

## EDITORIAL

## Addressing Overtreatment in DCIS: What Should Physicians Do Now?

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Ductal carcinoma in situ (DCIS) is unique in the growing debate about overtreatment in breast cancer because the marked increase in rates of diagnosis has not reduced the incidence of invasive breast cancer (1) and breast cancer-specific mortality after treatment is extremely low (2). This has fueled concerns that many patients with DCIS receive treatment that is too extensive and that some may not require treatment at all. In this issue of the Journal, Worni et al. (3) examine trends in treatment patterns and mortality using data from the Surveillance, Epidemiology, and End Results (SEER) program on over 121 000 women diagnosed with DCIS between 1991 and 2010.

Much of the news here is good. Ten-year disease-specific survival across all locoregional treatment subgroups exceeds 98%. In general, patients have received less extensive surgery over time. Over the 20-year study period, rates of unilateral mastectomy declined from 44.9% of patients to 19.3%, while use of lumpectomy and radiotherapy increased from 24.2% to 46.8%. However, the rate of bilateral mastectomy also increased from 0% to 8.5%. Axillary dissection was largely replaced by sentinel node biopsy, although 15.3% and 2.8% of patients undergoing mastectomy and breast-conserving surgery, respectively, had an axillary dissection in 2010.

SEER data are ideal to track treatment trends over time and identify areas where practice does not match evidence. But using SEER data for comparative effectiveness studies is much more challenging. Indeed, it is misleading to draw conclusions from the Worni study (3) about tiny absolute differences in mortality outcomes between treatment groups. Attempts in the study to address baseline differences between treatment groups through propensity score stratification are flawed because of missing data. Even the most basic clinical factors such as histology, tumor size, and receptor status were missing for one-quarter to one-half of the patients and varied markedly across treatment groups. Furthermore, other potentially relevant clinical factors, such as medical comorbidity, extent of disease of DCIS in the breast, and margin status after lumpectomy, were not measured.

What do the Worni et al. (3) results suggest about the comparative effectiveness of lumpectomy alone vs lumpectomy with radiation? They suggest that patients who undergo lumpectomy alone have worse survival (Worni et al., Table 4 and Figure 3) (3). This paradox reinforces the nettlesome problem of accounting for treatment selection effects in an observational study design using SEER data: The finding that all-cause mortality is higher in patients who receive lumpectomy alone supports the idea that surgeons are selecting the least extensive treatment for patients at highest risk of death from other causes. More valid approaches have demonstrated the major benefit of radiation in reducing recurrence in DCIS patients (4). The Early Breast Cancer Trialists' Collaborative Group meta-analysis of randomized trials demonstrates a 50% reduction in the risk of local recurrence with the use of radiation, with 10-year rates of local recurrence in the excision-alone groups ranging from 24% to 30% (5). In a randomized trial examining the efficacy of radiotherapy in low-risk DCIS (low or intermediate grade, <2.5 cm in size, clear margins), the use of radiotherapy reduced local recurrence rates at seven years from 6.7% to 0.9% (6). Prospective studies of well-characterized patient populations thought to be at low risk for recurrence based on small tumor size and low to intermediate grade provide additional information to inform discussions with patients. The Eastern Cooperative Oncology Group (ECOG)-American College of Radiology Imaging Network (ACRIN) E5194 study reported a 12-year rate of local recurrence of 14.4% (7.5% invasive) for widely excised low to intermediate DCIS lesions with a median size of 0.6 cm and an annual recurrence risk of 1.2% per year, which had not plateaued at 12 years (7). Even for patients selected as low risk with a multigene expression score, 10-year rates of local recurrence were 10.6% (8). Thus, although cause-specific survival rates remain high across all surgical treatments for DCIS, the suggestion that outcomes are equivalent is not supported in randomized trials.

Of greatest concern is the misleading assertion by the authors that the excellent outcomes across all treatment

options “support implementation of less invasive treatment options including active surveillance in thoughtfully selected patients.” No patients were explicitly selected for active surveillance. Less than 1% of patients in the sample were coded as not receiving surgery or radiation, but many of the patients in this tiny group may have received excisional biopsy with clear margins. We know virtually nothing about the impact of active surveillance on survival. The studies that are used to inform us about the natural history of DCIS all include lesions that were initially diagnosed as benign and found to be DCIS on pathology re-review. Between 20% and 30% of these women subsequently developed invasive cancer, usually in the area of the DCIS (9–11). Rates of recurrence of DCIS diagnosed by core biopsy alone would be anticipated to be even higher because 20% of lesions initially categorized as low- or intermediate-grade DCIS on core biopsy actually contain invasive cancer (12). Thus, the risk of developing invasive cancer after excision alone in DCIS patients thought to be “low risk” is considerable, and improved selection criteria for excision alone, let alone surveillance after core biopsy, remain elusive. The Surgery versus Active Monitoring for Low Risk DCIS (LORIS) trial, ongoing in the United Kingdom, will provide important information about the safety and acceptability of this approach (13).

What can physicians do now to limit potential overtreatment? Progress in tailoring treatment to recurrence risk has been made (14), but there are opportunities to further decrease treatment morbidity. The study of Worni et al. (3) provides several important directions. First, primary axillary dissection has no role in DCIS and should be eliminated. Second, while sentinel node biopsy is standard when mastectomy is done for DCIS, it is not necessary with lumpectomy. While there are uncommon clinical circumstances that make this prudent, an 18% rate of sentinel node biopsy with lumpectomy is too high. Contralateral prophylactic mastectomy (CPM) rates, fueled by patient desire for more extensive surgery, have markedly increased in both patients with DCIS and patients with invasive cancer (14,15). Risk communication is a challenge in the exam room. Patients overestimate the risk of breast cancer recurrence and death after treatment (16,17) and overestimate the benefits of CPM (18). Patient reactions to the perceived disease threat and management plan often motivate preferences for treatment more extensive than is needed to maximize recurrence-free survival. Re-framing the goal of treatment in DCIS as prevention of the occurrence of invasive disease is a start, but whether this will change patient preference for aggressive therapies is unclear. The finding in Worni et al. (3) that 40% of deaths in women 70 years of age and older at diagnosis were because of cardiovascular disease and only 5.4% because of

breast cancer reinforces the need to discuss competing causes of mortality and overall health as part of DCIS management in older women. Unfortunately, DCIS is here to stay, despite calls to reduce the intensity of early detection strategies and response to findings on screening mammograms. DCIS will remain a major conundrum for physicians until the biology is more clearly elucidated, but much can be done now to reduce overtreatment and avoid unnecessary morbidity.

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