

Surgical resection margins after breast-conserving surgery: Senonetwork recommendations

Viviana Galimberti¹, Mario Taffurelli², Maria Cristina Leonardi³, Cynthia Aristei⁴, Chiara Trentin⁵, Enrico Cassano⁵, Francesca Pietribiasi⁶, Giovanni Corso¹, Elisabetta Munzone⁷, Carlo Tondini⁸, Alfonso Frigerio⁹, Luigi Cataliotti¹⁰, Donatella Santini¹¹

¹ Molecular Senology Unit, European Institute of Oncology, Milan - Italy

² Department of Medical and Surgical Sciences, University of Bologna, Policlinico S. Orsola-Malpighi, Bologna - Italy

³ Radiation Oncology Division, European Institute of Oncology, Milan - Italy

⁴ Radiation Oncology Section, University of Perugia and Santa Maria della Misericordia Hospital, Perugia - Italy

⁵ Breast Imaging Division, European Institute of Oncology, Milan - Italy

⁶ Pathology Unit, S. Croce Hospital, ASL TO 5, Moncalieri (Turin) - Italy

⁷ Division of Medical Senology, European Institute of Oncology, Milan - Italy

⁸ Unit of Medical Oncology, Department of Oncology and Hematology, Hospital Pope John XXIII, Bergamo - Italy

⁹ Regional Reference Center for Breast Cancer Screening, Turin - Italy

¹⁰ University of Florence, Senonetwork Italia, Florence - Italy

¹¹ Pathology Unit, University of Bologna, Policlinico S. Orsola-Malpighi, Bologna - Italy

ABSTRACT

This paper reports findings of the “Focus on Controversial Areas” Working Party of the Italian Senonetwork, which was set up to improve the care of breast cancer patients. After reviewing articles in English on the MEDLINE system on breast conserving surgery for invasive carcinoma, the Working Party presents their recommendations for identifying risk factors for positive margins, suggests how to manage them so as to achieve the highest possible percentage of negative margins, and proposes standards for investigating resection margins and therapeutic approaches according to margin status. When margins are positive, approaches include re-excision, mastectomy, or, as second-line treatment, radiotherapy with a high boost dose. When margins are negative, boost administration and its dose depend on the risk of local recurrence, which is linked to biopathological tumor features and surgical margin width. Although margin status does not affect the choice of systemic therapy, it may delay the start of chemotherapy when further surgery is required.

Keywords: Breast cancer, Breast network, Conservative surgery, Surgical margin

Introduction

The purpose of breast-conserving surgery (BCS) for women with cancer is to perform an oncologically radical procedure with disease-free margins at the final histological assessment and with the best aesthetic result possible (1).

Even if the margins are negative, cancer cells may be present in the apparently healthy tissue beyond them, which is why adjuvant radiotherapy is almost always administered in association with BCS (2). When the margin is frankly positive,

re-excision or mastectomy is indicated, since retrospective studies and meta-analyses show that patients who do not undergo re-excision are at increased risk of local recurrence (3-5). It is also important to note that re-excision may have a poor cosmetic outcome (obviating the reason for conservative treatment), delay adjuvant treatment, and cause the patient considerable stress (6).

Many recent studies aimed to identify prognostic factors of margin positivity in order to select patients who are most at risk of re-excision after BCS. Significant predictors of positive margins after BCS include microcalcifications (vs. nodular or mass lesions), size of the principal lesion (≥ 2 cm vs. < 1 cm) and ductal carcinoma in situ (7-10). According to some authors they permit a priori selection of patients at high risk of surgical re-excision (11), while other factors like multifocality or a lobular component (12) cannot always be ascertained before surgery.

The present report is based on a consensus reached by the Focus on Controversial Areas Working Party belonging to the Italian Network of Senology Centers (Senonetwork). Senonetwork Italy started in March 2012 to promote breast

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Corresponding author:

Viviana Galimberti
Molecular Senology Unit
European Institute of Oncology
Via G. Ripamonti 435
20141 Milano, Italy
viviana.galimberti@ieo.it



cancer treatment in Italy that conforms to the guidelines set out by the European Society of Breast Cancer Specialists (EUSOMA). All Italian breast cancer centers treating over 150 new cases per year are being urged to adhere to Senonetwork Italy initiatives.

After reviewing articles in English on the MEDLINE system, the Working Party here presents their recommendations for identifying risk factors for positive margins, suggests how to manage them so as to achieve the highest possible percentage of negative margins, and proposes standards for investigating resection margins and therapeutic approaches according to margin status.

Indications for breast-conserving surgery

When proposing BCS, proper indications are essential to obtain negative margins. Such indications include an appropriate ratio between breast size and tumor size, the presence or absence of microcalcifications in the area surrounding the tumor, the site of the tumor, targeted of radiotherapy, and patient preference. These indications are the fruit of careful multidisciplinary preoperative assessment involving specialists like surgical, medical and radiation oncologists, the plastic surgeon, the diagnostic radiologist, and the pathologist. According to the site of the tumor and its biological and pathological characteristics, the multidisciplinary team decides whether or not neoadjuvant chemotherapy is required to reduce the tumor volume before BCS (13). Marking the tumor before neoadjuvant chemotherapy is recommended, because any cancer downstaging after treatment may alter the initial anatomical landmarks. When microcalcifications are found over a wide area, the multidisciplinary team will decide along with the patient whether BCS is the best option.

Preoperative phase: breast imaging

BCS as an option is assessed based on the results of clinical and radiological tests that should be performed by expert radiologists working in the breast unit. Mammography and ultrasound, either alone or in combination, remain the primary diagnostic and preoperative imaging methods as they visualize the tumor (which manifests principally as a mass or microcalcifications), assess its extent, detect multiple foci and exclude contralateral carcinomas, which are found in 1%-3% of cases at diagnosis (14). Mammography detects both the tumor mass and/or microcalcifications, thus enabling the radiologist to map their distribution. Tomosynthesis, a special kind of mammography that produces a 3-dimensional image of the breast by using several low-dose x-rays obtained at different angles, detects and maps lesions that tissue overlap might hide in standard mammography (15). Initial clinical experiences seem to indicate it is particularly useful in elucidating parenchymal distortions in dense breasts. Moreover, in women with dense breast tissue or mammography findings of nodular/mass lesions, ultrasound is recommended according to the EUSOMA indications (16, 17).

Although ultrasound is used for preoperative mapping of multifocal cancer, its limitations may preclude a precise definition of disease extent, which may, at times, be underes-

timated (18, 19). Since ultrasound is an operator-dependent mode of measurement, standards are still lacking, despite a common terminology for the various degrees of suspicion (BI-RADS).

Magnetic resonance imaging (MRI) has come to play a key role in the preoperative workup for breast cancer. MRI is reported to be more sensitive than mammography and ultrasound in determining tumor size and disease extent, identifying multifocality, and assessing the response to neoadjuvant chemotherapy (20-25). Furthermore, contrary to what was initially believed, MRI is more accurate than mammography alone (range: 38%-64% vs. 27%-43%) in defining intraductal disease and an extended intraductal component (26-28). MRI highlights additional lesions in 6% to 34% of cases (29), with a higher frequency in high-risk women and women with invasive lobular carcinoma (30-32). Despite this advantage, MRI's specificity is low and the number of false positives significant (33). A MRI-guided biopsy of suspicious lesions detected only on MRI may lower the false positive rate (34).

A meta-analysis of 19 studies showed preoperative MRI led to a change in the surgical approach in 16.6% of cases, increasing the number of wide excisions and mastectomies correctly in 11.1% but amounting to overtreatment in 5.5% (35). Even though MRI slightly overestimated tumor size compared with histology, the overestimation was not clinically significant (36) and MRI does not appear to be of help in reducing the repeat operation rate (37). However, there are still some controversies regarding the clinical utility of MRI and whether its use improves surgical management; in fact, MRI cannot be considered suitable as the only approach for a preoperative evaluation of the breast.

Given these limitations, EUSOMA drew up international guidelines recommending preoperative MRI in the following cases (33): a) invasive lobular carcinoma; b) age under 60 years with a difference in tumor size >1 cm between mammography and ultrasound when expected to impact on treatment decision-making; and c) eligibility for partial breast irradiation. For preoperative MRI candidates who cannot have MRI for any reason, ultrasound was recommended.

Breast density is not an indication for preoperative MRI. According to EUSOMA, specifically designed randomized or observational studies are needed in patients with dense breasts who are <40 years of age or who have an intermediate lifetime risk (15%-20%) due to other factors.

To sum up, in preoperative breast imaging mammography alone defines disease extent in cases of microcalcifications, in fatty breasts, and in patients who are not eligible for partial breast irradiation. In all other cases mammography should be combined with ultrasound and/or MRI (according to the EUSOMA criteria). MRI should always be used if the preoperative biopsy demonstrated an invasive lobular lesion, an extensive intraductal component, or suspected multifocality.

Although modern imaging techniques provide much better definition of disease extent, thus improving treatment choice and outcomes, there is no evidence that they impact upon margin status. Among the new techniques that are currently under investigation, preliminary reports suggest elastosonography is promising as a potential method for reducing positive margins in invasive lobular tumors (38).

Intraoperative phase: breast surgery

To obtain negative margins and minimize the risk of reoperation, particularly in cases of occult breast cancer, certain techniques and preoperative procedures should be implemented. For example, charcoal, metal wire, and radioguided occult lesion localization (ROLL) help localize the cancer site but their accuracy depends on each center's volume of patients and experience (39-41).

For palpable lesions, the resection should include the tumor and an adequate amount of surrounding healthy tissue. Once the surgical specimen has been removed, the surgeon uses a method agreed on with the pathologist, to position guiding markers on the resection margin circumference for easy orientation. If the skin has not been removed, the upper margin must be indicated. Macroscopic evaluation of the resection margins is essential. The pathologist informs the surgeon which margin is nearest to the cancer, and whether and where any enlargement should be performed.

For microcalcifications and/or nonpalpable lesions a 2-dimensional x-ray of the specimen will ascertain whether they have been removed. When small nonpalpable lesions are visible on the x-ray, their distance from the margins can be measured. The x-ray will also show any clips that were left during biopsy sampling.

Although rarely considered in clinical practice, intraoperative ultrasound can be an alternative approach for obtaining negative margins.

In the last decade, routine frozen section evaluation of margins has been optional and does not guarantee negative margins after complete examination (42).

Postoperative phase

Pathology

The results of the microscopic examination provide a detailed description of the surgical sample and how it was analyzed (43). After BCS resection margins are marked with China ink or multiple color pigments for correct identification and assessment. Small-to-medium-sized specimens are sectioned at 3-5-mm intervals, perpendicularly to one of the spatial axes (e.g., medial-lateral) or parallel to the nipple and the fascia pectoral direction. Methods for analyzing specimens include a) perpendicular samples in ordinary blocks; b) perpendicular samples in large blocks (macro-sections); c) shaved samples (peeling); d) biopsies separate from the surgical cavity/bed. All procedures accurately assess the excision margins and measure the distance between the excision surfaces and the lesion precisely. With sequential sampling in ordinary blocks, lesion extension is calculated by multiplying the number of consecutive levels in the sample by level thickness. If this is not possible, an x-ray of the macro-sections is highly recommended.

Some of the common terminology for defining surgical resection margins is obsolete and hard to apply when selecting treatment approaches. In accordance with the Society of Surgical Oncology (SSO) and American Society for Radiation Oncology (ASTRO) consensus guideline (44), we opted

for positive or negative margins but decided to include further information:

Positive margin (ink on the lesion), specifying a) which margin(s); b) whether invasive foci are single or multiple; c) the linear extent of margin involvement in millimeters; d) an in situ component on the margin.

Tumor-free (negative) margin (no ink on the invasive neoplastic lesion and/or any in situ ductal component). The distance of the lesion from the margins that have been macroscopically sampled should be specified (including the distance from any in situ component).

The SSO guideline is applicable to invasive, early-stage breast cancer.

Radiotherapy

Besides margin status, clinical features, pathological and biopathological disease characteristics determine whether radiotherapy will be delivered and what total dose will be used. Decision-making is carried out by the multidisciplinary team.

Positive margin (tumor on inked margin)

In case of multiple positive margins a re-excision must always be requested because of the high risk of recurrence. Positive margins with anterior under skin and posterior to muscle locations (deep margin 10 mm) do not require re-excision or a boost dose increase, as there is no additional breast tissue left behind (45, 46).

When the patient refuses re-excision or when, after a re-excision with positive margins, a second conservative approach is not technically possible and/or the patient refuses to undergo a mastectomy, radiotherapy is recommended with the boost dose increased up to a maximum of 20 Gy (or equivalent dose in hypofractionated schedules) (47-50). Indeed, in the EORTC study, when margins were positive, high doses decreased the local recurrence rate (10.8% with a 26 Gy boost vs. 17.5% with a 10 Gy boost), although not significantly, probably due to the small population sample. Doses >20 Gy should be avoided because of the excess risk of side effects and poor cosmetic outcome (48). Informed consent is essential because radiotherapy in these cases is second-line treatment and even with the high-dose boost is not associated with the same success rate as surgery. Extensive discussion with the patient is required.

When only 1 margin is positive, the multidisciplinary team may opt for either re-excision or radiotherapy with increased but variable boost doses, generally up to a maximum of 20 Gy (or equivalent dose in hypofractionated schedules). The decision will be based on the linear margin extent and the presence of risk factors for local recurrence (e.g., young age, large tumor size, high grade, lymph node involvement, extensive intraductal component, high Ki-67) (49-58).

Negative margin (no tumor on inked margin)

The boost may be omitted in the absence of any risk factors for relapse (59), particularly in the elderly, as a clinically significant benefit from the boost is questionable in this age group (60). The boost is administered when unfavorable risk

factors for local recurrence are present, and the dose will vary accordingly: 10 Gy is the standard in Italy; 14–20 Gy (or equivalent doses in hypofractionated schedules) may be given in selected high-risk cases on account of the risk factors and short surgical margin distance from the tumor.

Systemic treatments

The choice of treatment depends mainly on the biological characteristics and partly on disease extent (T and N). Positive margin status may impact on systemic treatment as the need for re-excision could delay its start. According to recent ESMO guidelines (61), treatment should start preferably within 2 to 6 weeks of surgery. In particular, physicians should remember that the efficacy of systemic therapy is lower when it is administered more than 12 weeks after surgery (62).

The 12-week cut-off was derived from adjuvant chemotherapy trials, which established that time from surgery to chemotherapy should range from 8 to 12 weeks. However, since no patients were admitted to the trials after the 12-week deadline, the impact of starting chemotherapy later is as yet unknown.

Concluding remarks

In recent years, new imaging, diagnostic and surgical techniques ensure better selection of eligible patients for BCS, which is now established as treatment for breast cancer patients. Many previously absolute contraindications to BCS have become relative or are even no longer contraindications (63) and BCS plus radiotherapy, for example, is now considered safe even for patients ≤ 35 years of age at diagnosis (64, 65).

Although examination of surgical resection margins aims at complete removal of cancer embedded within the breast parenchyma, multidisciplinary teams and working parties that focus on breast cancer still encounter difficulties in selecting appropriate management strategies for different margin statuses.

The intraoperative phase is crucial in determining whether margins are positive or cancer free. Macroscopic examination provides useful information such as the distance between the tumor and the resection margins so that, if required, the surgical oncologist can perform a re-excision without the need for a deferred operation. Modern techniques such as ROLL facilitate the identification of clinically nonpalpable lesions in centers with appropriate expertise. An x-ray of the surgical specimen is a valid tool for determining whether microcalcifications and/or nonpalpable lesions have been removed.

In the postoperative phase microscopic examination of the surgical specimen provides information on margin status, on the distance between the margins and the tumor, and on the biological phenotype of the cancer. These data aid the multidisciplinary cancer care team in planning therapy so as to minimize the risk of recurrence.

When margins are positive, approaches may include re-excision, mastectomy or, as second-line treatment, radiotherapy with a high boost dose. In accordance with the SSO-ASTRO consensus guideline (44), the choice of boost administration and its dose for patients with negative margins should be based on the risk of local recurrence, which is linked to clinical, pathological and biopathological tumor

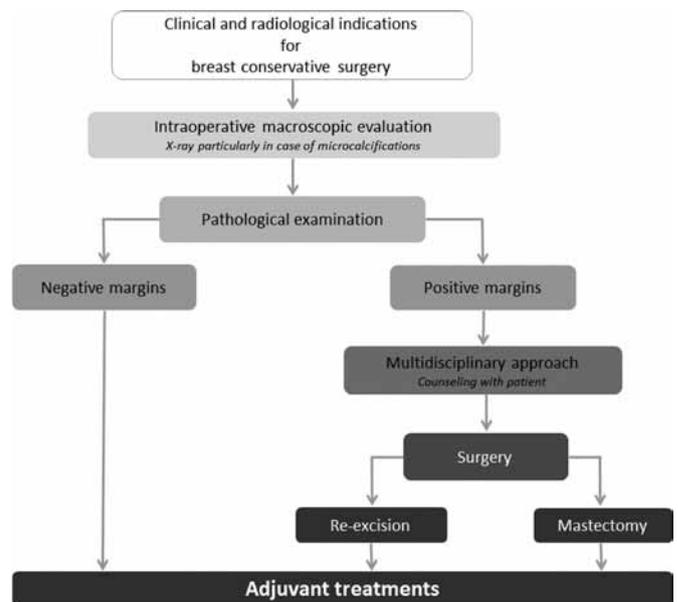


Fig. 1 - In this flowchart we propose a model for the management of resection margins in breast-conserving surgery. After the definition of clinical and radiological indications, the margins are macroscopically evaluated intraoperatively and in case of microcalcifications they are examined by x-ray. The pathologist defines the margins as negative or positive. In case of positive margins, surgical re-excision is required.

features and should not be based only on the width of the surgical margins. Differently from the SSO-ASTRO consensus guideline, the Senonetwork recommendations propose modulating the boost doses depending on risk factors and margin status. Although margin status does not affect the choice of systemic therapy, it may delay the start of chemotherapy when further surgery is required. The Senonetwork recommendations are summarized in Figure 1.

Finally, evidence shows that BCS is a valid strategy and that a targeted approach depends on knowledge of clinical features, diagnostic imaging, and biopathological and molecular tumor factors (65, 66). In the future, advances in what is known about the molecular and genetic factors underlying breast cancer development may ensure that every patient has her own targeted treatment protocol, with the greatest possible chances of cure.

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