Controversies and Clinical Trials for DCIS: Margins and Active Surveillance

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Abstract

Two controversial areas in the management of ductal carcinoma in situ (DCIS) involve appropriate negative margin width for conservative surgery and whether surgery is indicated in all cases with this diagnosis. Pure DCIS is a high-risk breast lesion as it can sometimes be associated with later development of invasive breast cancer in the absence of treatment. Recent national practice guidelines suggest that adequate margins for DCIS should be ≥2 mm after breast-conserving surgery followed by radiotherapy (RT). This guideline is being utilized by many groups as an absolute indication for additional surgery, although clinical judgment was recommended. We evaluated contemporary patient local recurrence outcomes at The University of Texas MD Anderson Cancer Center. The cases had been handled using multidisciplinary DCIS practices, including extensive preoperative, intraoperative pathologic image-guided assessment of margins; offering some patients with small low- or intermediate-grade DCIS the option of no RT; the use/magnitude of radiation boost tailored to margin width; and offering endocrine therapy for estrogen receptor–positive DCIS. Use of these MD Anderson practices has resulted in 10-year local recurrence rates below 5% for patients with margins <2 mm who received RT. Patients with margins <2 mm who do not receive RT experience significantly higher local failure rates, in the 30% range, and are recommended to repeat surgery. Individualized patient care is determined by a multidisciplinary team and there is not an absolute requirement to achieve wider negative surgical margins when margins are found to be <2 mm if the patient will be treated with RT. Globally, there are at least 3 clinical trials ongoing that are testing the hypothesis that biopsy alone with active surveillance is not inferior to immediate breast-conserving surgery with or without radiotherapy for DCIS. In the United States, one study is the COMET trial, run by the Alliance Foundation Trials group. COMET is a randomized trial in which 1200 patients over age 40 years with hormone-positive DCIS, without a mass lesion, will have stereotactic core biopsy; they will then receive guideline-concordant care versus no surgery, with choice of endocrine therapy and close follow-up. The primary endpoints for these trials are invasive breast cancer recurrence.

AJHO. 2017;13(9):4-7

Introduction

The management of ductal carcinoma in situ (DCIS) is one of the most controversial areas in breast cancer management. It is curious that on the one hand we continue to debate whether 1 or 2 mm margins are clinically relevant compared with no tumor on ink for breast conservation, and at the same time, we have begun randomized trials of biopsy alone for DCIS without surgery—just active surveillance. Taken together, this suggests that many therapeutic questions and potential areas for clinical care improvements remain in this field.

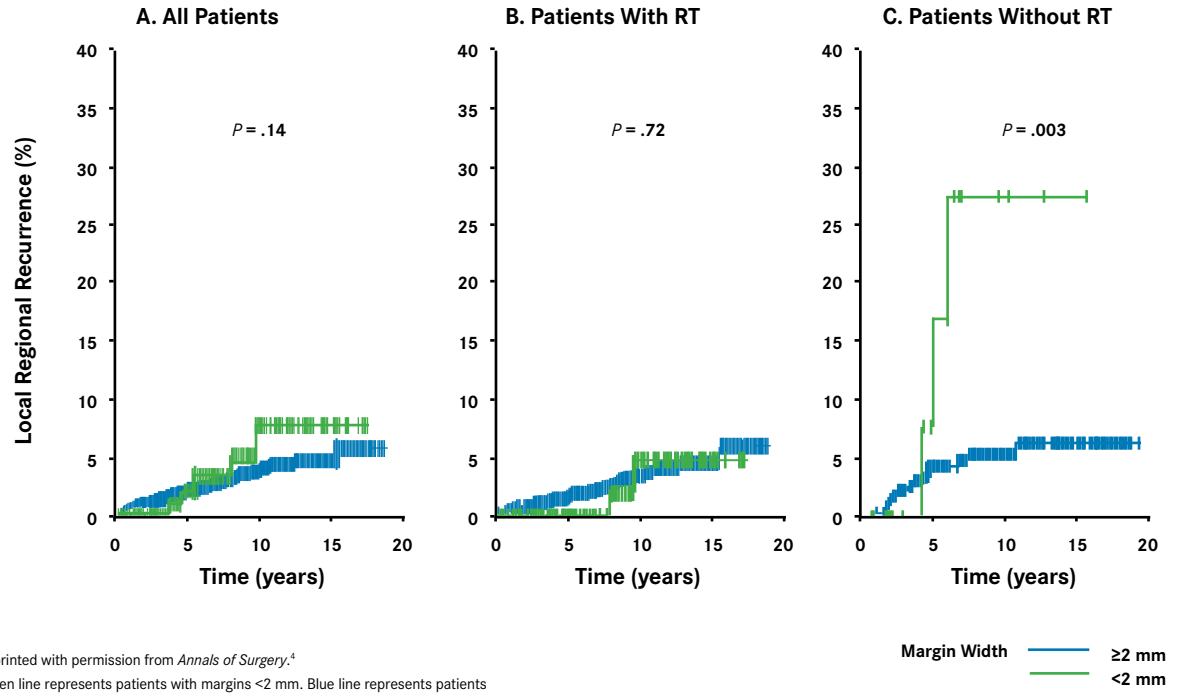
Margins for DCIS

For invasive breast cancer, national consensus guidelines state that negative margin width is considered adequate when the tumor is not present on ink when patients are receiving breast-conserving surgery followed by whole breast radiotherapy (RT).[1] These guidelines have definitely resulted in fewer repeat surgeries and mastectomies in the United States.[2]

However, there is concern regarding the new margin guideline recently endorsed—an optimal margin width of DCIS of 2 mm—by the Society of Surgical Oncology, the American Society of Radiation Oncology, and the American Society of Clinical Oncology.[3] The guideline clearly stated that individualized patient decisions based on clinical judgment should be utilized. The main issue that has been raised is that it is a paradox to have 2 different margin guidelines—one for invasive cancer with DCIS, and another for pure DCIS—when receiving postoperative RT. These guidelines were based on a meta-analysis of retrospective studies beginning in the 1960s. Theoretically, differences in margin guidelines for negative margin width for pure DCIS have to do with early pathologic studies related to multifocality seen in pure DCIS, but this pathologic finding also applies when DCIS accompanies invasive breast cancer.

Therefore, our group looked at our own recent contemporary experience treating DCIS at The University of Texas MD Anderson Cancer Center, reviewing data involving about 1500 patients from 1996 to 2010. These data were recently presented at the American Society of Clinical Oncology Annual Meeting & Exhibition.[4,5] The 10-year rate of local recurrence for patients with negative margins of <2 mm versus >2 mm were not significantly different, both being less than 5%. There was no statistically significant difference in local recurrence between patients with <2 mm

FIGURE 1. MD Anderson Contemporary (1996-2010) Local Regional Recurrence Among Patients With DCIS Treated With Breast-Conserving Surgery, With and Without Radiation Therapy According to Negative Margin Status of ≥ or <2 mm



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Green line represents patients with margins <2 mm. Blue line represents patients with margins ≥2 mm. RT indicates radiation therapy.

and >2 mm negative margins who underwent RT (10-year local recurrence rate, 4.8% vs 3.3%, respectively; hazard ratio, 0.8; 95% CI, 0.2-3.2; *P* = .72) (**Figure 1**). Being younger than 40 years was also an independent risk factor for local recurrence in patients receiving RT. For patients with close margins and no RT, recurrence rates are about 5 times the risk and in the 30% range. For those patients, we routinely recommend re-excision. MD Anderson utilizes detailed multidisciplinary practices including extensive preoperative/intraoperative pathologic/histologic image-guided assessment of margins; offering some patients with small, low- to intermediate-grade DCIS the option of no RT; the use/magnitude of radiation boost tailored to margin width; and endocrine therapy for estrogen receptor–positive DCIS. These practices can be labor-intensive and require meticulous multidisciplinary collaboration.

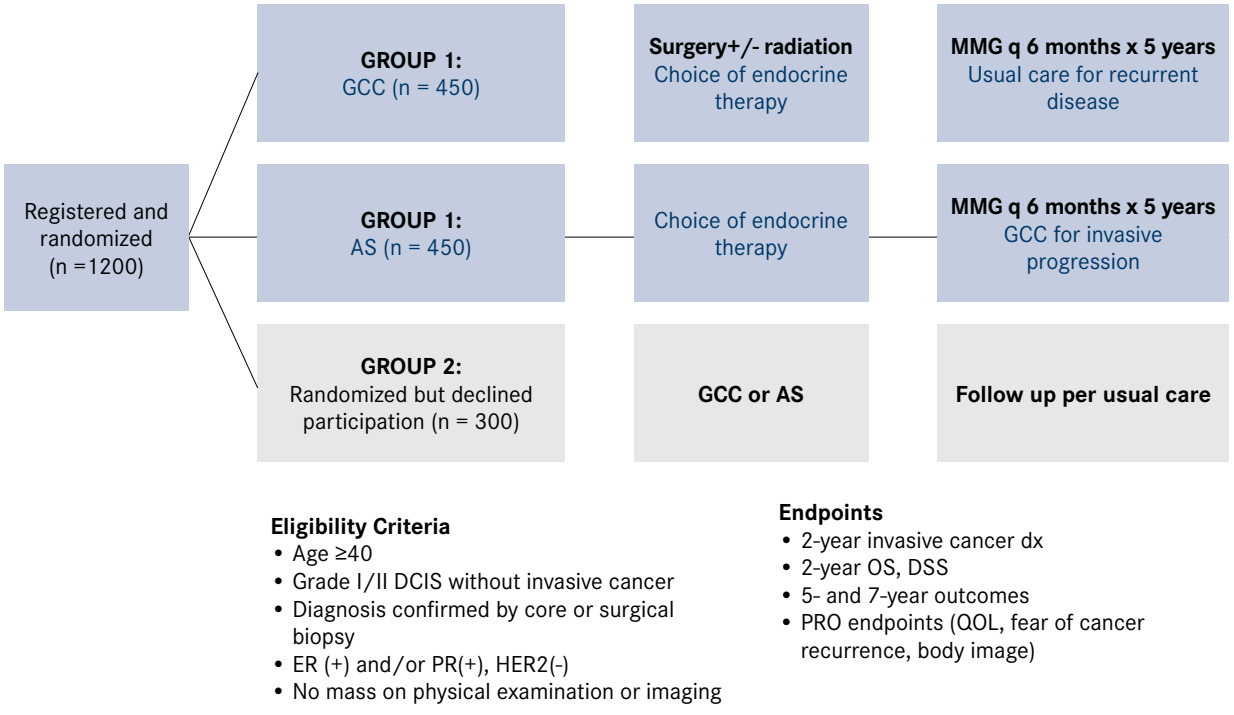
Based on our results, about 8% to 10% of cases would need additional surgery, potentially without benefit, when receiving RT; therefore, each case needs to be evaluated by a multidisciplinary team that takes into account the patient's age, the extent of margin involvement, and the patient's values. The main issue is that many multidisciplinary groups now use the 2 mm margin as an absolute indication for repeat surgery, and not all patients with DCIS and margins <2 mm need repeat surgery when receiving RT.

Active Surveillance Trials for DCIS

We treat DCIS to prevent invasive breast cancer.[6] DCIS in and of itself is not harmful to patients. In effect, DCIS really may belong in a high-risk breast lesion category. Screening mammography, since its introduction in the mid-1980s, has resulted in about a 500-fold increase in detection of DCIS, and perhaps a significant proportion of these patients, particularly with low-grade and intermediate-grade DCIS, will not go on to develop invasive breast cancers during the patient's lifetime.

To address this clinical scenario, there are at least 3 currently ongoing clinical trials globally that are testing the hypothesis that biopsy alone with active surveillance is not inferior to immediate breast-conserving surgery with or without RT for DCIS.[7] In the United States, 1 such trial is COMET,[8] run by the Alliance Foundation Trials group. It is a randomized trial in which 1200 patients over age 40 years with hormone-receptor–positive DCIS without a mass lesion will undergo stereotactic core biopsy (**Figure 2**). In a randomized manner, patients will receive guideline-concordant care consisting of breast-conserving surgery with or without

FIGURE 2. COMET (Comparison of Operative to Monitoring and Endocrine Therapy) Trial for Low-Risk DCIS[8]



Used with permission from Shelley Hwang, MD, MPH, principal investigator. AS indicates active surveillance; DSS, disease specific survival, dx, diagnosis; ER, estrogen receptor, GCC, guideline concordant care; HER2, human epidermal growth factor receptor 2; MMG, mammography, OS, overall survival, PR, progesterone receptor; QOL, quality of life.

radiation and endocrine therapy, versus choice of endocrine therapy alone and then followed for multiple endpoints with the primary being the development of invasive breast cancer on follow-up. The second trial, LORIS,[9] based in the United Kingdom, randomizes patients with low- and intermediate-grade DCIS, and the third trial, LORD,[10] based in the Netherlands (now through the European Organisation for the Research and Treatment of Cancer cooperative group), is enrolling patients with low-grade DCIS only.

Many of our patients are fearful of the consequences of potential overdiagnosis and overtreatment, and they will welcome the results of these trials. Currently, they are followed closely with 6-month follow-up mammograms in the United States.

Conclusions

DCIS is a common preinvasive breast disease that is detected through screening mammography and often treated similarly to invasive breast cancer. One of the most controversial aspects in the management of breast diseases, and specifically breast cancer, is the appropriate management of DCIS. This brief review highlights important data regarding what constitutes an acceptable negative margin for patients treated with breast-conserving therapy and who receive RT. Not all patients with negative margins less than or equal to 2 mm require repeat surgery when receiving RT, as the local control is extremely high. Outcomes are not significantly different for patients with margins greater than 2 mm, as the results of our large contemporary series indicate. Finally, several key international trials are now addressing the hypothesis that the outcomes of patients with percutaneous biopsy alone for low-risk DCIS are not inferior to outcomes of surgery with or without RT.

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Financial disclosures: Henry M. Kuerer, MD, PhD, receives compensation from the NEJM Group, Inc and McGraw-Hill publishing for editorial work.

Presented in part at the 16th Annual International Congress on the Future of Breast Cancer, July 15, 2017.

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