Practical consensus recommendations for tumor margins and breast conservative surgery

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Abstract

My suggestion: There is no difference in survival of breast cancer patients treated with either mastectomy or with breast conservation therapy combined with external beam radiotherapy. A positive margin (s) is an important factor contributing to the increased risk of local recurrence. However, in published literature, there is a lack of consensus on the definition of acceptable margin (s). As a result, decision process about need for re-excision after positive margins remains unclear.

Key words: Acceptable margin, extensive intraductal component, nodal metastasis, original size, re-excision, resection

Introduction

Breast cancer is the commonest cancer among women worldwide, with the lowest incidence being reported from far eastern and south eastern Asian countries. In recent years, breast cancer has emerged as the commonest malignancy affecting women in the majority of Asian countries. The breast cancer cause-specific mortality in most Asian countries is also higher as compared to western countries. Larger proportions of breast cancer patients in developing Asian countries are younger than patients in developed Asian and western countries.

The adoption of screening mammography has led to the identification of smaller, often non-palpable, tumors that can be treated with breast-conserving surgical approaches as opposed to mastectomy. Breast-conserving therapy (BCT) followed by irradiation nowadays is the treatment of choice for early-stage disease. There is no difference in long-term survival (more than 20 years) between mastectomy and BCT combined with external radiotherapy. The main goal of BCT is the complete removal of cancer with clear surgical margins while maintaining the natural shape of the breast. The principal risk with the conservative option is local recurrence, ranging between 0.6% and 1.5% per year, and is directly related to the presence of residual tumor in the remaining mammary gland, since isolated local recurrence (i.e., without systemic metastases) is mainly observed in the first 2–3 years after surgery.

Expert group of oncologists met in the update in oncology-X-2017 to discuss on available strategies and approaches to tumor margins and breast conservative surgery for the treatment of breast cancer.

The update in oncology-X-2017 was organized by Sir Ganga Ram Hospital discuss and arrive at a consensus statement to provide community oncologists practical guidelines for challenging common case scenarios in Breast Cancer out of these we are discus about tumor margins and breast conservative surgery in this chapter. While the discussions will take the scenario as exists in India as a representative country with limited resources, the final manuscript is applicable globally.

The discussion was based on domain expertise of the National as well as international faculty, published evidence and practical experience in real life management of breast cancer patients. Opinion of the 250 oncologist including medical oncologist, radiation oncologist, surgical oncologist, molecular oncologist and radiologist are present in the update in oncology-X-2017 was taken into consideration by the expert panel.

The expert group was chaired by Dr. Rajiv Kumar and Dr. Somsekhar whereas the discussions were moderated by Dr. Ramesh Sarin. The core expert group consisted of Dr. Pawan Gupta, Dr. Sumeet Jain, Dr. Pramoj Jindal, Dr. Vaishali Zamre, Dr. Firoz Pasha and Dr. Sarah P Cate.

Consensus answers were used as the basis of formulating the consensus statement providing community oncologists with ready-to-use practical recommendations. The survey answers were used as the basis for formulating the consensus statement so that community oncologists have a ready-to-use practical recommendations for tumor margins and breast conservative surgery.

As part of the background work, the best existing evidence was compiled and provided to the expert group panel members for review in preparation for the expert group meeting. The national and international experts invited to this meeting were also provided the data on the voting by the audience delegates from the update in oncology-X-2017. Members of the panel were also allowed to share their personal experiences, make comments and record dissent while voting for the consensus statements. Total of sixteen broad question categories were part of the expert group discussions.

The American Society of Clinical Oncology (ASCO) Clinical Practice Guidelines Committee (CPGC) identified a guideline for endorsement that addressed margins for breast-conserving surgery.
Table 1: Should the entire area of the original primary be resected after downstaging

| Options (%) | Yes | No | Abstain |
|-------------|-----|----|--------|
| Percentage of polled oncologists at update in oncology-X-2017 | 70 | 20 | 0 |
| Percentage of polled oncologists at St. Gallen’s consensus - 2017 | 14 | 82 | 4 |

Expert group consensus: Even after taking into consideration the St. Galen’s 2017 statement, the current consensus for India still remains that entire area of the original primary needs to be resected.

Table 2: What should be the minimum acceptable surgical margin to avoid re-excision (with multifocal residual disease in their pathological specimen)?

| Options (%) | No ink on invasive tumor or DCIS? | 2 mm clearance? | 2-5 mm clearance? | >5 mm clearance? |
|-------------|----------------------------------|-----------------|-------------------|-----------------|
| Percentage of polled oncologists at update in oncology-X-2017 | 0 | 0 | 100 | 0 |
| Percentage of polled oncologists at St. Gallen’s consensus - 2017 | 95.8 | 4.2 | 0 | 0 |

Expert group consensus: The minimum acceptable surgical margin for avoiding the need for re-excision is 2–5 mm of clearance. DCIS = Ductal carcinoma in situ.

Table 3: How many times should frozen section for margin status be sent before abandoning breast conserving surgery?

| Options (%) | 1-2 | 3-4 | Abandonment will depend on the size of tumor to be excised in relation to the size of the breast concerned |
|-------------|-----|-----|--------------------------------------------------|
| Percentage of polled oncologists | 33.3 | 33.3 | 33.3 |

Expert group consensus: The expert group recommendation is that abandonment of BCS needs to be individualized for each patient and will depend on the relative size of tumor with respect to the breast concerned. BCS = Breast conserving surgery.

Table 4: If whole breast radiation treatment is planned, what is the minimum margin width sufficient to avoid re-excision?

| Options (%) | No ink on invasive tumor or DCIS | 2 mm clearance | 5 mm clearance | Abstain |
|-------------|----------------------------------|----------------|----------------|--------|
| Percentage of polled oncologists at update in oncology-X-2017 | 16.7 | 16.7 | 66.6 | 0 |
| Percentage of polled oncologists at St. Gallen’s consensus - 2017 | 25 | 25 | 25 | 25 |

Expert group consensus: While the majority of polled oncologists preferred a 5 mm clearance, the expert group consensus recommendation was that a 2 mm clear margin is sufficient to avoid re-excision when breast irradiation is part of the treatment plan. DCIS = Ductal carcinoma in situ.

Table 5: Tumor foci contained in one “quadrant” of the breast (multifocal) can be treated with breast conservation; provided margins are clear and adequate radiotherapy is planned

| Options (%) | Yes | No | Abstain |
|-------------|-----|----|--------|
| Percentage of polled oncologists at update in oncology-X-2017 | 83.3 | 16.7 | 0 |
| Percentage of polled oncologists at St. Gallen’s consensus - 2017 | 97.1 | 2.9 | 0 |

Expert group consensus: Yes, it is possible to recommend BCS to such patients. BCS = Breast conserving surgery.

Table 6: Tumor foci in more than one “quadrant” of the breast (multicentric) can it be treated with breast conservation; provided margins are clear and adequate radiotherapy is planned

| Options (%) | Yes | No | Abstain |
|-------------|-----|----|--------|
| Percentage of polled oncologists at update in oncology-X-2017 | 0 | 100 | 0 |
| Percentage of polled oncologists at St. Gallen’s consensus - 2017 | 60.6 | 33.3 | 6.1 |

Expert group consensus: Even after taking into consideration the St. Galen’s 2017 statement, the current consensus for India is that BSC is NOT recommended to patients who have tumor in more than one quadrant of the breast (multicentric).

Breast conserving surgery (BCS) is widely considered to be the standard operative approach for treating most patients with early stage breast cancers. The goal of BCS is to achieve adequate surgical margins during the initial surgical resection while optimizing the aesthetic appearance of the breast. Additional surgery with re-excision may not only compromise cosmesis, but also can increase morbidity and costs. It is standard practice to re-excite additional breast tissue for positive margins to reduce the risk of local recurrence. The therapeutic decisions for positive margins are relatively straightforward; however, only recently has there been published consensus over what constitutes an adequate negative margin. Historically, the criteria for an adequate negative margin had relatively arbitrary thresholds ranging from “no tumor at inked margin” to 10 mm or more. Although absence of tumor at the inked margin is the current recommendation from national clinical consensus guidelines, there has been a considerable variation in practice patterns among surgeons regarding the decision to re-excite or perform a mastectomy based on margin distance. The status of the surgical margins is assessed by applying ink to the surface of the lumpectomy specimen and determining the microscopic distance between tumor cells and the inked surface. The exact definition of an adequate surgical margin after breast cancer resection has long been debated among physicians and represents an area of considerable variation in clinical practice.
Pathological Evaluation

There is no standard method of margin evaluation for breast cancer specimens and there is no standard number of histologic sections examined from each margin surface. Margins can be evaluated (A) by a radial method, (B) by a shaved method, or (C) by shaving the walls of the lumpectomy cavity.

(A) The most common method of margin assessment is the radial (or perpendicular) margin technique, which allows for a precise measurement of the distance from the tumor to the inked margin. With this method the specimen is received with at least two of the margins marked with metal clips or sutures for specimen orientation. The six margins of the specimen are then inked in six different colors by the processor. The inked breast tissue is cut into 0.2-0.3 cm sequential sections perpendicular to its long axis so that the perimeter of each tissue section contains few (two to four) margins identified by the different ink colors.

With this technique the pathologist can report the exact microscopic distance from the tumor to each margin and can distinguish between a truly positive margin (tumor at ink) and a close margin. The disadvantages of this method include running ink, imprecise margin orientation and surface complexity of the breast specimen.

(B) The use of shaved (en face) margins allows the oriented specimen to be inked entirely in one color, as long as the processor is able to maintain the proper orientation, and eliminates the problem of different color inks running together.

With this technique the pathologist can report the exact microscopic distance from the tumor to the inked margin and can distinguish between a truly positive margin (tumor at ink) and a close margin. The disadvantages of this method include running ink, imprecise margin orientation and surface complexity of the breast specimen.

(C) The third method, shaving the walls of the lumpectomy cavity, provides a nice solution to margin evaluation and combines the advantages of the radial and en face margin assessments: the surgeon resects the index lesion and then takes separate shaved margins from the cavity. The main breast specimen containing the tumor is received unoriented and does not need to be inked. Each shaved specimen represents a margin (medial, lateral, superior, inferior and posterior walls of the cavity) and is received oriented with a suture or metal clip designating the final surgical margin. The anterior margin may or may not be submitted by the surgeon. This technique allows precise margin designation and an accurate measurement of the margin width, and limits additional manipulation of the breast tissue since compression devices used for the specimen radiography may alter measurements of the margin distances. Although an increase in the number of histologic blocks and slides is the main concern for this method, a number of studies report that this method reduces the rate of re-excision for close margins.

Surgical Margins

The possible scenarios of margin assessment encountered at the microscope are: broadly positive margin, focally positive margin, close margin, negative margin, and cauterized margin. As previously mentioned, there is a lack of standardization in the pathological methods of margin evaluation, which yields little consensus regarding what constitutes an adequate negative margin. Patient management varies widely based on the threshold that surgeons accept for adequate margins and the subsequent need for re-excision. Morrow et al. recently proposed that the negative margin used in the National Surgical...
Table 11: Question 1 (II) - In patients with macro-metastases in 1-2 sentinel nodes, completion of axillary dissection can safely be omitted following breast conservative surgery if radiotherapy is part of treatment plan

| Options (%) | Conservative resection with radiotherapy using standard tangents | Conservative resection with radiotherapy using high tangents | Both | No | Abstain |
|-------------|---------------------------------------------------------------|-----------------------------------------------------------|------|----|--------|
| Percentage of polled oncologists at update in oncology-X-2017 | 20 | 20 | 20 | 20 | 20 |
| Percentage of polled oncologists at St. Gallen's consensus - 2017 | 0 | 0 | 78.1 | 18.8 | 3.1 |

Expert group consensus: Expert panel agree that in patients with macro-metastases in 1-2 sentinel nodes, completion of axillary dissection can safely be omitted following breast conservative surgery if radiotherapy is part of treatment plan, irrespective of whether radiotherapy is with standard or high tangents.

Table 12: Question 12 - In patients with macro-metastases in 1-2 sentinel nodes, completion of axillary dissection can safely be omitted irrespective of tumor biology (LVI, estrogen receptor negative, Grade 3 etc.)

| Options (%) | Yes | No | Abstain |
|-------------|-----|----|--------|
| Percentage of polled oncologists at update in oncology-X-2017 | 33.3 | 33.3 | 33.3 |
| Percentage of polled oncologists at St. Gallen's consensus - 2017 | 76.9 | 23.1 | 0 |

Expert group consensus: Tumor biology should be taken into consideration when deciding about need for completion axillary dissection if macro-metastases is present in 1-2 sentinel node(s).

Table 13: Question 13 - In a patient who is clinically (at palpation and on ultrasonography) node-negative at diagnosis: Is sentinel node biopsy appropriate?

| Options (%) | Yes | No | Abstain |
|-------------|-----|----|--------|
| Percentage of polled oncologists at update in oncology-X-2017 | 33.3 | 33.3 | 33.3 |
| Percentage of polled oncologists at St. Gallen's consensus - 2017 | 95.7 | 4.3 | 0 |

Expert group consensus: Yes, sentinel node biopsy is appropriate even for patients with clinically node negative disease.

Adjuvant Breast and Bowel Project (NSABP) trials should be adopted as the definition of an adequate margin, and the close margin, as described by pathologists and interpreted by patients and clinicians as evidence of inadequate surgery, should be replaced by the measurement of the distance of the tumor from the inked resection margin, without any additional qualifications.

It is also important to recognize that a reported negative margin does not confirm that there is no residual tumor in the breast; rather it indicates that the residual tumor burden is low enough to be likely controlled by radiotherapy. In recognition of the multiple factors impacting local control of breast cancer, a consensus conference concluded that the only negative margin width for all patients with invasive carcinoma was tumor not touching the inked margin.[33]

The criteria for surgical re-excision by mastectomy after BCT, according to the Standards, Options and Recommendations (SOR) guidelines are positive resection margins, the extension of intraductal lesions extending beyond 3 cm, and the presence of multifocal lesions.[47,48] However, according to the literature, 30–65% of mastectomies performed after BCT are free of residual tumor, which therefore casts doubt on the validity of these procedures providing no therapeutic benefit, impairing cosmesis and increasing morbidity and costs.[49,50] In daily clinical practice it is important to know predictors of the risk of residual cancer in the presence of positive or close margins in order to identify patients in whom unnecessary re-excision (s) or mastectomies could be avoided. Young age, tumor size, nodal status, number of involved margins, multifocality and extent of the tumoral lesion, presence of an extensive intraductal component have been found to be associated with the risk of residual cancer in the tumor cavity.[20,51-54]

In any case, no predictive factor has yet been proven to be reliable enough to exactly identify patients with involved margins in whom re-excision (s) or mastectomies could safely be omitted. However, it is also important to establish the exact anatomical situation of the positive margins; the absence of re-excision in the case of positive margins, whether anterior (close to skin) or posterior (close to pectoral muscle), does not appear to significantly increase the risk of recurrence, whereas positive margins are a risk factor for local recurrence when in contact with the remnant gland.[55]

The definition of acceptable margin width is similar for invasive cancer and for DCIS with RT; in DCIS treated without RT larger margins are favored. The case is different for lobular carcinoma in situ (LCIS) which is known to be a marker for breast cancer and not necessarily a precursor. A larger recent study has shown classic LCIS near the margin does not increase local recurrence.[56]

Neoadjuvant chemotherapy (NACT) has the potential to allow removal of a smaller amount of breast tissue than if surgery was performed at initial presentation. Shrinkage of the locally advanced breast tumor in response to NACT has been shown to occur in two different ways: concentrically and in a honeycomb or buckshot pattern. In patients with a pathologic complete response or concentric tumor shrinkage, consideration of margin width does not differ from that in a non-NACT setting. In contrast, in patients with the buckshot pattern of tumor shrinkage, determination of the appropriate extent of resection may be problematic perhaps due to the biologic features of the tumor, suggesting that if viable residual tumor is present scattered throughout the lumpectomy, even if it is not at the inked margin, re-excision should be considered.[57]

Sentinel Lymph Node Biopsy

If the patient has clinically positive axillary lymph node(s) at diagnosis, and then is given systemic therapy (neoadjuvant), the role of SLNB has remained controversial.

SLNB without level I and II axillary dissection hasn’t been performed in patients with clinical N+ at diagnosis even when the axillary status has been downstaged by the systemic treatment.

SENTINA trial, a prospective trial in Germany and Austria, showed that after treatment, the detection rate of metastases by sentinel lymph node dissection becomes low with a high FNR.
Abandonment of BCS needs to be individualized for each tumor biology should be taken into consideration when making decisions about the necessity of tumor margin. A 2 mm clear margin is sufficient to avoid re-excision when the primary tumor, the minimum acceptable surgical margin for avoiding need for re-excision is 2–5 mm of clearance. Abstain

In patients with macro-metastases in 1-2 sentinel nodes, it is possible to offer breast conservation to patients after taking into consideration the St Gallen’s 2017 statement, if it is plan of treatment. A 2 mm clear margin is sufficient to avoid re-excision when breast irradiation is part of treatment plan.

The treating oncologist usually will take into consideration several factors, including but not limited to, tumor biology and histology while planning tumor margin. Age has no bearing on the requirement of tumor margin for that patient.

The tumor margin is NOT required to be greater in the presence of EIC. In patients with macro-metastases in 1-2 sentinel nodes, completion of axillary dissection can safely be omitted following mastectomy irrespective of whether radiotherapy is planned or not.

In patients with macro-metastases in 1-2 sentinel nodes, completion of axillary dissection can safely be omitted following Breast Conservative Surgery if radiotherapy is a part of treatment plan, irrespective of whether radiotherapy is with standard or high tangents. Tumor biology should be taken into consideration when deciding about need for completion axillary dissection if macro-metastases are present in 1-2 sentinel node(s).

Sentinel Node biopsy may be done after neo-adjuvant chemotherapy, provided it already forms plan of treatment for that patient. It is not recommended to do sentinel node biopsy if chemotherapy has resulted in successful downstaging of clinically axillary lymph node positive disease, except for carefully selected patients where more than two SLNs are removed for analysis.

Table 14: Question 14 - In a patient who is clinically (at palpation and ultrasonography) node-negative at diagnosis: When is the best time point for sentinel node biopsy?

| Options (%) | Before the start of neo-adjuvant chemotherapy | After neo-adjuvant chemotherapy | Either before or after chemo are valid options | Abstain |
|-------------|-----------------------------------------------|---------------------------------|-----------------------------------------------|---------|
| Percentage of polled oncologists at update in oncology-X-2017 | 25 | 25 | 25 | 25 |
| Percentage of polled oncologists at St. Gallen’s consensus - 2017 | 20 | 60 | 16.7 | 3.3 |

Expert group consensus: Sentinel Node biopsy should be done after neo-adjuvant chemotherapy has been given, if it is plan of treatment.

Table 15: Question 15 - In a patient who is clinically node-positive at diagnosis and who downstage (becomes clinically node negative) after chemotherapy, is sentinel node biopsy appropriate with 1-2 lymph node detected?

| Options (%) | Yes | No | Abstain |
|-------------|-----|----|---------|
| Percentage of polled oncologists at update in oncology-X-2017 | 33.3 | 33.3 | 33.3 |
| Percentage of polled oncologists at St. Gallen’s consensus - 2017 | 42.9 | 53.6 | 3.6 |

Expert group consensus: As a general rule, it is not recommended to do sentinel node biopsy if patient has already received systemic chemotherapy because it leads to low detection rates and high false negative rates.

Table 16: Question 16 - In a patient who is clinically node-positive at diagnosis and who downstage (becomes clinically node negative) after chemotherapy, is sentinel node biopsy appropriate only in selected cases such as >2 sentinel node evaluated?

| Options (%) | Yes | No | Abstain |
|-------------|-----|----|---------|
| Percentage of polled oncologists at update in oncology-X-2017 | 33.3 | 33.3 | 33.3 |
| Percentage of polled oncologists at St. Gallen’s consensus - 2017 | 52.2 | 30.4 | 17.4 |

Expert group consensus: There is not enough data for a consensus on this. Hence the decision needs to be individualized.

(False Negative Rate: 24.3% for one SLN removed and 18.5% for two SLNs). Following downstaging of cN+ to cN- by systemic treatment, SLNB procedure is contraindicated because:

- Possibility of alteration of intramammary lymphatic drainage
- Potentially multiple obscured sources of lymphatic drainage for larger tumors
- Possibility of non-uniform cytotoxic response of axillary metastases.

The only data in favour of continuing with SLNB in a subgroup of patients comes from Swedish prospective multicentre trial evaluating SLNB after neoadjuvant systemic therapy in cN+ patients of breast carcinoma. Here the overall FNR dropped from 14.1% to 4% when two or more SLNs were analyzed.

Conclusion

A positive margin is associated with increased risk of local recurrences after BCT for invasive breast cancer and DCIS. Surgeons may be influenced by the level of compliance in pathology reporting when making decisions about the necessity for additional surgical procedures following initial BCS. Improving communication between surgeons and pathologists will help achieve standardized margin reporting, which could help streamline the decision process for need of re-excision and mastectomy following breast conserving surgery. Currently the entire area of the original primary tumor needs to be resected, even after downstaging with neoadjuvant systemic therapy. The cut margins should be at least 2 mm to avoid need for re-excision. When margins are clear, it is still possible to offer breast conservation to patients having tumor foci contained in one ‘quadrant’ of the breast (multifocal). Even after taking into consideration the St Gallen’s 2017 statement, our current consensus is that BSC (breast conserving surgery) is NOT recommended to patients who have tumor in more than one quadrant of the breast (multi-centric). In patients...
with macro-metastases in 1-2 sentinel nodes, completion of axillary dissection can safely be omitted following mastectomy irrespective of whether radiotherapy is planned or not. SLNB is an acceptable standard of care and has resulted in significant reduction in morbidity of arm oedema. SLNB is appropriate for patients with clinically node negative disease. It is not recommended to do sentinel node biopsy if chemotherapy has resulted in successful downstaging of clinically axillary lymph node positive disease, except for carefully selected patients where more than two SLNs are removed for analysis.

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