

# Toward Minimizing Overtreatment and Undertreatment of Ductal Carcinoma In Situ in the United States

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See accompanying article on page 1190

Radiation therapy (RT) is an effective adjuvant local therapy for ductal carcinoma in situ (DCIS) of the breast. RT decreased ipsilateral breast events by approximately half after breast-conserving surgery (BCS), from 18% to 8% at 5 years and from 28% to 13% at 10 years in a meta-analysis of randomized prospective studies that enrolled patients with diverse pathologic features.<sup>1</sup> However, this local benefit never translated into a survival benefit in these meta-analytic data. This is in contrast to adjuvant RT after BCS for early-stage invasive breast cancer, where prospective studies clearly demonstrated up to a 7.8% improvement in risk of breast cancer death at 15 years, particularly in patients at higher baseline risk of local recurrence.<sup>2</sup> Thus, to date, for any individual patient with DCIS, the risk-benefit discussion for or against adjuvant RT has generally hinged upon the patient's expected absolute local benefit from RT.

Fundamentally, the absolute local benefit from RT depends on the patient's baseline risk features. For example, in a patient with high-risk pathologic features such as high histologic or nuclear grade, the risk of in-breast recurrence is estimated to be 24% at 5 years with BCS alone, compared with a risk of 12% at 5 years with BCS plus RT.<sup>1</sup> In such a patient, with such a high absolute recurrence risk and a large absolute benefit with RT, adjuvant treatment is typically recommended. In contrast, in a patient with lower risk features, in-breast recurrence is only 3% at 5 years with BCS alone. A local benefit of adjuvant RT is still seen in such patients, with an in-breast recurrence rate of only 0.4% at 5 years after RT.<sup>3</sup> However, with low absolute recurrence risk after BCS alone and small absolute benefit after adding RT, BCS alone is frequently considered an acceptable treatment recommendation.

## **Good-Risk DCIS and the Risk of RT Overtreatment**

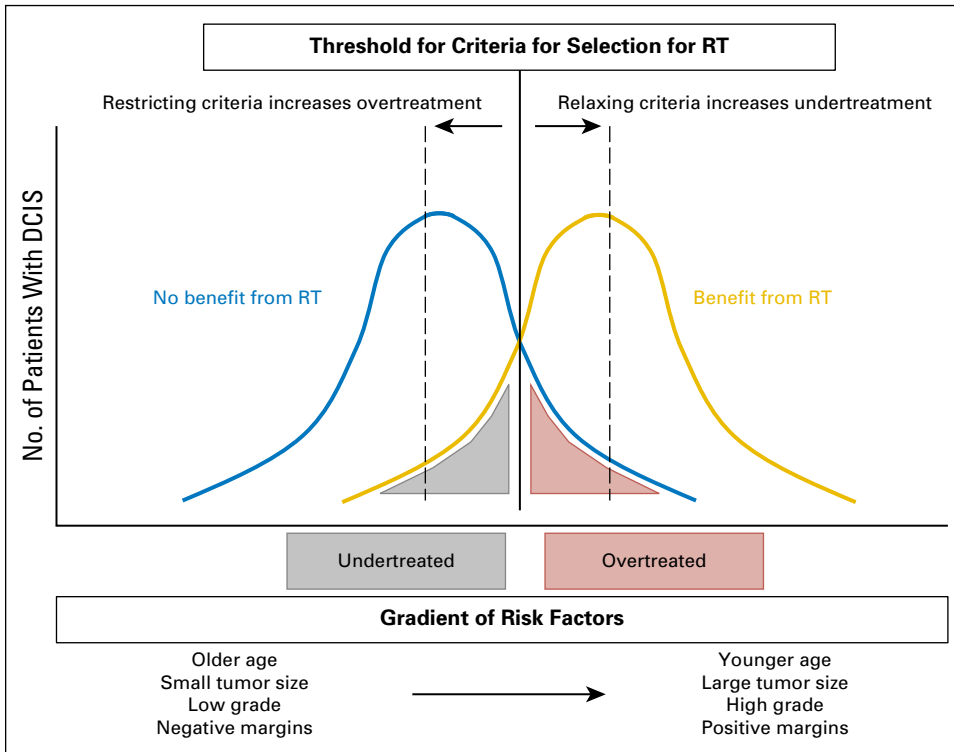
Considerable effort has been spent to define the characteristics of patients with good-risk DCIS, recognizing that in this group there is only a small local benefit of RT. Therefore, seeking to guide clinicians toward selecting out a subgroup of patients in whom observation after BCS would be not only a reasonable treatment option, but also possibly a favorable one. The Eastern Cooperative Oncology Group–American College of Radiology Imaging Network E5194 registry trial reported that in patients with low- to intermediate-grade DCIS measuring 2.5 cm or less, the in-breast

recurrence rate was 6% at 5 years and 14% at 12 years.<sup>4</sup> The Van Nuys prognostic index importantly also included surgical margin width and age to help stratify patients at low, intermediate, and high risk for local recurrence.<sup>5</sup> Most recently, the Radiation Therapy Oncology Group 9804 trial identified good-risk patients as those with screen-detected, low- or intermediate-grade DCIS  $\leq$  2.5 cm and a  $\geq$  3-mm surgical margin. Beyond the 3% recurrence rate at 5 years, subsequently, a recurrence rate of 7% was found at 7 years with BCS alone. With the addition of RT in these patients with excellent prognosis, the recurrence rate remained less than 1% even on longer term follow-up.<sup>3</sup>

As clinicians, we ideally seek to avoid overtreatment in the lowest risk group of patients—those patients who experience a minimum local benefit and in whom treatment is accompanied by the trade-offs of local toxicity risks as well as the personal and financial burden of treatment. Further, within an increasingly value-driven treatment decision-making framework, the societal opportunity cost of adjuvant RT is becoming a gradually relevant consideration as well.

## **The Overtreatment/Undertreatment Dichotomy**

From a population standpoint, another trade-off when considering adjuvant RT must be considered. A central tension in defining cutoffs for overtreatment is that by adjusting the criteria for defining low-risk features to decrease the overall number of patients who are overtreated, the number of higher risk patients who are undertreated is increased (Fig 1). In reality, however, a binary approach to defining overtreatment/undertreatment criteria is oversimplified. For many patients, the treatment decision requires additional nuance, and we must acknowledge that persistent unknowns can complicate actual decision making for or against adjuvant RT. First, the patient's preferences and priorities regarding breast cosmesis, breast preservation, local recurrence, and survival must be taken into account.<sup>6</sup> Because randomized data have not definitively demonstrated a clinically relevant survival impact with the addition of RT, the decision for or against adjuvant RT has not typically been driven by patients' concerns about breast cancer-specific survival. The study by Sagara et al,<sup>7</sup> which accompanies this editorial and is further discussed in the next section, is thought provoking and newly brings this aspect to



**Fig 1.** Choosing thresholds for selecting patients for radiation therapy (RT) impacts undertreatment and overtreatment. These curves represent the populations of patients with ductal carcinoma in situ (DCIS) who benefit from RT (ie, they will develop local recurrence without RT) and who do not benefit from RT (ie, even without RT, they will never develop a local recurrence). Both groups are composed of patients with a range of risk factors, although risk factors tend to be lower in those who do not need RT. Relaxing risk factor criteria for recommending radiation (ie, shifting the vertical solid line to the right) decreases overtreatment but risks increasing undertreatment. Restricting risk factor criteria (ie, shifting the vertical solid line to the left) decreases undertreatment but increases overtreatment.

the forefront of the treatment discussion. Second, more detailed clinicopathologic features can be incorporated to determine local risk, as determined by published nomograms or molecular testing algorithms such as Oncotype Dx.<sup>8</sup> These data may further risk stratify patients. The available risk-stratification tools emphasize that there is a continuum of risk for local recurrence and underscore that the risks and benefits weighed by patients are rarely binary. However, the process of incorporating quantitative results from such testing into the daily shared decision-making process between patients and physicians is not yet well established. Finally, there is an emerging treatment framework that includes an even less invasive option of active surveillance,<sup>9</sup> which may ultimately impact our definition of overtreatment altogether. The major unknown still influencing the emergence of active surveillance criteria is the critical issue of follow-up time. Life expectancy is fundamental to the active surveillance decision-making schema in patients with prostate cancer and similarly impacts patients with DCIS. The 7% recurrence risk at 7 years in the Radiation Therapy Oncology Group 9804 trial and 14% risk at 12 years in the Eastern Cooperative Oncology Group–American College of Radiology Imaging Network E5194 trial for patients undergoing BCS plus observation accentuate no clear plateau for in-breast recurrence risk over the long term, and presumably, long-term progression risk must be balanced against life expectancy in patients who undergo active surveillance.

**Another Perspective on RT Undertreatment**

It is clear that the extensive efforts to define good-risk DCIS in the recent literature are driven by a justifiable rationale to avoid overtreatment and unnecessary harms to the patient in what is typically characterized as a relatively indolent disease process.

However, the overtreatment debate in low-risk patients could risk overshadowing important but separate considerations about the prevalence of undertreatment of high-risk patients, the continued need to refine thresholds identifying high-risk features, and the prognostic impact high-risk features have on RT effectiveness.

In the article that accompanies this editorial, Sagara et al<sup>7</sup> performed an analysis of more than 34,000 patients in the SEER database to examine the association between RT and breast cancer mortality in patients with DCIS. Given the already low risk of death as a result of breast cancer in the DCIS population, SEER represents one of the few observational databases available with adequate sample size and follow-up duration to even begin addressing such a question. Results overall demonstrated an association between RT and breast cancer mortality. For the entire group of patients, the absolute mortality benefit, although statistically significant, was exceedingly low—only 0.3% at 10 years. However, the mortality benefit seemed to be modified by clinicopathologic prognostic factors. Authors used available stratification factors including age, size, and histology to categorize patients’ baseline risk for local recurrence, generally based on the original Van Nuys prognostic index stratification scheme.

A key provocative finding from this study is that, although the subgroups of patients with lower risk recurrence factors did not demonstrate a breast cancer mortality benefit with RT, the group of patients with high-risk factors did, with an absolute mortality benefit of 4% at 10 years. This approaches the magnitude of mortality benefit we expect from adjuvant RT after BCS for patients with early-stage, invasive breast cancer; in such patients with invasive cancer, the national undertreatment rate is only approximately 6%.<sup>10,11</sup> In contrast, this study reported that in higher risk patients with DCIS, approximately 38% did not receive RT. Moreover, this observation rate was essentially no different in

patients with lower risk features. Such results provoke a worthwhile invigoration of the undertreatment discussion in patients with DCIS with high-risk features for local relapse undergoing BCS.

The most important caveat to the analysis by Sagara et al<sup>7</sup> is the retrospective observational study design. Potentially unmeasured confounding can exist, the most important for this study being that receipt of RT may serve as a proxy indicator for other important, potentially nonclinical factors that could impact cancer mortality, such as socioeconomic factors. The authors did attempt to account for income and race and also conducted a propensity score analysis to consider known confounders. Nonetheless, their results may be interpreted with some caution given this limitation. Yet notably, arguing against this finding as merely spurious is the stratified effect on breast cancer mortality based on the clinicopathologic risk score features alone, as well as a suggestion for a dose-response relationship in the magnitude of mortality benefit of RT with increasing clinicopathologic risk score. This stratified analysis strengthens the study design and findings. Both scenarios can be challenging: defining low-risk patients with DCIS in whom RT confers small or minimal absolute disease control benefits, as well as identifying high-risk patients in whom RT can provide disease control benefits that rival benefits seen in early invasive cancer. Continued efforts to translate this challenging discussion into informed patient counseling regarding the risk-benefit profile of postoperative RT can reap benefits by decreasing both over-treatment and undertreatment in the community.

#### AUTHOR'S DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Disclosures provided by the authors are available with this article at [www.jco.org](http://www.jco.org).

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DOI: 10.1200/JCO.2015.66.2064; published online ahead of print at [www.jco.org](http://www.jco.org) on February 16, 2016.

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No relationship to disclose

***Acknowledgment***

Supported in part by Grant No. RP140020 from the Cancer Prevention and Research Institute of Texas.