EDITORIAL

Rethinking the Standard for Ductal Carcinoma In Situ Treatment

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The original goal of mammographic screening was to identify invasive cancers at the earliest stage, because of the superior prognosis of stage I cancers. Prior to the advent of screening, ductal carcinoma in situ (DCIS) made up approximately 3% of breast cancers detected. As we pushed to find smaller and smaller cancers, and targeted calcifications instead of just masses, we began to identify DCIS more frequently. Now DCIS accounts for approximately 20% to 25% of screen-detected breast cancers. The cells that make up DCIS look like invasive cancer both pathologically and molecularly, and therefore the presumption was made that these lesions were the precursors of cancer and that early removal and treatment would reduce cancer incidence and mortality. However, long-term epidemiology studies have demonstrated that the removal of 50 000 to 60 000 DCIS lesions annually has not been accompanied by a reduction in the incidence of invasive breast cancers.[1] This is in contrast to the experience with removal of colonic polyps and intraepithelial neoplasia lesions of the cervix, in which the removal of precursor lesions has led to a decrease in the incidence of colon and cervical cancer, respectively.[2] We now know that breast cancer encompasses a range of behaviors, from aggressive to indolent; the latter are more likely to surface with screening.[3] The analysis of Narod et al[4] fuels a growing concern that we should rethink our strategy for the detection and treatment of DCIS.

Related article page 888

As demonstrated by Narod and colleagues[4] in this large observational study of more than 100 000 women with a diagnosis of DCIS, the risk of dying from breast cancer is low. Less than 1% of patients in this 20-year study died of breast cancer (compared with 5% of patients who died of other causes). Using the Kaplan-Meier method, the breast cancer–specific mortality rate is 3.3% at 20 years, not dissimilar to the statistic that the American Cancer Society[5] says is the chance that the average woman will die of breast cancer. This is welcome news and suggests that we can embrace evaluation of alternative strategies to surgery and radiation therapy. CALGB 40903,[6] a neoadjuvant study of 6 months of letrozole therapy, is an example of a new approach and should open the door to trials of observation and endocrine risk-reducing therapy. If invasive cancer develops after DCIS, the risk of dying of breast cancer increases substantially. Because the biological characteristics of DCIS often predict the type of cancer that may develop in the future, the value of a DCIS diagnosis may be in providing a clue about how to more specifically prevent a potentially lethal breast cancer.

A second important insight from the article by Narod et al[4] is that there are uncommon cases in which DCIS has a higher risk than has been appreciated. When DCIS is diagnosed before the age of 35 or even 40 years, some of these lesions do pose an increased risk of breast cancer–specific mortality. Ductal carcinoma in situ diagnosed before the age of 40 years is likely different because it would present as a symptomatic event (eg, a mass or bloody nipple discharge), as screening prior to the age of 40 years is rare.

Among patients with DCIS, breast cancer–specific mortality is associated with age at diagnosis, ethnicity, and DCIS characteristics such as estrogen receptor status, grade, size (>5 cm), and comedonecrosis. Despite their significance in a multivariable analysis, we note that high-risk characteristics, such as hormone receptor negativity, HER2 positivity, and high grade, often overlap. But only a small minority of patients will have 1 or more of these high-risk characteristics.

For young women (<40 years) who present with symptomatic DCIS—approximately 5% of the population—we should be cognizant that this is a different disease than the typical DCIS. As well, African American women (who have higher risk for hormone receptor–negative breast cancer) and women with hormone receptor–negative or HER2-positive DCIS should continue to be treated according to today's aggressive standards. In total, these groups probably constitute approximately 20% of the population of patients with DCIS.

The majority of DCIS is detected in women undergoing screening and who are recalled for biopsy of calcifications. To minimize the risk of overdiagnosis and/or overtreatment, it is time to reassess whether clustered amorphous calcifications should be a target for screening, recall, and biopsy, especially in older women.[7] Our focus should be instead on lesions (eg, pleomorphic, linear) that more commonly accompany invasive cancer or are associated with hormone receptor–negative or HER2-positive DCIS. Breast imagers should be reassured by the low mortality rate associated with a DCIS diagnosis.

A third key insight is that aggressive treatment (radiation therapy after lumpectomy) of almost all DCIS does not lead to a reduction in breast cancer mortality (eFigure 7 in the Supplement of Narod et al[4]), confirming the conclusions from the analysis of the NSABP trials.[8] Worse, there may be a slight increase in mortality with radiation therapy, especially if the disease is on the left side.[9] We can test alternatives, either no radiation therapy or intraoperative radiation therapy,[10] and reserve external-beam radiation therapy largely for breast conservation if invasive cancer occurs.

Numerous studies have demonstrated that the type of DCIS is predictive of the type of invasive cancer that develops. Some DCIS detected may be the precursor of luminal and ultralow-risk invasive cancer in which there is only a small but very late mortality risk.[11] Many of these invasive lesions do not require radiation therapy in postmenopausal patients with invasive cancer.[12] It should not be a surprise that there is no mortality benefit of radiation therapy in patients with noninvasive cancer.

A fourth insight is bilateral risk over the long term. We have always assumed that DCIS meant a higher local risk—but the similarity of the ipsilateral and contralateral invasive breast cancer risk (5.9% and 6.2%) in this study suggests that we need to think about DCIS as if it were a risk factor like atypia. A unilateral recurrence of DCIS or contralateral DCIS event has no impact on mortality, but an invasive cancer does—18-fold for unilateral and 13-fold for contralateral—suggesting that all risk depends on whether you get an invasive cancer.

Ductal carcinoma in situ may best represent an opportunity to alter the environment of the breast. For the lowest-risk lesions, observation and prevention interventions alone should be tested. Diet, exercise, moderate alcohol intake, and avoidance of postmenopausal hormone therapy with progesterone-containing regimens should be the starting point for prevention. We should think about ways to better characterize the biology of the DCIS lesions, using available tools such as Oncotype DCIS, which demonstrate that low-risk lesions simply excised appear to carry the risk equivalent to a Gail risk of 2.5.[13] For premenopausal women, tamoxifen therapy is a good choice for hormone-positive DCIS. For postmenopausal women, aromatase inhibitor therapy has been shown to have a bigger impact on risk reduction.[14] Raloxifene hydrochloride is a better-tolerated prevention alternative. Adverse effects of endocrine risk-reducing agents can be a problem. Different doses and schedules should be investigated to mitigate adverse effects, improve tolerability, and avoid serious complications.[15]

High-risk lesions (eg, HER2 positive, patient age <40 years, hormone receptor negative, large size) are lesions that should still be aggressively treated, but the analysis of Narod et al[4] suggests that our current approach of surgical removal and radiation therapy may not suffice for the rare cases that lead to breast cancer mortality and thus new approaches are needed. In a study characterizing the immune microenvironment of high-risk lesions most likely to recur, we found that the tumor microenvironment associated with recurrence was replete with activated macrophages, and a paucity of activated T cells.[11] On the basis of these data, we will be starting studies to determine whether we can activate the immune system and reverse these lesions, with a more targeted approach to address the specific mortality risk.

Narod and colleagues[4] have assembled an impressive analysis on the basis of SEER data. There are limitations of SEER, but the large numbers and long-term follow-up provide a compelling case that it is time for change. The community of radiologists and surgeons needs to be part of the call for change. Given the low breast cancer mortality risk, we should stop telling women that DCIS is an emergency and that they should schedule definitive surgery within 2 weeks of diagnosis. The sum total of the data on DCIS to date now suggest that:

1. Much of DCIS should be considered a "risk factor" for invasive breast cancer and an opportunity for targeted prevention.
2. Radiation therapy should not be routinely offered after lumpectomy for DCIS lesions that are not high risk because it does not affect mortality.
3. Low- and intermediate-grade DCIS does not need to be a target for screening or early detection.
4. We should continue to better understand the biological characteristics of the highest-risk DCIS (large, high grade, hormone receptor negative, HER2 positive, especially in very young and African American women) and test targeted approaches to reduce death from breast cancer.

Questions remain—but there is room to innovate. If we want the future to be better for women with DCIS, we have to be committed to testing new approaches to care.

ARTICLE INFORMATION

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Published Online: August 20, 2015. doi:10.1001/jamaoncol.2015.2607.

Conflict of Interest Disclosures: None reported.

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Dose-Escalated Radiotherapy for Prostate Cancer
Is the Sky the Limit?

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Technologic improvements have allowed radiation treatment to be administered with greater precision, improved safety, and an enhanced potential for disease control. Higher, and theoretically more efficacious, doses can now be delivered routinely. This concept of "dose escalation" is exemplified in the treatment of prostate cancer, with multiple randomized clinical trials (RCTs) showing a benefit when higher total doses of radiation are delivered to the prostate.[1-5] However, these benefits have been shown only for intermediate end points, such as biochemical disease-free survival, local progression, or development of distant metastases. To date, an improvement in overall survival has not been demonstrated even in studies with a decade or more of follow-up. An overall survival benefit resulting from a moderate increase in radiation dose is particularly difficult to elicit in prostate cancer given its heterogeneous presentation, long natural history, and recent improvements in the care of advanced disease that allow patients who have developed metastatic disease to survive for many years.

Related article page 897

It is possible that the inability to identify any survival advantage in randomized trials is due to a small effect size, competing risks, stringent inclusion criteria, and underpowered studies. In an attempt to get beyond these issues, Kalbasi and colleagues[6] examined the effect of modern radiation dose escalation on overall survival using the National Cancer Data Base (NCDB). By virtue of its huge size, the NCDB represents a powerful tool for researchers and physicians in the United States. These authors were able to study the outcomes of more than 300 000 patients with prostate cancer who received external beam radiotherapy. Unfettered by the limitations of RCTs, they sought to define the "real-world" utility of dose escalation. Using statistical techniques, such as Cox proportional hazards models and adjustment by propensity score, a significant survival advantage was seen for dose-escalated radiotherapy in patients with intermediate-risk (hazard ratio [HR], 0.84; $P < .001$) and high-risk (HR, 0.82; $P < .001$) prostate cancer. No benefit was seen among those identified as having low-risk disease (HR, 0.98; $P = .54$) by the current guidelines of the National Comprehensive Cancer Network.

The lack of a benefit seen in patients with low-risk disease is hardly surprising because the risk of cancer-specific death in this population is already very low. Indeed, mounting evidence suggests that for many, if not most, low-risk patients the most appropriate dose of radiation may in fact be 0 Gy. For patients with more aggressive disease, however, death from prostate cancer is of considerable concern, and in such patients local failure is strongly associated with subsequent cancer-related death.[7] It is these patients who stand to derive the most benefit from intensification of therapy. While hormone therapy clearly improves survival in these patients, it is not an adequate substitute for insufficient radiation dose.[1] The significant survival benefit seen by Kalbasi et al[6] for patients with intermediate- and high-risk disease seems to suggest a true relationship between dose and survival that appears to have been missed in the RCTs mentioned herein. The authors'[6] suggestion of a causal link, while plausible, must, however, be examined with the eye of scrutiny.

The biggest concern is whether a true survival benefit from an enhanced local therapy can be present only 7 years after definitive treatment. While a difference in survival at early time points can be seen for patients with very advanced local disease, the median time from treatment to prostate cancer death exceeds 10 years in most patients with nonmetastatic disease in the modern era.[8-10] Most of the early deaths are likely the consequence of occult micrometastatic disease present at the time of diagnosis. Metastases seeded from poorly controlled local disease seem to emerge as a "second wave" many years later.[11] Because information on disease-specific survival is not available in the NCDB, other factors may be contributing to the observed differences in overall survival. While Kalbasi et al[6] made every attempt to adjust their models to account for this, such as including comorbidity scores, no statistical technique can fully account for unidentified confounding in a retrospective study. Indeed, one of the greatest limitations from this analysis is an understanding of *why* patients received a particular radiation dose. Patients selected to receive a lower dose owing to underlying diabetes mellitus, bowel disease, use of anticoagulants, or other factors would certainly be at increased risk of death from other causes, potentially skewing the results in favor of those receiving dose escalation. Similarly, patients who had planned to receive dose-escalated therapy but did not complete treatment owing to clinically significant acute toxic effects (often due to these same factors) would be scored as receiving lower-dose therapy again intro-