When Is Good Enough Really Good Enough? Defining the Role of Radiation in Low-Risk Ductal Carcinoma In Situ

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The Oncology Grand Rounds series is designed to place original reports published in the Journal into clinical context. A case presentation is followed by a description of diagnostic and management challenges, a review of the relevant literature, and a summary of the authors’ suggested management approaches. The goal of this series is to help readers better understand how to apply the results of key studies, including those published in Journal of Clinical Oncology, to patients seen in their own clinical practice.

A 67-year-old woman undergoing screening mammography was found to have a new focus of clustered microcalcifications at 9 o’clock in the left breast. Magnification views confirmed this focus, which measured 5 mm (Fig 1). Stereotactic core biopsy revealed ductal carcinoma in situ (DCIS), low nuclear grade, and cribriform pattern without necrosis (Fig 2). Subsequent needle-localized segmental mastectomy revealed a 5-mm focus of low-grade DCIS, cribriform type without necrosis, positive for both estrogen receptor and progesterone receptor. Surgical margins were negative at a minimum of 3 mm. The patient is healthy without major medical problems but has an elevated body mass index. She is now referred for consideration of adjuvant radiation therapy. Examination shows an excellent cosmetic outcome, D-cup breasts, and a well-healed curvilinear scar in the medial left breast with minimal underlying postoperative induration.

CHALLENGES IN DIAGNOSIS AND MANAGEMENT

DCIS is a non obligate precursor lesion to invasive carcinoma of the breast. Although cytologically malignant, DCIS, as defined, has not invaded through myoepithelial cells covering the basement membrane lining the duct and is thus noninvasive. This pathologic feature underscores the necessity of core biopsy, which reveals histologic architecture necessary for determining the presence or absence of stromal invasion. Because fine-needle aspiration reveals cytologic features alone, fine-needle aspiration of the breast cannot accurately classify a lesion as invasive carcinoma versus DCIS. The precise risk of malignant transformation from DCIS to invasive cancer is not well understood because there are relatively few case series of patients with untreated DCIS. An oft-quoted longitudinal study of 28 women with small, non comedo DCIS who were followed for more than 30 years after biopsy alone estimated that the risk of transformation to invasive carcinoma was approximately 40%, with five patients ultimately developing metastatic disease.

In 2014, it is estimated that 63,000 women in the United States will be diagnosed with DCIS, accounting for 27% of all breast cancer diagnoses. From 1983 to 2003, the age-adjusted incidence of DCIS among women age 50 years or older increased by approximately 500%, coincident with dissemination of screening mammography. Since 2003, incidence has declined for women age 50 years or older but has continued to increase for women younger than age 50 years. It has been estimated that one in every 1,300 mammography examinations performed will yield a diagnosis of DCIS. Over the next 20 years, the total number of DCIS cases diagnosed on an annual basis in the United States is expected to increase by 26% because of a greater number of older women in the population.

Overall, mortality from DCIS is low, regardless of chosen treatment, with 10-year risk of death as a result of invasive breast cancer ranging from 1.0% to 2.6%. For older women specifically, those diagnosed with DCIS experience lower all-cause mortality than age- and race-matched controls. It is likely that the health behaviors associated with a DCIS diagnosis, particularly participation in screening mammography, identify a population of older women who are, on average, healthier than the general population of older women.

When treating DCIS, the principal goal is to minimize both the risk of progression to invasive cancer and the impact of treatment on quality of life. Because the vast majority of recurrences occur in the breast itself, rather than in regional or distant sites, achieving these goals requires careful attention to selecting the best local therapy strategy for each individual patient.

SUMMARY OF THE RELEVANT LITERATURE

Historically, mastectomy was the standard of care for treatment of DCIS. Mastectomy confers excellent oncologic outcomes, with case...
series estimating the long-term recurrence risk to be approximately 1% to 3%.\(^\text{12,13}\) Mastectomy for DCIS has never been directly compared with breast-conserving therapy in a randomized trial. Instead, randomized trials have focused on evaluating the incremental benefit of radiation after breast-conserving surgery, with a specific focus on risk of ipsilateral breast tumor recurrence (IBTR), defined as a subsequent in situ or invasive event occurring in the index breast. Before publication of a report on Radiation Therapy Oncology Group 9804 (RTOG 9804; Phase III Trial of Observation +/- Tamoxifen vs. RT +/- Tamoxifen for Good Risk Ductal Carcinoma In Situ [DCIS] of the Female Breast) in this issue of Journal of Clinical Oncology, four randomized trials informed understanding of the benefit of whole-breast irradiation (50 Gy in 25 fractions) after breast-conserving surgery for DCIS.\(^\text{8,14-18}\) These trials included a broader mix of patients than were included in RTOG 9804, representing both lower- and higher-risk DCIS. A meta-analysis based on individual patient-level data for these four initial trials concluded that radiation lowered the risk for IBTR, with a 54% relative reduction and a 15% absolute reduction at 10 years.\(^\text{19}\) Of note, the only clinical factor found to modify the benefit of radiation was age, with younger women deriving a smaller percent benefit (31% relative reduction) than older women (62% relative reduction).

Given that many women treated with conservative surgery for DCIS will not personally benefit from receiving radiation therapy, there has been great interest in determining which patients may safely avoid radiation therapy without a clinically meaningful increase in risk of IBTR. To that end, two high-quality, prospective phase II studies sought to evaluate outcomes in highly selected patients with low-risk DCIS in whom radiation was omitted. The first trial, conducted at the Dana-Farber Cancer Institute, was closed early when the number of IBTRs met predetermined stopping rules, with a 5-year IBTR risk of 12%.\(^\text{20}\) The second trial, Eastern Cooperative Oncology Group 5194 (ECOG 5194; Evaluation of Breast Cancer Recurrence Rates Following Surgery in Women With Ductal Carcinoma In Situ), reported a 5-year IBTR risk of 6% in 565 women with low- to intermediate-grade DCIS, \(\leq 2.5\) cm in size, resected with a minimum of 3-mm negative margins.\(^\text{21}\) However, IBTR risk was higher (15% at 5 years) for 105 women with high-grade DCIS \(\leq 1.0\) cm in size who also participated in this trial. Subsequently, DCIS tissue from 327 patients who participated in ECOG 5194 was used to develop Oncotype DX, which is a commercially available test that uses expression levels of 12 genes within the resected DCIS specimen to estimate the 10-year risk of IBTR after conservative surgery without radiation (with or without tamoxifen).\(^\text{22}\) By using this test, the 10-year estimated IBTR risk ranges from approximately 9% to 27%. Accordingly, this test may be used to estimate IBTR risk among patients opting for conservative surgery alone who meet the ECOG 5194 inclusion criteria. The test does not, however, predict benefit from radiation or tamoxifen.

Within this context, the results of RTOG 9804 illuminate several important and clinically relevant conclusions. First, the 7-year IBTR risk of 6.7% in the no-radiation arm strongly demonstrates that within...
a multi-institutional context with careful attention to pathologic assessment, selected patients with low-risk DCIS experience excellent outcomes through 7 years of follow-up when whole-breast irradiation is omitted. It is noteworthy that the aggregate IBTR risk in the no-radiation arm of RTOG 9804 is considerably lower than the range of IBTR risk reported by the Oncotype DX DCIS score, although this difference may ultimately be explained by the difference in the time points reported (ie, 7-year outcomes reported for RTOG 9804 v 10-year outcomes estimated by the Oncotype DX DCIS score). However, despite the low risk of IBTR without radiation, the addition of radiation still conferred a measurable and statistically significant reduction in IBTR risk. With 7 years of follow-up, the absolute reduction conferred by radiation was 5.8%. This benefit is comparable to the 5.2% absolute benefit of 5 years of tamoxifen reported by National Surgical Adjuvant Breast and Bowel Project B-24 (NSABP-B-24; Phase III Randomized Trial of Adjuvant Tamoxifen vs Placebo Following Breast Irradiation in Patients Who Have Undergone Lumpectomy for Noninvasive Intraductal Carcinoma [DCIS] of the Breast) in patients with DCIS treated with conservative surgery and radiation and modestly exceeds the 3% absolute chemopreventive benefit of tamoxifen reported by NSABP P-1 in women at high risk for developing breast cancer. Third, the risk of IBTR essentially doubled between 5 years after treatment and 7 years after treatment. This observation underscores the long natural history of low-risk DCIS, the need for long-term follow-up, and the difficulty in extrapolating the published results of RTOG 9804 beyond 7 years.

**SUGGESTED APPROACHES TO MANAGEMENT**

The inclusion criteria for RTOG 9804—mammographically detected DCIS, low or intermediate grade, ≤ 2.5 cm in size, resected margins negative at a minimum of 3 mm—now serve as the gold standard for defining low-risk DCIS. Integrating the results of RTOG 9804 into
clinical practice remains challenging, however, because the field of radiation oncology lacks a consistent framework for facilitating clinical decision making when the anticipated local control benefit of adjuvant radiation is measurable yet relatively small. Nevertheless, starting from the assumption that radiation will confer a 5.8% absolute reduction in IBTR risk for low-risk DCIS and no meaningful survival benefit, it is possible to apply clinical judgment to develop a rational approach to decision making (Fig 3).

The first important consideration specifically for older patients with low-risk DCIS is to thoroughly evaluate their functional status and comorbid illness to facilitate estimation of their long-term survival. For example, given that the IBTR risk within the first 5 years of conservative surgery without radiation is only 3.5%, it would be advisable to recommend against radiation in patients with a high likelihood of death as a result of intercurrent disease within 5 years. For the patient described at the beginning of the article, the validated Lee-Schonberg index (calculated by using the calculators found on the ePrognosis Web site) estimates that her 5-year mortality is 2% and 10-year mortality is 8%. Such a patient is likely to live long enough to potentially derive a benefit from adjuvant therapy. In contrast, if the predicted 5-year mortality were high, for example ≥ 50%, the likelihood of benefit from radiation would be significantly attenuated. We previously illustrated this concept by using population-based data, estimating that the number needed to treat to prevent one breast event was 11 for a healthy woman diagnosed with low-risk DCIS in her late 60s compared with a number needed to treat of 29 for a woman in her late 80s with significant comorbid illness.

The second key factor to evaluate is the anticipated risk of radiation therapy. Although whole-breast irradiation is generally well tolerated, there are certain situations in which risk of complications may be meaningful. For example, patients with collagen vascular disease, particularly scleroderma or active lupus with cutaneous involvement, likely experience increased skin and soft tissue complications from radiation. Considering these risks in light of the modest benefit from radiation for low-risk DCIS, it would generally be advisable to omit radiation in favor of breast-conserving surgery alone for patients with such collagen vascular diseases. Another important consideration is anticipated cardiac dose. Although most patients can be treated with heart-sparing techniques, if the mean heart dose were anticipated to exceed 2 Gy, or if a considerable portion of the left anterior descending coronary artery were to receive a potentially atherogenic dose (perhaps ≥ 25 Gy), omission of radiation is likely the wiser treatment choice, particularly in a patient with cardiac risk factors or known disease.

Considering the lack of a breast cancer survival benefit from radiation in the treatment of low-risk DCIS, excess mortality resulting from radiation is unacceptable. The case scenario presented here illustrates the challenge of cardiac sparing in certain cases (Fig 4A). It should be noted, however, that use of deep inspiration breath gating displaces the heart from the geometric projection of the radiation beams (Fig 4B) and thereby substantially reduces cardiac dose and, presumably, long-term cardiac risks. Finally, patients with

![Fig 4](https://example.com/figure4.png)

**Fig 4.** (A) Radiation treatment plan in free breathing for a patient with a medially located, low-risk ductal carcinoma in situ status post conservative surgery. The aqua contour is the tissue immediately surrounding the tumor bed. The pink contour is the left anterior descending coronary artery. Isodose lines are as follows: blue, 52 Gy; red, 50 Gy; yellow, 45 Gy; green, 25 Gy; purple, 10 Gy; brown, 5 Gy. In this scan obtained in free breathing, the mean heart dose would have been 4.4 Gy and the maximum dose to the left anterior descending coronary artery would have been 47 Gy if the prescription dose were 50 Gy in 25 fractions. These cardiac metrics were considered unacceptable, and the patient was not treated with this plan. (B) Radiation treatment plan in deep inspiration breath hold for a different patient with a medially located ductal carcinoma in situ, assuming a prescription dose of 50 Gy in 25 fractions. Because deep inspiration breath hold displaces the heart from the geometric projection of the radiation beams, the cardiac parameters tend to be significantly improved. For this patient, the mean heart dose was 0.7 Gy and the maximum dose to the left anterior descending coronary artery was 5 Gy. This was thought to be an acceptable plan, and the patient received whole-breast irradiation but with a hypofractionated schedule of 40 Gy in 15 fractions.
morbid obesity are difficult to position and treat and may experience elevated risks of acute skin toxicity and fibrosis. Such patients may also be better served by omitting radiation.

The third key factor is patient preference. Given that radiation only modestly improves IBTR risk and does not influence survival, the decision for or against radiation should strongly consider patient preference. For patients with high numeracy, the findings of RTOG 9804 are helpful for framing this conversation. For patients with lower numeracy, decision aids are in development to assist clinicians with describing the trade-offs of radiation for women with DCIS. When counseling patients, physicians should be mindful of the terms they use to describe DCIS. A thought-provoking study illustrated that women are more likely to opt for surgical treatment when DCIS is called “noninvasive breast cancer” than when it is called “abnormal cells” or a “breast lesion.” With careful, risk-based counseling, many patients with low-risk DCIS will readily decide to opt out of radiation, whereas others will strongly desire it.

The fourth key factor to consider when crafting a recommendation for or against radiation is the type of salvage surgery that would be needed if the patient were to develop an IBTR. For example, in the case presented here, the patient has relatively large breasts and an excellent cosmetic outcome after index conservative surgery. If this patient were to develop an IBTR, it is highly likely that a second conservative surgery could be offered with reasonable cosmetic outcome. Thus, although this patient would be expected to experience a modest absolute decrease in IBTR risk from whole-breast irradiation, this benefit would not necessarily translate into a breast preservation benefit, because she is likely to remain a good candidate for conservative surgery followed by whole-breast irradiation if she were to develop an IBTR. The opposite consideration is relevant for women with smaller breasts who would require mastectomy to salvage an IBTR; in such cases, radiation may be recommended with the express goal of optimizing the likelihood of long-term breast preservation.

By using these four factors, many patients can be guided to a thoughtful decision about use of radiotherapy after conservative surgery for low-risk DCIS. Those who remain undecided can be reassured that they may expect a high probability of a good outcome regardless of their treatment choice. For those who seek to avoid radiation but would consider endocrine therapy, the post hoc analysis of tamoxifen use in RTOG 9804 seems to support this approach, with overall IBTR risk among patients receiving tamoxifen of only 1% to 2% (including patients treated with and without radiation). However, some patients may prefer a relatively brief course of radiation to 5 years of tamoxifen. Further, the best randomized data suggest a more meaningful benefit from radiation than from tamoxifen in the adjuvant treatment of DCIS.

For patients who do opt for radiation, the historical standard of care has been 50 Gy in 25 fractions. Although patients with DCIS were excluded from the trials that compared this conventional course of whole-breast irradiation to a hypofractionated course, it appears reasonable at this time to extrapolate the findings of hypofractionated radiation trials to patients with DCIS. For low-risk patients, 40 Gy in 15 fractions without a boost is now my preferred dose-fractionation scheme, because it is less costly, less toxic, and more convenient than the historical standard. Alternative, accelerated partial breast irradiation schedules are even more appealing from a convenience perspective, and randomized trial data should be forthcoming in the relatively near future to guide judicious adoption of this treatment approach for DCIS.

For the patient in the case vignette above, she was encouraged to consider observation but was also offered whole-breast irradiation or enrollment onto a phase II protocol evaluating proton partial breast irradiation. She declined observation and whole-breast irradiation, electing to enroll onto the protocol. She received 34 cobalt-Gy equivalent in 10 fractions delivered twice daily to the tumor bed plus margin. Mean heart dose was 0.05 Gy. At her 6-week follow-up visit, she was noted to have grade 2 dermatitis with brisk erythema localized to the upper inner quadrant of the left breast, grade 1 pruritus, and grade 1 breast pain.

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REFERENCES


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DOI: 10.1200/JCO.2014.59.4259; published online ahead of print at www.jco.org on January 20, 2015

Radiation for Low-Risk DCIS
AUTHOR’S DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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Benjamin D. Smith
Research Funding: Varian Medical Systems
Acknowledgment

Supported by Varian Medical Systems, the Conquer Cancer Foundation, and Cancer Prevention and Research Institute of Texas Grant No. RP140020.