The incidence of ductal carcinoma in situ (DCIS) has seen a dramatic rise in the United States, particularly over the last three decades. Since the use of screening mammography in the 1980s and with improved technology, DCIS now accounts for 14% to 30% of all diagnosed breast cancers (1,2).

An ipsilateral breast event (IBE) remains the most common first failure event in DCIS management. Mastectomy was once the standard treatment for DCIS, with recurrence rates as low as 1.4% (3,4). Breast-conserving surgery (BCS) has now gained widespread acceptance as an alternative approach, based on the results of four

References


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randomized clinical studies led by the National Surgical Adjuvant Breast and Bowel Project (NSABP) B-17 trial (5–8).

Although the use of BCS for DCIS is not a debatable issue, the need for adjuvant radiation therapy (RT) is (9). There is substantial heterogeneity in the management of DCIS. Patients at low enough risk that they do not require RT after BCS have not been identified reliably in prospective clinical trials (10–12). However, four, large, prospective, randomized clinical trials have studied the benefit of adding RT after BCS in the treatment of DCIS. The addition of RT after BCS in these trials was shown to reduce the risk of local invasive recurrence and overall recurrence by 50% without a survival benefit (13). The NSABP B-24 trial (14,15) and the United Kingdom, Australia, New Zealand trial (16) evaluated both RT and tamoxifen in the treatment of DCIS. Although ipsilateral breast tumor recurrence (IBTR) is reduced by 25% (14,15) with tamoxifen, it is not a substitute for RT after excision of DCIS (5,14,16–20).

The Eastern Cooperative Oncology Group (ECOG) E5194 trial (21) studied patients with nonpalpable low-/intermediate-risk and high-risk DCIS treated with excision alone with or without tamoxifen. The low- or intermediate-grade DCIS was defined as less than or equal to 2.5 cm, whereas high-grade DCIS was defined as less than or equal to 1 cm in greatest dimension. Acceptable minimum margin width was greater than or equal to 3 mm. At 7 years of follow-up, the trial showed an overall local recurrence rate of 10.5% in the low-risk population and a rate of 18% in the high-risk population (21). Radiation Therapy Oncology Group (RTOG) 9084 (22) studied RT vs observation for the management of “good-risk” DCIS. Eligibility criteria included low- or intermediate-grade DCIS detected mammographically or found incidentally, with size less than or equal to 2.5 cm and margins greater than 3 mm. Eight-year results showed local recurrence rates of 3.2% in the excision-alone group and 4.4% in the excision-followed-by-RT group, demonstrating the benefit of radiation for the “good risk” DCIS.

These studies generated questions about the use of RT for locally excised DCIS and whether there is a subset of patients who do not require RT. The need to better identify the risk of recurrence associated with DCIS has led to the development of the DCIS Score (23). This genomic-based score is the first attempt to predict local recurrence regardless of tamoxifen use. The DCIS Score was developed from analysis of the results of multiple correlative science studies that compared gene expression in invasive breast cancer (IBC) and DCIS. The analysis revealed that the tumor biology of IBC and DCIS is similar, with differences seen in the distribution of proliferation genes. Seven genes that predicted recurrence risk and five reference genes were selected for the DCIS Score. In this issue of the Journal, Solin et al. aimed to determine whether there is an association between the DCIS Score and the risk of an IBE (23). The ECOG E5194 study was used to validate the DCIS score. This methodology was not used to identify patients who are necessarily at low risk, but rather to identify what the risk would be based on surgical excision alone. Excluding the DCIS Score, in the study’s multivariable analysis of risk for an IBE, the most statistically significant predictors of recurrence were tumor size and postmenopausal status. When the DCIS Score was included, it proved to be the most statistically significant predictor of recurrence. The study reports that the DCIS Score, when adjusted for tamoxifen use, was statistically significantly associated with the development of an IBE. The 10-year risk of IBE increased continuously as the DCIS Score increased (23).

The DCIS Score does not make recommendations regarding RT. Rather, it provides information that assists the decision-making process for the clinician and patient. The score predicts the risk of recurrence without RT; however, the clinician may advise the patient that the calculated risk is decreased further with the addition of RT. Based on potential benefit, a decision can be made on how to proceed. The patient must be counseled that whether the recurrence is noninvasive or an IBC with possible lymph node metastasis is not predicted by the DCIS Score. Such information would be valuable because an invasive IBE is associated with an increase in mortality (14). Although the information provided by the DCIS Score may be useful in the correct setting and application, it is not a definitive guide. The study by Solin et al. (23) does not address the use or lack of RT and has not yet been validated against DCIS treated with whole breast irradiation. The data used to develop the DCIS Score may be affected by the low number of estrogen receptor (ER)–negative and Her2/neu (H2N)–positive patients included, small subgroup sample sizes, the need to develop its algorithm based on mixed IBC and DCIS samples, and limited patients who have taken tamoxifen. This is important because H2N-positive DCIS has historically been associated with high-risk DCIS lesions (24); this subject is currently being evaluated in the NSABP B-43 trial (8). Tamoxifen use and its substantial benefit in ER-positive DCIS should be part of the decision for treatment.

In conclusion, DCIS shares genetic similarities with IBC. Patients that will not progress to invasive cancer are difficult to predict; therefore, biomarkers indicative of risk recurrence are needed. Solin et al. (23) should be applauded for their efforts in introducing the Oncotype DCIS Score as the first molecular approach and for their attempt at validation of risk of recurrence in patients with DCIS. The DCIS Score should complement traditional clinical and pathologic factors used to guide decision-making in the treatment of DCIS. Prospective clinical trials with long-term follow-up that use the DCIS Score in patients who undergo RT are necessary before we can conclude that a subset of DCIS does not require RT. We look forward to such validation trials.

References

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Is It Time to Reevaluate Definitive Therapy in Prostate Cancer?

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In this issue of the Journal, Hoffman et al. (1) explore one of the many unanswered questions confronting newly diagnosed prostate cancer patients: Which definitive treatment is superior—radical prostatectomy (RP) or external beam radiotherapy (EBRT)? The authors analyzed an observational cohort from the population-based Prostate Cancer Outcomes Study treated in the mid-1990s, and the resulting data suggested a survival benefit associated with RP over EBRT (1). A propensity score analysis was used to adjust for treatment selection bias in this cohort of men aged 55 to 74 years with clinically localized disease. In men with high-risk tumors (Gleason score ≥ 8 or prostate-specific antigen ≥ 10), both overall and prostate cancer-specific mortality were statistically significantly lower in the group that received RP than the group that received EBRT. In men with low-risk tumors (Gleason score ≤ 6 and prostate-specific antigen ≤ 10), there was no difference in prostate cancer mortality and a modest but statistically significant difference in overall mortality. Notably, this analysis did not include intermediate-risk patients. It is also interesting to note that acceptance of active surveillance as a treatment option for most, if not all, patients with low-volume, low-risk disease is much greater now that it was when this study was initiated.

Although this analysis is provocative, it has several limitations. First and foremost, as in most studies comparing RP and EBRT, there is substantial concern that patients who receive EBRT have a higher risk of disease recurrence. This analysis employed propensity scoring...