Review Article

Margins in Breast Cancer: How Much Is Enough?

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The appropriate negative margin width for women undergoing breast-conserving surgery for both ductal carcinoma in situ (DCIS) and invasive carcinoma is controversial. This review examines the available data on the margin status for invasive breast cancer and DCIS, and highlights the similarities and differences in tumor biology and standard treatments that affect the local recurrence (LR) risk and, therefore, the optimal surgical margin. Consensus guidelines support a negative margin, defined as no ink on tumor, for invasive carcinoma treated with breast-conserving therapy. Because of differences in the growth pattern and utilization of systemic therapy, a margin of 2 mm has been found to minimize the LR risk for women with DCIS undergoing lumpectomy and radiation therapy (RT). Wider negative margins do not improve local control for DCIS or invasive carcinoma when they are treated with lumpectomy and RT. Re-excision for negative margins should be individualized, and the routine practice of performing additional surgery to obtain a wider negative margin is not supported by the literature. ***Cancer*** **2018;124:1335-41**. © *2018 American Cancer Society.*

KEYWORDS: breast cancer, breast-conserving therapy, local recurrence, margins, negative margins.

INTRODUCTION

There has been considerable controversy regarding the optimal negative margin width for minimizing local recurrence (LR) in patients undergoing breast-conserving therapy (BCT) for both invasive carcinoma and intraductal carcinoma. The only defined microscopic margin width in the prospective randomized trials that established the safety of BCT in invasive carcinoma was no ink on tumor, the margin definition in the National Surgical Adjuvant Breast and Bowel Project (NSABP) B06 study.[1] Other studies, widely perceived as requiring larger negative margins,[2,3] have defined only gross margin widths and have not contributed to our understanding of the impact of the margin width on LR because the actual margin widths are unknown. In the 4 original randomized trials of ductal carcinoma in situ (DCIS) treated with and without radiotherapy, no ink on tumor was the margin definition used in 3 studies,[4-6] whereas the fourth study did not require negative margins.[7] Recently, several factors have led to a re-examination of the issue of margins in BCT. These include the lack of consensus regarding margin width, which has resulted in high rates of re-excision,[8,9] the recognition that margin measurement is an inexact science, and changes in our understanding of the biology underlying LR.

Approximately 25% of patients with invasive carcinoma and one-third of those with DCIS undergo re-excision,[9,10] with approximately half of the re-excisions performed in patients with negative margins (defined as no ink on tumor), apparently in the belief that a larger negative margin improves patient outcomes. The negative margin width reported by the pathologist is dependent on multiple factors, including the number of sections examined, the technique of margin assessment (perpendicular, shaved, or cavity margins), what is defined as the margin when ink tracks through the irregular fatty surface overlying the tumor (Fig. 1), and the use of specimen-compression devices for radiography. In a study comparing measurements of the anterior-posterior diameter of breast specimens in the operating room and the pathology laboratory, 46% of the specimen height was lost by the time of measurement in the pathology laboratory, and this increased with the use of specimen-compression devices.[11] It has been estimated that 3000 sections would be required to completely examine the margin surfaces of a spherical lumpectomy specimen.[12] This, coupled with the fact that a negative margin does not guarantee the absence of residual tumor in the breast,[13] suggests that a negative margin is best regarded as one indicating that the residual tumor burden in the breast is low enough that it is likely to be controlled with radiotherapy.

Changes in our understanding of breast cancer biology and the widespread use of adjuvant systemic therapy for early-stage breast cancers have also influenced attitudes about margins. For many years, the tumor burden was thought to be the primary determinant of LR, and the belief that large negative margins improved outcomes was a logical extension of this view of biology. It is now clear that the rate of LR varies with the hormone receptor (HR) and human epidermal growth factor receptor 2 (HER2) status: it is lowest among patients with HR+, HER2– tumors and highest among those

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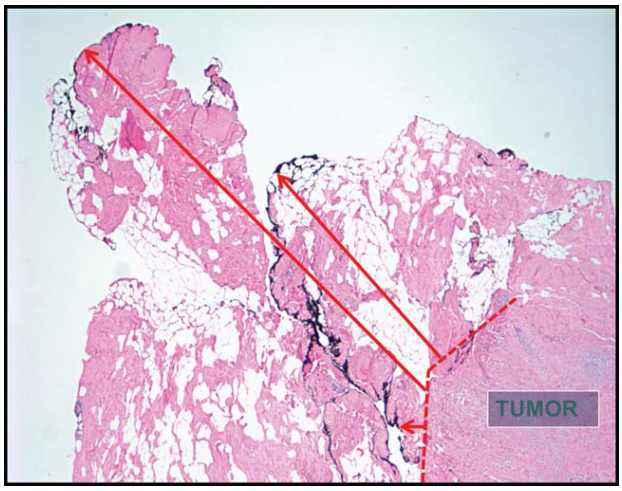

Figure 1. Ink used to define the margin surface can be seen at various distances from the tumor edge because of the irregular nature of the specimen surface and ink tracking through the breast fat. This makes reproducible measurements of the margin width challenging. Published with permission from Stuart Schnitt, MD.

with triple-negative tumors, regardless of whether the treatment includes BCT or mastectomy.[14] Among those with HR+, HER2– tumors, the risk of LR also varies significantly with the 21-gene recurrence score.[15] Variation in the risk of LR can be observed even among the smallest cancers (microinvasive, T1a,b),[16] and this indicates that this is a fundamental tumor characteristic and not one that is acquired over time. Systemic therapy, used in the majority of patients with invasive breast cancer, also significantly affects the risk of LR. Five years of adjuvant tamoxifen reduces the risk of LR by approximately 50%,[17,18] and newer endocrine therapies, such as the use of aromatase inhibitors and more prolonged treatment durations, provide further risk reductions.[18] Conventional cytotoxic chemotherapy in women younger than 50 years reduces the relative risk of LR to 0.63 in comparison with no treatment, and the use of trastuzumab provides a further relative risk reduction of 0.47.[18] The practical impact of this is illustrated in 2 retrospective studies of LR outcomes for HER2+ patients.[19,20] In those undergoing BCT, the 3-year rate of LR was 7% before the use of adjuvant trastuzumab, and it decreased to 1% ($P = .01$) in the period immediately after the adoption of trastuzumab.[19] A similar decrease in 5-year LR rates after mastectomy was seen before and after trastuzumab (6.6% vs 1.5%; $P = .04$).[20] Between 1990 and 2011, LR decreased from 30% to 15% of all first recurrences in a study of 86,598 women treated in phase 3 drug trials.[21] These findings, coupled with the demonstration that microscopic disease left behind in the axilla can be controlled with systemic therapy,[22,23] opened the door to a re-examination of margin width in patients undergoing BCT.

MARGIN WIDTH AND LR RISK IN INVASIVE CANCER

A positive margin, defined as ink on tumor, is associated with a significant increase in LR risk and warrants consideration for additional surgery.[24] Houssami et al[25] performed a study-level meta-analysis that included 33 eligible studies and more than 28,000 women with early-stage breast cancer. A positive margin was associated with increasing LR (odds ratio for positive margins versus negative margins, 2.44; 95% confidence interval, 1.97-3.03; $P < .001$), even after they had controlled for the use of a radiation boost or adjuvant endocrine therapy. Importantly, there was no evidence of a decreased LR risk with negative margin widths increasing from 1 to 2 to 5 mm ($P = .90$). These data confirm that even with modern multimodality treatment, a negative margin reduces the risk of LR; however, increasing the size of a negative margin is not significantly associated with an improvement in local control.

In 2014, the Society of Surgical Oncology (SSO) and the American Society for Radiation Oncology (ASTRO) convened a multidisciplinary panel to develop a consensus guideline on the appropriate margin width to minimize the risk of LR in patients with invasive cancer treated with BCT and whole-breast radiation therapy (RT). Using data from the meta-analysis of Houssami et al[25] as well as other published literature, the panel concluded that a negative margin of no ink on tumor optimizes local control and that the routine practice of obtaining a more widely negative margin than no ink on tumor is not indicated.[26] This negative margin definition was endorsed by the National Comprehensive Cancer Network, the American Society of Clinical Oncology (ASCO), the American Society of Breast Surgery, and the St. Gallen International Expert Consensus Group.[27] Notably, the guideline of no ink on tumor does not apply to patients receiving neoadjuvant chemotherapy or those treated with partial breast irradiation.

The panel also addressed the need for wider negative margins within select high-risk subsets. Young age and triple-negative cancers are both independent risk factors for LR, but the available evidence indicates that it is the tumor biology, not the extent of surgical excision, that is associated with a worse outcome because LR rates are similar among women in these high-risk groups treated with

BCT or mastectomy.[28] A single-institution series examining margin width and LR among women with triple-negative breast cancer found no difference in 5-year LR rates between margins $\leq$ 2 mm and margins $>$ 2 mm (4.7% and 3.7%, respectively; $P = .11$).[29] Studies performed before the routine inking of margins suggested that an extensive intraductal component (EIC) was associated with an increased risk of LR[30]; however, more recent reports of patients with EIC-positive tumors excised to negative margins have found LR rates similar to the rates of those without an EIC.[31,32] An EIC is an indicator of the potential for a heavy residual burden of DCIS, and postexcision mammography and the extent of DCIS in proximity to the margin are important factors when the benefit of re-excision is being considered. Although the consensus guideline states that margins more widely clear than no ink on tumor are not routinely indicated, it should not be interpreted as meaning that re-excision is never appropriate when a minimal negative margin has been obtained. The patient, tumor, and treatment variables influencing the risk of LR should be considered when one is determining the need for re-excision. The key point of the consensus statement is that routinely mandating negative margin widths greater than no ink on tumor is not supported by evidence.

The development of the consensus guideline appears to have resulted in a rapid reduction in the use of additional surgery after initial lumpectomy. In a single-institution study, the re-excision rate fell from 21% to 15% ($P = .006$) in the immediate 10-month window after the guideline's dissemination.[33] In a population-based cohort survey of patients identified from the Georgia and Los Angeles County, California, Surveillance, Epidemiology, and End Results registries and treated in the period immediately before and after the guideline's dissemination and publication (2013-2015), the initial lumpectomy rate (67%) was unchanged; however, the rate of additional surgery after initial lumpectomy, including both re-excision and conversion to mastectomy, decreased by 16% ($P < .001$) over this 2-year period. Overall, the final lumpectomy rate increased by 13%, and this increase was accompanied by a decrease in both unilateral and bilateral mastectomy ($P = .002$). The treating surgeons were surveyed on their attitudes regarding margin width, and 63% endorsed no ink on tumor as an adequate negative margin to avoid re-excision[34]; this proportion was much greater than the 11% accepting this definition a decade earlier.[8] It is estimated that the adoption of the margin guideline would save the health care system more than $18 million annually, and this does not include the time and costs saved by patients and families for missed work.[35]

MARGINS IN DCIS

DCIS has a 10-year cause-specific mortality rate under 1% after BCT,[36] but optimizing local control is important because half of all LR events are invasive cancers[37] with an associated increased risk of breast cancer–specific mortality.[38] Although the risk of LR after BCT for DCIS is affected by a number of factors, including young patient age, symptomatic presentation, extent of disease, and presence of necrosis, the margin width and the use of adjuvant therapy are modifiable risk factors.[39-41] The 4 randomized controlled trials examining the benefit of RT after lumpectomy for women with DCIS[4-7] were not designed to evaluate the association of margin width and LR, and provide minimal guidance on defining the optimal margin width for patients with DCIS; and surveys of surgeons and radiation oncologists report significant heterogeneity regarding what constitutes an acceptable margin width for DCIS treated with BCT, which ranges from no ink on tumor to $>$ 1 cm.[8,42-44] Although these findings mirror the experience with invasive carcinoma, there are important differences between DCIS and invasive breast cancer, including the growth pattern of the lesion and the utilization of adjuvant therapy, that must be considered when one is determining the optimal surgical margin.

DCIS GROWTH PATTERN

Multicentric DCIS is uncommon, but DCIS within one quadrant may be extensive, with 46% of the lesions measuring $>$ 3 cm in one study.[13] Faverly et al[45] examined the growth pattern of DCIS and found that although 90% of poorly differentiated lesions grew continuously, 70% of well-differentiated lesions had a multifocal, skip pattern, with 82% of skip lesions measuring between 0 and 5 mm, and only 8% having skip lesions $>$ 10 mm. These studies suggest that that a small negative margin may lie within a skip lesion and may be associated with a substantial residual tumor burden.

In addition to anatomic differences that may affect margin assessment, there are significant differences in the utilization of adjuvant therapy between invasive and in situ carcinomas that affect LR. Approximately 55% to 70% of women with DCIS treated with lumpectomy receive adjuvant RT, and only 20% to 50% receive adjuvant endocrine therapy: these numbers are significantly lower than those seen for invasive carcinoma.[36,39,46] For women treated with lumpectomy and RT, the optimal margin is that which leaves a subclinical volume of residual microscopic disease

TABLE 1. LR Rates for Ductal Carcinoma In Situ Treated With Excision Alone by the Margin Status

Source	Minimum Margin Required/Margin Cohort, mm	Additional Inclusion Criteria	Patients With Margins ≥ 10 mm, n/N (%)	Median Tumor Size, mm	Years for Reported LR	LR Rate, %
Silverstein 1999[48]	< 1	—	93/256 (36)	19	8	58
	1-10			8		20
	> 10			9		3
MacDonald 2005[54]	10	—	272/272 (100)	—[a]	12	14
Van Zee 2015[39]	≤ 2	—	669/1374 (49)	Not reported	10	27
	> 2-10					23
	> 10					16
Hughes 2009[53]	< 10[b]	Low-intermediate grade, tumor size ≤ 2.5 cm	274/565 (48)	6	5	6
	≥ 10					7
	< 10[b]	High grade, tumor size < 1 cm	56/105 (53)	5	7	15
	≥ 10					16
Wehner 2013[51]	2	Tumor size ≤ 2 cm, age ≥ 50 y, not high grade	119/205 (58)	8	12	8
Wong 2014[49]	10	Low-intermediate grade, tumor size ≤ 2.5 cm	143/143 (100)	8[c]	10	16
McCormick 2015[55]	3	Low-intermediate grade, tumor size < 2.5 cm	48/298 (16)	5	7	7
Solin 2015[52]	3	Low-intermediate grade, tumor size ≤ 2.5 cm	119/561 (21)	6	12	14
		High grade, tumor size ≤ 1 cm	25/104 (24)	7		25

Abbreviation: LR, local recurrence.
[a] The tumor size was reported as follows: ≥ 15 mm, 72%; 15 to 40 mm, 24%; and > 40 mm, 4%.
[b] The minimum margin required in the study was 3 mm.
[c] Mammographic size of ductal carcinoma in situ.

within the breast that can likely be controlled by RT. For women treated with excision alone, the goal of surgery is to remove all microscopic disease to minimize the LR risk; therefore, a wider margin may be appropriate.

MARGIN WIDTH AND LR RISK IN DCIS TREATED WITH EXCISION ALONE

The proportion of women with DCIS treated by excision alone ranges from 17% to 44%,[47] with 31% of those undergoing BCT and reported to the Surveillance, Epidemiology, and End Results program between 1988 and 2011 having excision alone.[36] An early study by Silverstein et al[48] suggested that a margin of 1 cm or greater negated the benefit of RT; however, these findings have not been replicated in subsequent studies.[49-51] In a study of 1374 women undergoing excision alone, margin width was significantly associated with LR, with 10-year LR rates ranging from 41% with a positive margin to 16% with a > 1 cm margin ($P = .00003$). In a multivariate analysis controlling for age, family history, presentation, number of excisions, use of adjuvant endocrine therapy, and year of surgery, incremental increases in margin width were associated with decreasing LR risk ($P < .0001$).[39] In contrast, after 12 years of follow-up in the Eastern Cooperative Oncology Group–American College of Radiology Imaging Network E5194 trial, which included women with low- to intermediate-grade DCIS ≤ 2.5 cm in size or high-grade DCIS ≤ 1 cm in size treated with excision alone and with a negative margin of at least 3 mm, no significant relation between the margin widths of < 5 mm, 5 to 9 mm, and ≥ 1 cm was observed.[52] Table 1 reviews studies examining rates of LR for DCIS treated with excision alone and highlights that there are cohorts of low-risk patients undergoing excision alone who have low local failure rates with a range of negative margin widths.[48,49,51-55] The decision for re-excision or RT for DCIS is multifactorial, with the margin width being one factor that may affect the decision for further risk-reducing therapy. The patient's age, the size of the DCIS, the tumor grade, the margin width, and the patient's comfort with recurrence risk are all taken into consideration when the decision is made to omit RT or return to the operating room because, as shown in Table 1, there is no uniform negative margin width reported in the literature that is routinely associated with a low recurrence risk among women with DCIS treated with excision alone.

TABLE 2. Estimated Margin Threshold Effects on Local Recurrence in Ductal Carcinoma In Situ Treated With Lumpectomy and Radiation Therapy From a Meta-Analysis

	Threshold Distance for Negative Margins Relative to > 0 or 1 mm OR and 95% CI Adjusted for Follow-up				
Frequentist Model	> 0 or 1 mm	2 mm	3 or 5 mm	10 mm	*P*
	Reference	0.5 (0.31-0.85)	0.4 (0.18-0.97)	0.6 (0.33-1.08)	.046
	Threshold Distance for Negative Margins With Respect to Positive Margins Mean OR and 95% CrI Adjusted for Follow-up				
Bayesian Model	> 0 or 1 mm	2 mm	3 mm	10 mm	
	0.5 (0.32-0.61)	0.3 (0.21-0.48)	0.3 (0.12-0.76)	0.3 (0.19-0.49)	

Abbreviations: CI, confidence interval; CrI, credible interval; OR, odds ratio.
Data were derived from Marinovich et al.[56]

MARGIN WIDTH AND LR RISK IN DCIS TREATED WITH EXCISION AND RT

A study-level meta-analysis including 6353 women treated with BCT and RT was conducted to evaluate the impact of the margin status on LR. Because of the heterogeneity of the data, both a Bayesian network analysis and a frequentist analysis were used to examine the data. Both analyses confirmed that the odds of LR are reduced by more than 50% with a negative margin versus a positive margin (odds ratio, 0.45; 95% credible interval, 0.30-0.62). In the Bayesian analysis, with respect to a positive margin, significant reductions were seen for all negative margin widths (Table 2).[56] When a 2 mm margin was compared with a smaller negative margin, a nonsignificant trend toward a decrease in LR was observed (relative odds ratio, 0.72; 95% credible interval, 0.47-1.08). In the frequentist analysis, a 2 mm margin was associated with a significant reduction in LR in comparison with a smaller negative margin (odds ratio, 0.51; 95% confidence interval, 0.31-0.85; $P = .01$; Table 2). Importantly, in both analyses, no additional benefit was seen for margins greater than 2 mm.[56] Subsequently, in 2015, an SSO-ASTRO-ASCO multidisciplinary consensus panel concluded that a 2 mm margin minimizes the risk of LR in comparison with smaller negative margins, but more widely clear margins do not further reduce the risk of LR.[57] Two large, single-institution studies reported on their experience with DCIS treated with BCT, and both found that close margins (< 2 mm) were not inferior to wider negative margins among women treated with RT.[39,58]

Although the previously discussed meta-analysis found that a margin of 2 mm reduces LR in comparison with smaller negative margins, the findings of single-institution studies, the favorable long-term outcomes observed in NSABP trials using a margin definition of no ink on tumor, and the recognition that small differences in local control do not affect survival for patients with DCIS led members of the SSO-ASTRO-ASCO consensus panel on DCIS margins to emphasize that the decision to perform a re-excision for negative margins < 2 mm should be individualized on the basis of multiple factors, including the volume of disease near a margin, the results of a postexcision mammogram, the cosmetic impact of re-excision, the patient's age, the tumor's size and grade, the life expectancy, and the patient's tolerance of risk. In particular, it was emphasized that a negative margin < 2 mm is not by itself an indication for mastectomy.

DCIS AND INVASIVE CANCER: WHICH GUIDELINE TO USE?

The invasive cancer margin guideline endorses no ink on tumor, whereas the DCIS guideline states that 2 mm is an optimal margin. This raises the question of which guideline to apply in microinvasive carcinoma, or which guideline to apply when DCIS occurs in association with invasive carcinoma and the DCIS component is in proximity to the margin. The margin consensus panel opted to draw the line for the DCIS guideline at microinvasive cancer, including this with DCIS because most of the lesion is composed of DCIS, and because small retrospective studies suggest that the behavior of microinvasive carcinoma is more similar to the behavior of DCIS than invasive cancer[59] and that the use of systemic therapy is more similar to that seen in DCIS. In contrast, invasive cancer with associated DCIS, whether an EIC or lesser amounts, should be managed according to the invasive guideline. In these cases, the biology of the invasive cancer is the primary determinant of outcome, and the majority of

patients will receive systemic therapy. In addition, an EIC excised to clear margins does not increase LR,[31,32] although, as discussed previously, it is a potential marker for a heavier residual disease burden.

In conclusion, in the modern era of multimodality therapy for invasive and in situ breast carcinomas, the margin status is one of a number of factors affecting LR risk, and the tumor biology rather than an arbitrary anatomic margin cutoff is the major determinant of LR. For invasive breast cancer, the data support obtaining a negative margin, defined as no ink on tumor, and do not identify an additional benefit for more widely clear margins. In patients with DCIS receiving RT, a margin of 2 mm minimizes LR, but larger margins do not provide added benefit. The adoption of these evidence-based margin guidelines will decrease the burden of surgery for patients and their families, and reduce health care costs.

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REFERENCES

1. Fisher B, Anderson S, Redmond CK, Wolmark N, Wickerham DL, Cronin WM. Reanalysis and results after 12 years of follow-up in a randomized clinical trial comparing total mastectomy with lumpectomy with or without irradiation in the treatment of breast cancer. *N Engl J Med.* 1995;333:1456-1461.
2. Veronesi U, Cascinelli N, Mariani L, et al. Twenty-year follow-up of a randomized study comparing breast-conserving surgery with radical mastectomy for early breast cancer. *N Engl J Med.* 2002;347: 1227-1232.
3. van Dongen JA, Bartelink H, Fentiman IS, et al. Factors influencing local relapse and survival and results of salvage treatment after breast-conserving therapy in operable breast cancer: EORTC trial 10801, breast conservation compared with mastectomy in TNM stage I and II breast cancer. *Eur J Cancer.* 1992;28A:801-805.
4. Fisher B, Dignam J, Wolmark N, et al. Lumpectomy and radiation therapy for the treatment of intraductal breast cancer: findings from National Surgical Adjuvant Breast and Bowel Project B-17. *J Clin Oncol.* 1998;16:441-452.
5. Houghton J, George WD, Cuzick J, et al. Radiotherapy and tamoxifen in women with completely excised ductal carcinoma in situ of the breast in the UK, Australia, and New Zealand: randomised controlled trial. *Lancet.* 2003;362:95-102.
6. Julien JP, Bijker N, Fentiman IS, et al. Radiotherapy in breast-conserving treatment for ductal carcinoma in situ: first results of the EORTC randomised phase III trial 10853. EORTC Breast Cancer Cooperative Group and EORTC Radiotherapy Group. *Lancet.* 2000;355:528-533.
7. Emdin SO, Granstrand B, Ringberg A, et al. SweDCIS: radiotherapy after sector resection for ductal carcinoma in situ of the breast. Results of a randomised trial in a population offered mammography screening. *Acta Oncol.* 2006;45:536-543.
8. Azu M, Abrahamse P, Katz SJ, Jagsi R, Morrow M. What is an adequate margin for breast-conserving surgery? Surgeon attitudes and correlates. *Ann Surg Oncol.* 2010;17:558-563.
9. Morrow M, Jagsi R, Alderman AK, et al. Surgeon recommendations and receipt of mastectomy for treatment of breast cancer. *JAMA.* 2009;302:1551-1556.
10. McCahill LE, Single RM, Aiello Bowles EJ, et al. Variability in reexcision following breast conservation surgery. *JAMA.* 2012;307:467-475.
11. Graham RA, Homer MJ, Katz J, Rothschild J, Safaii H, Supran S. The pancake phenomenon contributes to the inaccuracy of margin assessment in patients with breast cancer. *Am J Surg.* 2002;184:89-93.
12. Carter D. Margins of "lumpectomy" for breast cancer. *Hum Pathol.* 1986;17:330-332.
13. Holland R, Veling SH, Mravunac M, Hendriks JH. Histologic multifocality of Tis, T1-2 breast carcinomas. Implications for clinical trials of breast-conserving surgery. *Cancer.* 1985;56:979-990.
14. Lowery AJ, Kell MR, Glynn RW, Kerin MJ, Sweeney KJ. Locoregional recurrence after breast cancer surgery: a systematic review by receptor phenotype. *Breast Cancer Res Treat.* 2012;133:831-841.
15. Mamounas EP, Tang G, Fisher B, et al. Association between the 21-gene recurrence score assay and risk of locoregional recurrence in node-negative, estrogen receptor–positive breast cancer: results from NSABP B-14 and NSABP B-20. *J Clin Oncol.* 2010;28: 1677-1683.
16. Cancello G, Maisonneuve P, Rotmensz N, et al. Prognosis in women with small (T1mic,T1a,T1b) node-negative operable breast cancer by immunohistochemically selected subtypes. *Breast Cancer Res Treat.* 2011;127:713-720.
17. Clarke M, Collins R, Darby S, et al. Effects of radiotherapy and of differences in the extent of surgery for early breast cancer on local recurrence and 15-year survival: an overview of the randomised trials. *Lancet.* 2005;366:2087-2106.
18. Mannino M, Yarnold JR. Local relapse rates are falling after breast conserving surgery and systemic therapy for early breast cancer: can radiotherapy ever be safely withheld? *Radiother Oncol.* 2009;90:14-22.
19. Kiess AP, McArthur HL, Mahoney K, et al. Adjuvant trastuzumab reduces locoregional recurrence in women who receive breast-conservation therapy for lymph node–negative, human epidermal growth factor receptor 2–positive breast cancer. *Cancer.* 2012;118:1982-1988.
20. Lanning RM, Morrow M, Riaz N, et al. The effect of adjuvant trastuzumab on locoregional recurrence of human epidermal growth factor receptor 2–positive breast cancer treated with mastectomy. *Ann Surg Oncol.* 2015;22:2517-2525.
21. Bouganim N, Tsvetkova E, Clemons M, Amir E. Evolution of sites of recurrence after early breast cancer over the last 20 years: implications for patient care and future research. *Breast Cancer Res Treat.* 2013;139:603-606.
22. Giuliano AE, Hunt KK, Ballman KV, et al. Axillary dissection vs no axillary dissection in women with invasive breast cancer and sentinel node metastasis: a randomized clinical trial. *JAMA.* 2011;305:569-575.
23. Galimberti V, Cole BF, Zurrida S, 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.
24. Houssami N, Macaskill P, Marinovich ML, 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;46:3219-3232.
25. Houssami N, Macaskill P, Marinovich ML, Morrow M. The association of surgical margins and local recurrence in women with early-stage invasive breast cancer treated with breast-conserving therapy: a meta-analysis. *Ann Surg Oncol.* 2014;21:717-730.
26. Moran MS, Schnitt SJ, Giuliano AE, 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;32:1507-1515.
27. Curigliano G, Burstein HJ, Winer EP, et al. De-escalating and escalating treatments for early-stage breast cancer: the St. Gallen

International Expert Consensus Conference on the Primary Therapy of Early Breast Cancer 2017. *Ann Oncol.* 2017;28:1700-1712.
28. Pilewskie M, King TA. Age and molecular subtypes: impact on surgical decisions. *J Surg Oncol.* 2014;110:8-14.
29. Pilewskie M, Ho A, Orell E, et al. Effect of margin width on local recurrence in triple-negative breast cancer patients treated with breast-conserving therapy. *Ann Surg Oncol.* 2014;21:1209-1214.
30. Harris JR. Breast-conserving therapy as a model for creating new knowledge in clinical oncology. *Int J Radiat Oncol Biol Phys.* 1996; 35:641-648.
31. Bartelink H, Horiot JC, Poortmans P, et al. Recurrence rates after treatment of breast cancer with standard radiotherapy with or without additional radiation. *N Engl J Med.* 2001;345:1378-1387.
32. Park CC, Mitsumori M, Nixon A, et al. Outcome at 8 years after breast-conserving surgery and radiation therapy for invasive breast cancer: influence of margin status and systemic therapy on local recurrence. *J Clin Oncol.* 2000;18:1668-1675.
33. Rosenberger LH, Mamtani A, Fuzesi S, et al. Early adoption of the SSO-ASTRO consensus guidelines on margins for breast-conserving surgery with whole-breast irradiation in stage I and II invasive breast cancer: initial experience from Memorial Sloan Kettering Cancer Center. *Ann Surg Oncol.* 2016;23:3239-3246.
34. Pilewskie M, Morrow M. Axillary nodal management following neoadjuvant chemotherapy: a review. *JAMA Oncol.* 2017;3:549-555.
35. Abe SE, Hill JS, Han Y, et al. Margin re-excision and local recurrence in invasive breast cancer: a cost analysis using a decision tree model. *J Surg Oncol.* 2015;112:443-448.
36. Narod SA, Iqbal J, Giannakeas V, Sopik V, Sun P. Breast cancer mortality after a diagnosis of ductal carcinoma in situ. *JAMA Oncol.* 2015;1:888-896.
37. Correa C, McGale P, Taylor C, et al; Early Breast Cancer Trialists' Collaborative Group. Overview of the randomized trials of radiotherapy in ductal carcinoma in situ of the breast. *J Natl Cancer Inst Monogr.* 2010;2010:162-177.
38. Wapnir IL, Dignam JJ, Fisher B, et al. Long-term outcomes of invasive ipsilateral breast tumor recurrences after lumpectomy in NSABP B-17 and B-24 randomized clinical trials for DCIS. *J Natl Cancer Inst.* 2011;103:478-488.
39. Van Zee KJ, Subhedar P, Olcese C, Patil S, Morrow M. Relationship between margin width and recurrence of ductal carcinoma in situ: analysis of 2996 women treated with breast-conserving surgery for 30 years. *Ann Surg.* 2015;262:623-631.
40. Donker M, Litiere S, Werutsky G, et al. Breast-conserving treatment with or without radiotherapy in ductal carcinoma in situ: 15-year recurrence rates and outcome after a recurrence, from the EORTC 10853 randomized phase III trial. *J Clin Oncol.* 2013;31:4054-4059.
41. Rodrigues N, Carter D, Dillon D, Parisot N, Choi DH, Haffty BG. Correlation of clinical and pathologic features with outcome in patients with ductal carcinoma in situ of the breast treated with breast-conserving surgery and radiotherapy. *Int J Radiat Oncol Biol Phys.* 2002;54:1331-1335.
42. Taghian A, Mohiuddin M, Jagsi R, Goldberg S, Ceilley E, Powell S. Current perceptions regarding surgical margin status after breast-conserving therapy: results of a survey. *Ann Surg.* 2005;241:629-639.
43. Blair SL, Thompson K, Rococco J, Malcarne V, Beitsch PD, Ollila DW. Attaining negative margins in breast-conservation operations: is there a consensus among breast surgeons? *J Am Coll Surg.* 2009;209:608-613.
44. Hassani A, Griffith C, Harvey J. Size does matter: high volume breast surgeons accept smaller excision margins for wide local excision—a national survey of the surgical management of wide local excision margins in UK breast cancer patients. *Breast.* 2013;22:718-722.
45. Faverly DR, Burgers L, Bult P, Holland R. Three dimensional imaging of mammary ductal carcinoma in situ: clinical implications. *Semin Diagn Pathol.* 1994;11:193-198.
46. Sagara Y, Freedman RA, Wong SM, et al. Trends in adjuvant therapies after breast-conserving surgery for hormone receptor–positive ductal carcinoma in situ: findings from the National Cancer Database, 2004-2013. *Breast Cancer Res Treat.* 2017;166:583-592.
47. Smith GL, Smith BD, Haffty BG. Rationalization and regionalization of treatment for ductal carcinoma in situ of the breast. *Int J Radiat Oncol Biol Phys.* 2006;65:1397-1403.
48. Silverstein MJ, Lagios MD, Groshen S, et al. The influence of margin width on local control of ductal carcinoma in situ of the breast. *N Engl J Med.* 1999;340:1455-1461.
49. Wong JS, Chen YH, Gadd MA, et al. Eight-year update of a prospective study of wide excision alone for small low- or intermediate-grade ductal carcinoma in situ (DCIS). *Breast Cancer Res Treat.* 2014;143:343-350.
50. Macdonald HR, Silverstein MJ, Lee LA, et al. Margin width as the sole determinant of local recurrence after breast conservation in patients with ductal carcinoma in situ of the breast. *Am J Surg.* 2006;192:420-422.
51. Wehner P, Lagios MD, Silverstein MJ. DCIS treated with excision alone using the National Comprehensive Cancer Network (NCCN) guidelines. *Ann Surg Oncol.* 2013;20:3175-3179.
52. Solin LJ, Gray R, Hughes LL, et al. Surgical excision without radiation for ductal carcinoma in situ of the breast: 12-year results from the ECOG-ACRIN E5194 study. *J Clin Oncol.* 2015;33:3938-3944.
53. Hughes LL, Wang M, Page DL, et al. Local excision alone without irradiation for ductal carcinoma in situ of the breast: a trial of the Eastern Cooperative Oncology Group. *J Clin Oncol.* 2009;27:5319-5324.
54. MacDonald HR, Silverstein MJ, Mabry H, et al. Local control in ductal carcinoma in situ treated by excision alone: incremental benefit of larger margins. *Am J Surg.* 2005;190:521-525.
55. McCormick B, Winter K, Hudis C, et al. RTOG 9804: a prospective randomized trial for good-risk ductal carcinoma in situ comparing radiotherapy with observation. *J Clin Oncol.* 2015;33:709-715.
56. Marinovich ML, Azizi L, Macaskill P, et al. The association of surgical margins and local recurrence in women with ductal carcinoma in situ treated with breast-conserving therapy: a meta-analysis. *Ann Surg Oncol.* 2016;23:3811-3821.
57. Morrow M, Van Zee KJ, Solin LJ, 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. *J Clin Oncol.* 2016;34:4040-4046.
58. Kuerer HM, Smith BD, Chavez-MacGregor M, et al. DCIS margins and breast conservation: MD Anderson Cancer Center multidisciplinary practice guidelines and outcomes. *J Cancer.* 2017;8:2653-2662.
59. Parikh RR, Haffty BG, Lannin D, Moran MS. Ductal carcinoma in situ with microinvasion: prognostic implications, long-term outcomes, and role of axillary evaluation. *Int J Radiat Oncol Biol Phys.* 2012;82:7-13.