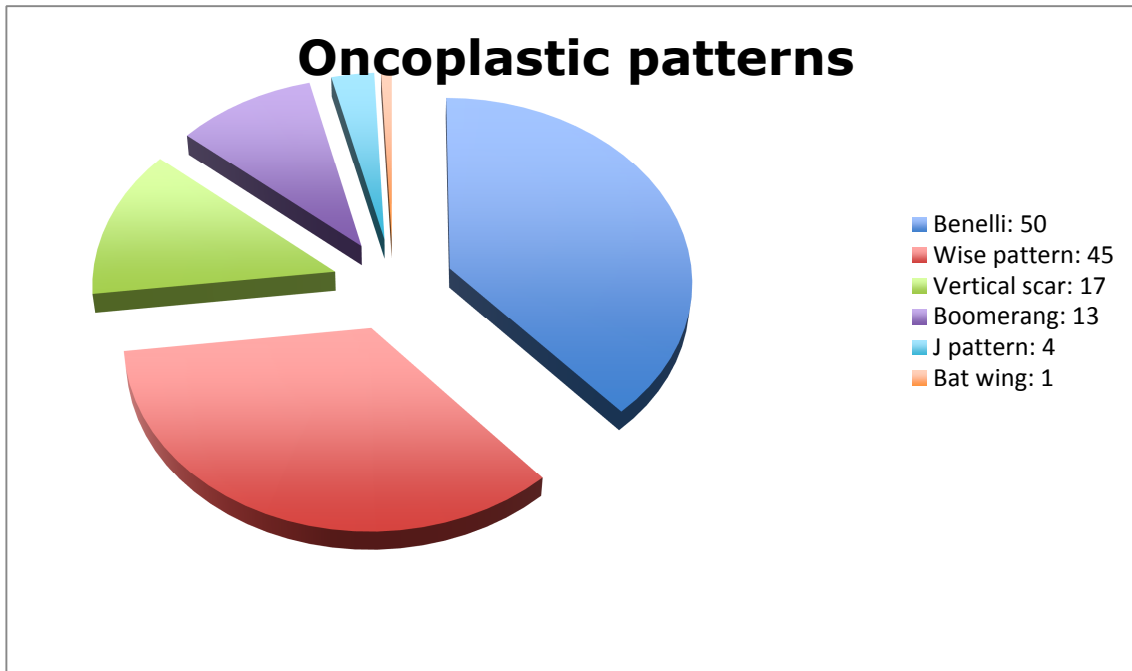
Table**1**

Data and characteristics of the lesions of patients treated by intraoperative ultrasound and oncoplastic combined approach. Mean dimension, and histological types grouped according to palpable or not palpable lesions are reported.

Abbreviations:

- IDC = Invasive ductal carcinoma
- DCIS = Ductal carcinoma in situ
- ILC = Invasive lobular carcinoma

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Figure

Oncoplastic patterns adopted in this series of patients are presented.