

Practical consensus recommendations regarding the management of sentinel lymph node issues in early breast cancer

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Abstract

Axillary lymph node involvement is a very important poor prognostic factor in the clinical staging and management of breast cancer patients. Traditionally, axillary lymph node dissection (ALND) has been used for determining the status of the axillary lymph nodes. More recently the sentinel lymph node biopsy (SLNB) procedure has gained wider acceptance as the standard of care, having the advantage of being less invasive while providing good accuracy. This expert group used data from published literature, practical experience and opinion of a large group of academic oncologists to arrive at these practical consensus recommendations in regards with the use of the two different procedures and other issues in patients with early breast cancer for the benefit of community oncologists.

Key words: Areolar tumor, Breast conserving surgery, ductal carcinoma *in situ*, frozen section, ink on tumor margin, magnetic resonance mammography, micrometastasis

Introduction

Sentinel lymph node is the hypothetical first lymph node in the axilla that receives the draining lymph from a suspected breast cancer primary – and may contain metastasizing cancerous cells, if any.^[1] The sentinel lymph node is the first filter to trap any metastasizing malignant cells and hence its status is well established as an important prognostic factor in patients with breast cancer.^[2] The two methods used for determining the status of the axillary lymph nodes are SLNB and ALND. Axillary lymph node dissection is an invasive technique in which almost all the axillary lymph nodes are dissected and has the potential to result in significant lymphedema as an important side effect in almost a quarter of patients. Since SLNB is not as invasive as ALND, it causes less prominent side effects.^[3,4] The high sensitivity rates and the low false negative rates of SLNB gave impetus for widespread acceptance of the technique.^[5,6] Does currently available evidence indicate that SLNB alone is sufficient for accurately staging the axilla or does it require to be combined with ALND for accurate prognosis? This manuscript was prepared to help community oncologists better understand application of these two techniques along with insights on some diagnostic and surgical issues with regards to early breast cancer patients.

Expert oncologists from all over India met to discuss and reach a consensus statement to provide community oncologists with practical guidelines on the use of SLNB and ALND in different scenarios in early breast cancer patients. The discussion was based on published evidence and practical experience in real life management of such

patients. The expert group discussions were moderated by Dr. Rajeev Aggarwal and Dr. Vedant Kabra. The core expert group consisted of Dr. Shanti Vardhan, Dr. Mandeep Singh, Dr. Rohan Khandelwal, Dr. Sumeet Jain, Dr. Siddharth Sahai, Dr. Sarah P. Cate, Dr. Narendra Deo and Dr. Rakesh Kaul. The members of the panel were also allowed to share their personal experiences and make comments. This manuscript is the outcome of the expert group discussion and consensus arrived at in 2017.

Defining Clinical Cohort and Practice of Expert Group Panel Members

The primary objective was to provide a consensus statement for community oncologists that could be applicable as ready-to-use practical recommendations. Hence, the applicable setting was outlined by defining the clinical cohort and current practice of the delegates and expert group panel members – on the basis of which this document was prepared. The experts discussed the case of a 62 year old lady who presented with a clinically mobile and painless 2.5 × 2 cm lump in upper outer quadrant of her right breast. Skin overlying the lump was observed to be normal. Clinically there were no palpable axillary lymph nodes. Bilateral mammographic findings were consistent with BIRADS 5 with right breast lump being at 10 o'clock axis, 10 cm from the nipple. There was no significant axillary lymphadenopathy on ultrasonography. Core needle biopsy (CNB) was suggestive of infiltrating ductal carcinoma (IDC), Grade 1, ER 90%, PR 90% and HER2 negative. Staging investigations ruled out regional or distant metastases. Based on this scenario, a series of questions were voted upon. Each question had multiple-choice options from which participants were to select the one that was most appropriate for their clinical practice setting. The expert group then discussed the options and arrived at the practical consensus recommendations for the community oncologists.

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Role of Magnetic Resonance-Mammography before Breast Conserving Surgery

MR-mammography is an imaging modality that has recently gained a specific role in selected cases for clinically staging newly diagnosed breast cancer patients.^[7] Its wider role in women with moderate risk is still controversial as established data supporting its use in such patients is lacking.^[8] A total of 60% of the polled oncologists were of the opinion that MR-Mammogram is an indispensable imaging tool and should be recommended pre-operatively in all patients before undergoing BCS [Table 1]. The panel did not completely agree with the polled oncologists as MRI has been known to give false positive results which leads to unnecessary tests, biopsies and surgeries.^[9-13] This is mainly because of breast MRI's high sensitivity but low specificity.^[9-15] The panel was of the opinion that breast MRI findings may be the reason behind the increasing recommendations for mastectomy instead of BCS in early breast cancer patients, depriving patients the option of BCS. This is important since it is a less invasive procedure that allows preservation of body image and gives overall survival equal to mastectomy.^[16-20] Another reason not to recommend breast MRI more widely are the results of COMICE and MONET trials. They showed that breast MRI does not result into a reduced re-excision rate in patients with primary breast cancer.^[21,22] The MONET trial findings paradoxically observed breast MRI to be associated with an increased re-excision rate. The panel consensus was that MR-Mammography is not necessary before BCS in all the patients, however, it can be considered in high risk patients (such as BRCA positive patients and those with dense breasts on mammogram).

Can Sentinel Lymph Node Biopsy Replace Axillary Lymph Node Dissection?

SLNB is now an established procedure for predicting axillary lymph node metastasis in early breast cancer. However, it is still not widely available across India.^[23] For centers where SLNB is available/practiced, whether SLNB alone is sufficient for accurate staging of the axilla or does it require to be followed by ALND is an important question. The polled oncologists were presented with two different scenarios regarding the number of positive sentinel lymph nodes observed after SLNB and were asked whether they would recommend complete ALND. The polling results for the two scenarios, 1 out of 3 sentinel lymph nodes being positive and 3 out of 4 sentinel lymph nodes being found to have micrometastases are shown in Tables 2 and 3. The ACSOG Z0011 trial discussed the possibility of avoiding ALND in early breast cancer patients with limited sentinel lymph node positivity.^[24] The trial randomized 891 early breast cancer patients with 1-2 positive sentinel lymph nodes into two groups: further axillary dissection versus only observation. The 5-year OS and 5-year DFS were similar in both the groups and it was concluded that the use of SLNB alone as compared to ALND in early breast cancer patients with limited sentinel lymph node metastases did not result in an inferior survival. The IBCSG 23-01 study also reported similar findings with regards to the use of SLNB in early breast cancer patients with limited sentinel lymph node metastases.^[25-28] With regards to the prognostic impact of micrometastases and isolated tumour cells in lymph nodes, it is comparable as observed in the MIRROR study.^[29]

The Indian scenario is varied with frozen section not being available at all centres. For patients in whom a sentinel lymph node is found to be positive during frozen section, the consensus of the panel was to recommend axillary nodal dissection as an abundant precaution.^[30] If the micrometastasis in sentinel node (s) was identified only on final histopathology, the panel did not recommend repeat completion surgery with ALND. Adequate sampling of lymph node is to be done with standard method to ensure "micrometastasis" label is appropriate.

Acceptable Surgical Margins for Breast Conserving Surgery

BCS followed by radiation therapy is the accepted standard of care for most early breast cancer patients.^[16-20] A negative margin (free of any tumour cells) reduces the local recurrence rate. But the definition of negative margin may be different for different cancer surgeons.^[31,32] There is some debate over what are the minimum acceptable surgical margins required for BCS to be successful. Majority of the polled oncologists were of the opinion that getting no ink on the invasive tumour should be the minimum acceptable surgical margin in patients with early stage invasive breast cancer undergoing BCS followed by radiation and systemic adjuvant therapy [Table 4].

A meta-analysis by Houssami *et al.*^[33] was carried out to study the impact of surgical margins on the local recurrence in women

Table 1: Question 1 - Is magnetic resonance-mammogram important before breast conserving surgery in all patients?

Options	Yes	No
Percentage of polled oncologists	60	40

Expert group consensus: MR-mammography is not routinely necessary as preoperative workup in patients being considered for BCS. It should be considered in high risk patients (such as BRCA positive patients). MR=Magnetic resonance, BCS=Breast conserving surgery

Table 2: Question 2 - Will you proceed with axillary lymph node dissection if 1 out of 3 sentinel lymph nodes is positive?

Options	Yes	No
Percentage of polled oncologists	50	50

Expert group consensus: Axillary lymph node dissection should be done in patients with positive frozen section

Table 3: Question 3 - Will you proceed with axillary lymph node dissection if 3 out of 4 sentinel lymph nodes have micro-metastases?

Options	Yes	No
Percentage of polled oncologists	60	40

Expert group consensus: Axillary lymph node dissection should be avoided in these patients

Table 4: Question 4 - What is the minimum acceptable surgical margin in an invasive early breast cancer patient undergoing breast conserving surgery followed by radiation and systemic therapy?

Options	No ink on invasive tumour	1-2 mm clearance	>2-5 mm clearance	>5 mm clearance
Percentage of polled oncologists	80	20	0	0

Expert group consensus: No ink on tumour should be used as the standard minimum acceptable safety margin for invasive breast cancer patients while 2 mm margin can be used as the minimum acceptable safety margin for ductal carcinoma *in situ*

with early stage invasive breast cancer. The analysis took into account 21 studies which included 14,571 patients. The local recurrence odds ratio for positive margins versus negative margins was observed to be 2.42; however, no significant difference was observed in local recurrence associated with different margin widths (e.g., more than 1 mm, more than 2 mm, or more than 5 mm). The Society of Surgical Oncology (SSO) and the American Society for Radiation Oncology (ASTRO) carried out two different meta-analyses for providing a consensus on surgical margins for BCS with whole breast radiation therapy in patients with invasive carcinoma and ductal carcinoma in-situ.^[35,36] The meta-analysis for invasive carcinoma included 33 studies with 28,162 patients while that for ductal carcinoma in-situ included 20 studies with 7,883 patients. The guidelines formed after the meta-analyses were that no ink on tumour in case of invasive carcinoma while 2 mm in case of ductal carcinoma in-situ should be used as the standard for adequate margins as they are associated with reduction in recurrence and re-excision rates. In view of these established reviews, the expert panel concluded that no ink on tumour should be used as the minimum acceptable safety margin in patients who have invasive breast cancer and 2 mm margin should be used as the minimum safety margin in patients with ductal carcinoma in-situ. The expert group also considered Frozen section unreliable for negative margin status due to its high variance in diagnostic sensitivity.^[34]

Breast Conserving Surgery in Multi-Focal or Multi-Centric Cancers

Multi-focal (MF) breast cancers are defined as having at-least 2 invasive tumours in the same quadrant while multi-centric (MC) breast cancers are defined as having at-least 2 invasive tumours in 2 different quadrants.^[37] The frequency of these tumours ranges from 5% to 44% in published series.^[38-42] The use of BCS in patients with such tumours is controversial and no specific consensus exists. When asked the question as to whether they would recommend BCS in patients with MF/MC tumours if clear margins are achievable and WBRT is planned, 60% of the polled oncologist gave an affirmative answer [Table 5]. MF and MC tumours are many times considered as relative contraindications for BCS due to the concern over increase in local recurrence.^[43-46] Some studies have reported increased risk of local recurrence after BCS in patients with MF and MC breast cancers as compared to that in patients with unifocal tumours.^[45,47] However, these are all old studies and many recent studies have reported BCS in MF/MC cancers not to be associated with increased risk of local recurrence.^[39,48,49] The panel recommended that a very careful selection of patients with MF/MC breast cancers needs to be done prior to providing them BCS as the results are generally acceptable only in a subset of these patients.^[39] A good radiological workup is essential in MC disease. In MF disease, the panel recommended BCS only if it is possible to remove all the tumours in a single incision. The panel consensus was that BCS should be provided to only a subset of patients with MF/MC breast cancers, particularly to women aged between 50 and 69, having small tumours and without excessive ductal carcinoma in-situ.

Breast Conserving Surgery in Subareolar/Retroareolar Breast Cancers

BCS has been in the past excluded from the treatment options for patients with centrally located tumours in retro-areolar

location with or without involvement the nipple-areola complex (NAC).^[50] One of the reasons behind this exclusion may be the unsatisfactory cosmetic results. However, BCS has now been widely accepted as a mode of treatment for patients with subareolar breast cancers.^[51] When asked to give their opinion on this matter, the polled oncologists unanimously supported recommending BCS in subareolar breast cancer patients [Table 6]. Traditionally BCS has been suggested as a relative contraindication for patients presenting with tumours within 2 cm of the NAC.^[50] BCS in these patients requires the removal of some or all of the NAC for proper tumour excision. This is the main reason why BCS is avoided by some surgeons due to the apparent higher incidence of multifocality and multicentricity in central tumours.^[52-59] However, there have been studies reporting BCS to be equally efficient in patients with subareolar breast cancers as compared to that in patients with peripheral breast cancers. A prospective study by Tausch *et al.*^[60] included 44 women who had suspected nipple involvement and underwent BCS with the removal of NAC. The study reported no local failure in any of the patients at 51 months and the cosmetic results were satisfactory to excellent. This study deemed BCS as safe in subareolar breast cancers. Some other studies have also reported similar outcomes and thus BCS is now accepted as an efficient alternative to mastectomy in patients with tumours involving the NAC.^[50,51,61] The panel agreed with the polled oncologists and the studies and concluded that BCS is a feasible option in subareolar breast cancers in light of its acceptable rates of local recurrence as well as the cosmetic results. BCS should be extended to these patients as an alternative to mastectomy.

Repeat Sentinel Node Biopsy after Local Recurrence

Patients with locally recurrent breast cancer undergo axillary staging for obtaining locoregional control and predicting prognosis. Most locally recurrent patients undergo ALND but SLNB can provide regional nodal status and is now the standard for axillary staging in early breast cancer patients as it is accurate as well as sensitive but less invasive than ALND. However, the high sensitivity and the low false negative rate of SLNB may not be the same in case of local recurrence. When asked whether repeat SLNB is feasible in case of an isolated local recurrence 10 years down the line, the polled oncologists unanimously supported recommending it [Table 7]. Recently, some studies

Table 5: Question 5 - Can breast conserving surgery be considered in patients with multifocal/multi-centric tumours if clear margins are achievable and WBRT is planned?

Options	Yes	No
Percentage of polled oncologists	60	40

Expert group consensus: BCS should be considered in a select subset of patients with multi-focal or multi-centric tumours. BCS=Breast conserving surgery

Table 6: Question 6 - Can breast conserving surgery be considered in patients with a solitary subareolar tumour?

Options	Yes	No
Percentage of polled oncologists	100	0

Expert group consensus: BCS is a feasible option in patients with subareolar tumour and should be provided as an alternative to mastectomy. BCS=Breast conserving surgery

Table 7: Question 7 - Should repeat sentinel lymph node biopsy be done in case of local recurrence after 10 years?

Options	Yes	No
Percentage of polled oncologists	100	0

Expert group consensus: Repeat SLNB is feasible in case of local recurrence after 10 years as it provides reliable results and good negative predictive value. Lymphoscintigraphy must be done in all the patients preceding repeat SLNB. SLNB=Sentinel lymph node biopsy

have been undertaken for testing the feasibility of SLNB in patients who have had local recurrence. Two Dutch trials were conducted to determine feasibility, aberrant drainage rates and clinical consequences of repeat SLNB.^[62,63] One included 150 patients while the other included 536 patients with locally recurrent breast cancer, but the results reported were very similar. Lymphoscintigraphy was done in all the patients to determine any aberrant lymph drainage and then SLNB was provided. A sentinel node was identified in 60% of the patients and was successfully harvested in 50% of the patients. Aberrant lymph drainage was observed in about 55% of the patients. This aberrant lymph drainage was seen significantly more in patients who had undergone ALND earlier as compared in patients who had undergone SLNB. Change in adjuvant plans after the repeat SLNB was very different in the 2 studies with 16.5% of the patients with positive SLNB undergoing a change in adjuvant plan in 1 study as opposed to 63% in the other. Overall, both the studies concluded that repeat SLNB is indeed feasible with reliable results in patients with locally recurrent breast cancer. The panel reached a consensus that repeat SLNB is feasible in locally recurrent patients and provides accurate results with high negative predictive value, thus potentially helping in the omission of ALND in patients with negative repeat sentinel lymph node. The panel recommended that repeat SLNB should be preceded by lymphoscintigraphy and repeat SLNB should be provided to all locally recurrent breast cancer patients regardless of whether ALND or SLNB was done initially.

Take Home Messages

- MR-Mammography is not necessary before BCS in all the patients. It can be considered in high risk patients such as BRCA positive patients and those with dense breasts on mammogram
- Axillary lymph node dissection should be done in patients with positive frozen section
- Axillary lymph node dissection should be avoided in patients with micrometastases in sentinel lymph nodes
- No ink on tumour should be used as the standard minimum acceptable safety margin for invasive breast cancer patients while 2 mm margin can be used as the minimum acceptable safety margin for ductal carcinoma in-situ
- BCS should be considered in a select subset of patients with multi-focal or multi-centric tumours particularly to women aged between 50 and 69, having small tumours and without excessive ductal carcinoma in-situ. Good radiological workup should be done in all patients with MF/MC breast cancers
- BCS is a feasible option in patients with subareolar/retroareolar tumour and should be provided as an alternative to mastectomy
- Repeat SLNB is feasible in case of local recurrence after 10 years as it provides reliable results and good negative predictive value. Lymphoscintigraphy is recommended be done in all the patients preceding repeat SLNB. Repeat SLNB should be provided to patients regardless of the initial axilla staging course taken

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References

- Faries MB, Bedrosian I, Reynolds C, Nguyen HQ, Alavi A, Czerniecki BJ, et al. Active macromolecule uptake by lymph node antigen-presenting cells: A novel mechanism in determining sentinel lymph node status. *Ann Surg Oncol* 2000;7:98-105.
- Harlow SP, Weaver DL. Overview of sentinel lymph node biopsy in breast cancer. UpToDate; 2017.
- Swenson KK, Nissen MJ, Ceronsky C, Swenson L, Lee MW, Tuttle TM, et al. Comparison of side effects between sentinel lymph node and axillary lymph node dissection for breast cancer. *Ann Surg Oncol* 2002;9:745-53.
- Mansel RE, Fallowfield L, Kissin M, Goyal A, Newcombe RG, Dixon JM, et al. Randomized multicenter trial of sentinel node biopsy versus standard axillary treatment in operable breast cancer: The ALMANAC trial. *J Natl Cancer Inst* 2006;98:599-609.
- Veronesi U, Viale G, Paganelli G, Zurrada S, Luini A, Galimberti V, et al. Sentinel lymph node biopsy in breast cancer: Ten-year results of a randomized controlled study. *Ann Surg* 2010;251:595-600.
- Borgstein PJ, Pijpers R, Comans EF, van Diest PJ, Boom RP, Meijer S, et al. Sentinel lymph node biopsy in breast cancer: Guidelines and pitfalls of lymphoscintigraphy and gamma probe detection. *J Am Coll Surg* 1998;186:275-83.
- Le-Petross HT, Stafford RJ. The need for MRI before breast-conserving surgery. *Curr Breast Cancer Rep* 2009;1:98.
- Schrading S, Strobel K, Kuhl CK. Abstract S1-09: MRI screening of women at average risk of breast cancer. *Cancer Res* 2013;24 Suppl: S1-09. [DOI: 10.1158/0008-5472.SABCS13-S1-09].
- Brekelmans CT, Seynaeve C, Bartels CC, Tilanus-Linthorst MM, Meijers-Heijboer EJ, Crepin CM, et al. Effectiveness of breast cancer surveillance in BRCA1/2 gene mutation carriers and women with high familial risk. *J Clin Oncol* 2001;19:924-30.
- Kriege M, Brekelmans CT, Boetes C, Rutgers EJ, Oosterwijk JC, Tollenaar RA, et al. MRI screening for breast cancer in women with familial or genetic predisposition: Design of the Dutch National Study (MRISC). *Fam Cancer* 2001;1:163-8.
- Tilanus-Linthorst MM, Obdeijn IM, Bartels KC, de Koning HJ, Oudkerk M. First experiences in screening women at high risk for breast cancer with MR imaging. *Breast Cancer Res Treat* 2000;63:53-60.
- Kriege M, Brekelmans CT, Boetes C, Besnard PE, Zonderland HM, Obdeijn IM, et al. Efficacy of MRI and mammography for breast-cancer screening in women with a familial or genetic predisposition. *N Engl J Med* 2004;351:427-37.
- Weinstein SP, Localio AR, Conant EF, Rosen M, Thomas KM, Schnall MD, et al. Multimodality screening of high-risk women: A prospective cohort study. *J Clin Oncol* 2009;27:6124-8.
- Klijn JG. Early diagnosis of hereditary breast cancer by magnetic resonance imaging: What is realistic? *J Clin Oncol* 2010;28:1441-5.
- Leach MO, Boggis CR, Dixon AK, Easton DF, Eeles RA, Evans DG, et al. Screening with magnetic resonance imaging and mammography of a UK population at high familial risk of breast cancer: A prospective multicentre cohort study (MARIBS). *Lancet* 2005;365:1769-78.
- Houssami N, Turner RM, Morrow M. Meta-analysis of pre-operative magnetic resonance imaging (MRI) and surgical treatment for breast cancer. *Breast Cancer Res Treat* 2017;165:273-83.
- Houssami N, Hayes DF. Review of preoperative magnetic resonance imaging (MRI) in breast cancer: Should MRI be performed on all women with newly diagnosed, early stage breast cancer? *CA Cancer J Clin* 2009;59:290-302.
- Sardanelli F. Overview of the role of pre-operative breast MRI in the absence of evidence on patient outcomes. *Breast* 2010;19:3-6.
- Fisher B, Anderson S, Bryant J, Margolese RG, Deutsch M, Fisher ER, et al. Twenty-year follow-up of a randomized trial comparing total mastectomy, lumpectomy, and lumpectomy plus irradiation for the treatment of invasive breast cancer. *N Engl J Med* 2002;347:1233-41.
- Blichert-Toft M, Nielsen M, Düring M, Møller S, Rank F, Overgaard M, et al. Long-term results of breast conserving surgery vs. mastectomy for early stage invasive breast cancer: 20-year follow-up of the Danish randomized DBCG-82TM protocol. *Acta Oncol* 2008;47:672-81.
- Turnbull L, Brown S, Harvey I, Olivier C, Drew P, Napp V, et al. Comparative effectiveness of MRI in breast cancer (COMICE) trial: A randomised controlled trial. *Lancet* 2010;375:563-71.

22. Peters NH, van Esser S, van den Bosch MA, Storm RK, Plaisier PW, van Dalen T, *et al.* Preoperative MRI and surgical management in patients with nonpalpable breast cancer: The MONET – Randomised controlled trial. *Eur J Cancer* 2011;47:879-86.
23. Vijaykumar DK, Arunlal M. Management of axilla in 2015 in Indian scenario. *Indian J Surg Oncol* 2015;6:435-9.
24. Giuliano AE, Hunt KK, Ballman KV, Beitsch PD, Whitworth PW, Blumencranz PW, *et al.* Axillary dissection vs. no axillary dissection in women with invasive breast cancer and sentinel node metastasis: A randomized clinical trial. *JAMA* 2011;305:569-75.
25. Galimberti V, Cole BF, Zurrada S, Viale G, Luini A, Veronesi P, *et al.* Axillary dissection versus no axillary dissection in patients with sentinel-node micrometastases (IBCSG 23-01): A phase 3 randomised controlled trial. *Lancet Oncol* 2013;14:297-305.
26. Solá M, Alberro JA, Fraile M, Santesteban P, Ramos M, Fabregas R, *et al.* Complete axillary lymph node dissection versus clinical follow-up in breast cancer patients with sentinel node micrometastasis: Final results from the multicenter clinical trial AATRM 048/13/2000. *Ann Surg Oncol* 2013;20:120-7.
27. Sávolt A, Musonda P, Mátrai Z, Polgár C, Rényi-Vámos F, Rubovszky G, *et al.* Optimal treatment of the axilla after positive sentinel lymph node biopsy in early invasive breast cancer. Early results of the OTOASOR trial. *Orv Hetil* 2013;154:1934-42.
28. Donker M, van Tienhoven G, Straver ME, Meijnen P, van de Velde CJ, Mansel RE, *et al.* Radiotherapy or surgery of the axilla after a positive sentinel node in breast cancer (EORTC 10981-22023 AMAROS): A randomised, multicentre, open-label, phase 3 non-inferiority trial. *Lancet Oncol* 2014;15:1303-10.
29. de Boer M, van Deurzen CH, van Dijk JA, Borm GF, van Diest PJ, Adang EM, *et al.* Micrometastases or isolated tumor cells and the outcome of breast cancer. *N Engl J Med* 2009;361:653-63.
30. Somashekhar SP, Naikoo ZA, Zaveri SS, Holla S, Chandra S, Mishra S, *et al.* Intraoperative frozen section evaluation of sentinel lymph nodes in breast carcinoma: Single-institution Indian experience. *Indian J Surg* 2015;77:335-40.
31. Goldhirsch A, Ingle JN, Gelber RD, Coates AS, Thürlimann B, Senn HJ, *et al.* Thresholds for therapies: Highlights of the St. Gallen international expert consensus on the primary therapy of early breast cancer 2009. *Ann Oncol* 2009;20:1319-29.
32. Blair SL, Thompson K, Rococco J, Malcarne V, Beitsch PD, Ollila DW, *et al.* Attaining negative margins in breast-conservation operations: Is there a consensus among breast surgeons? *J Am Coll Surg* 2009;209:608-13.
33. Houssami N, Macaskill P, Marinovich ML, Dixon JM, Irwig L, Brennan ME, *et al.* Meta-analysis of the impact of surgical margins on local recurrence in women with early-stage invasive breast cancer treated with breast-conserving therapy. *Eur J Cancer* 2010;46:3219-32.
34. Pleijhuis RG, Graafland M, de Vries J, Bart J, de Jong JS, van Dam GM, *et al.* Obtaining adequate surgical margins in breast-conserving therapy for patients with early-stage breast cancer: Current modalities and future directions. *Ann Surg Oncol* 2009;16:2717-30.
35. Moran MS, Schnitt SJ, Giuliano AE, Harris JR, Khan SA, Horton J, *et al.* Society of Surgical Oncology-American Society for Radiation Oncology consensus guideline on margins for breast-conserving surgery with whole-breast irradiation in stages I and II invasive breast cancer. *J Clin Oncol* 2014;32:1507-15.
36. Morrow M, Van Zee KJ, Solin LJ, Houssami N, Chavez-MacGregor M, Harris JR, *et al.* Society of Surgical Oncology-American Society for Radiation Oncology-American Society of Clinical Oncology consensus guideline on margins for breast-conserving surgery with whole-breast irradiation in ductal carcinoma *in situ*. *Ann Surg Oncol* 2016;23:3801-10.
37. Houvenaeghel G, Tallet A, Jalaguier-Coudray A, Cohen M, Bannier M, Jauffret-Fara C, *et al.* Is breast conservative surgery a reasonable option in multifocal or multicentric tumors? *World J Clin Oncol* 2016;7:234-42.
38. Donker M, Straver ME, van Tienhoven G, van de Velde CJ, Mansel RE, Litière S, *et al.* Comparison of the sentinel node procedure between patients with multifocal and unifocal breast cancer in the EORTC 10981-22023 AMAROS trial: Identification rate and nodal outcome. *Eur J Cancer* 2013;49:2093-100.
39. Yerushalmi R, Tyldesley S, Woods R, Kennecke HF, Speers C, Gelmon KA, *et al.* Is breast-conserving therapy a safe option for patients with tumor multicentricity and multifocality? *Ann Oncol* 2012;23:876-81.
40. Gallager HS, Martin JE. The study of mammary carcinoma by mammography and whole organ sectioning. Early observations. *Cancer* 1969;23:855-73.
41. Holland R, Veling SH, Mravunac M, Hendriks JH. Histologic multifocality of T1-2 breast carcinomas. Implications for clinical trials of breast-conserving surgery. *Cancer* 1985;56:979-90.
42. Coombs NJ, Boyages J. Multifocal and multicentric breast cancer: Does each focus matter? *J Clin Oncol* 2005;23:7497-502.
43. Danoff BF, Haller DG, Glick JH, Goodman RL. Conservative surgery and irradiation in the treatment of early breast cancer. *Ann Intern Med* 1985;102:634-42.
44. Winchester DP, Cox JD. Standards for diagnosis and management of invasive breast carcinoma. American College of Radiology. American College of Surgeons. College of American Pathologists. Society of Surgical Oncology. *CA Cancer J Clin* 1998;48:83-107.
45. Kurtz JM, Jacquemier J, Amalric R, Brandone H, Ayme Y, Hans D, *et al.* Breast-conserving therapy for macroscopically multiple cancers. *Ann Surg* 1990;212:38-44.
46. Leopold KA, Recht A, Schnitt SJ, Connolly JL, Rose MA, Silver B, *et al.* Results of conservative surgery and radiation therapy for multiple synchronous cancers of one breast. *Int J Radiat Oncol Biol Phys* 1989;16:11-6.
47. Wilson LD, Beinfeld M, McKhann CF, Haffty BG. Conservative surgery and radiation in the treatment of synchronous ipsilateral breast cancers. *Cancer* 1993;72:137-42.
48. Lynch SP, Lei X, Hsu L, Meric-Bernstam F, Buchholz TA, Zhang H, *et al.* Breast cancer multifocality and multicentricity and locoregional recurrence. *Oncologist* 2013;18:1167-73.
49. Wolters R, Wöckel A, Janni W, Novopashenny I, Ebner F, Kreienberg R, *et al.* Comparing the outcome between multicentric and multifocal breast cancer: What is the impact on survival, and is there a role for guideline-adherent adjuvant therapy? A retrospective multicenter cohort study of 8,935 patients. *Breast Cancer Res Treat* 2013;142:579-90.
50. Haffty BG, Wilson LD, Smith R, Fischer D, Beinfeld M, Ward B, *et al.* Subareolar breast cancer: Long-term results with conservative surgery and radiation therapy. *Int J Radiat Oncol Biol Phys* 1995;33:53-7.
51. Gajdos C, Tarrter PI, Bleiweiss IJ. Subareolar breast cancers. *Am J Surg* 2000;180:167-70.
52. Fisher ER, Gregorio R, Redmond C, Vellios F, Sommers SC, Fisher B, *et al.* Pathologic findings from the national surgical adjuvant breast project (protocol no 4). I. Observations concerning the multicentricity of mammary cancer. *Cancer* 1975;35:247-54.
53. Lagios MD, Gates EA, Westdahl PR, Richards V, Alpert BS. A guide to the frequency of nipple involvement in breast cancer. A study of 149 consecutive mastectomies using a serial subgross and correlated radiographic technique. *Am J Surg* 1979;138:135-42.
54. Rosen PP, Fracchia AA, Urban JA, Schottenfeld D, Robbins GF. "Residual" mammary carcinoma following simulated partial mastectomy. *Cancer* 1975;35:739-47.
55. Andersen JA, Pallesen RM. Spread to the nipple and areola in carcinoma of the breast. *Ann Surg* 1979;189:367-72.
56. Suehiro S, Inai K, Tokuoka S, Hamada Y, Toi M, Niimoto M, *et al.* Involvement of the nipple in early carcinoma of the breast. *Surg Gynecol Obstet* 1989;168:244-8.
57. Santini D, Taffurelli M, Gelli MC, Grassigli A, Giosa F, Marrano D, *et al.* Neoplastic involvement of nipple-areolar complex in invasive breast cancer. *Am J Surg* 1989;158:399-403.
58. Parry R, Cochran T, Wolfert F. When is there nipple involvement in cancer of the breast? *Plast Reconstr Surg* 1977;59:535-7.
59. Vyas JJ, Chinoy RF, Vaidya JS. Prediction of nipple and areola involvement in breast cancer. *Eur J Surg Oncol* 1998;24:15-6.
60. Tausch C, Hintringer T, Kugler F, Schmidhammer C, Bauer M, Aufschneider M, *et al.* Breast-conserving surgery with resection of the nipple-areola complex for subareolar breast carcinoma. *Br J Surg* 2005;92:1368-71.
61. Pezzi CM, Kukora JS, Audet IM, Herbert SH, Horvick D, Richter MP, *et al.* Breast conservation surgery using nipple-areolar resection for central breast cancers. *Arch Surg* 2004;139:32-7.
62. Maaskant-Braat AJ, Roumen RM, Voogd AC, Pijpers R, Luiten EJ, Rutgers EJ, *et al.* Sentinel node and recurrent breast cancer (SNARB): Results of a nationwide registration study. *Ann Surg Oncol* 2013;20:620-6.
63. Vugts G, Maaskant-Braat AJ, Voogd AC, van Riet YE, Luiten EJ, Rutgers EJ, *et al.* Repeat sentinel node biopsy should be considered in patients with locally recurrent breast cancer. *Breast Cancer Res Treat* 2015;153:549-56.