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EDITORIAL – BREAST ONCOLOGY

How Low Can We Go—and Should We? Risk Reduction for Minimal-Volume DCIS

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The appropriate clinical management of ductal carcinoma in situ (DCIS) poses a dilemma with important public health implications. Each year, more than 50,000 women in the US are diagnosed with DCIS, and virtually all of them undergo surgery in the form of a lumpectomy (with or without radiation), mastectomy, or bilateral mastectomy. Some of these women likely have indolent or slow-growing disease that would not develop into symptomatic breast cancer in their natural lifetime, and thus would not benefit from intervention. To date, there remains considerable uncertainty about the true extent of this 'overtreatment'[1–4]; thus, the identification of patient subgroups in whom it is safe to de-escalate treatment for DCIS has been deemed a high priority for research.[5]

The study by Muhsen and colleagues[6] published in this issue of *Annals of Surgical Oncology* further contributes to this conversation. In the study, the authors report on DCIS lesions that were completely excised at core biopsy, called 'minimal-volume DCIS' (mDCIS), in order to determine whether mDCIS is a clinical setting in which patients might safely omit adjuvant radiation therapy (RT). Based on a high-quality, single-institution, retrospective dataset, the Kaplan–Meier rates for ipsilateral breast events (IBEs), as well as contralateral events, following excision of mDCIS were calculated. In a cohort of 290 patients, 25 patients had an IBE, of which eight were invasive cancer and 17 were DCIS. Not surprisingly, the 10-year IBE rate was higher in patients without radiation (14.7%) compared with those treated with adjuvant radiation (6.5%). Comparing these estimates with the corresponding 10-year rate of contralateral breast cancer in the overall cohort (6.8%), the authors concluded that mDCIS did *not* constitute a minimal-risk condition for omission of adjuvant RT, and that these lesions should be considered a precursor rather than a risk marker for invasive breast cancer.

The authors further state that "any volume of DCIS in the breast should be considered clinically relevant disease". However, it could be argued that those who subsequently had an *invasive* recurrence developed the most clinically meaningful disease. Given that 36% (8/22) of lesions among those not receiving RT were invasive cancer, the 10-year rate of *invasive* IBE was approximately 5.3%. For context, a 60-year-old White woman without a BRCA mutation with one first-degree family member with breast cancer, diagnosed with atypia on a core biopsy, has a 6.4% 5-year risk of developing breast cancer.[7] The authors do not provide additional information regarding the invasive ipsilateral recurrences, i.e. at what time interval and stage were the IBEs diagnosed; did any IBEs have node-positive disease; what were the phenotypes of invasive IBE; and were any IBEs treated with chemotherapy? Such data would be highly relevant to a better understanding of the clinical impact of an invasive IBE following treatment of mDCIS. Furthermore, we must bear in mind that for patients who were treated with radiation for the initial mDCIS, an IBE would likely prompt a recommendation for mastectomy, whereas those without prior radiation preserve the option of radiation for the treatment of a subsequent IBE.

When considering thresholds for intervening in a low-risk condition such as mDCIS, multiple competing risks must also be considered. These consist of the risk of an IBE, either invasive or in situ; the competing risk of a contralateral breast event, again invasive or in situ; and the risk of dying from a cause unrelated to breast cancer.

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Among those receiving RT, the risk of contralateral disease was in fact *higher* than that for ipsilateral disease (Fig. 2b and c). If we accept that the level of baseline contralateral risk is sufficiently low to not require routine intervention, additional treatments that seek to lower ipsilateral risk even further than the level of known contralateral risk must be carefully reassessed. Such knowledge about the absolute and relative magnitudes of competing risks can help a patient make a decision that is aligned with their personal risk tolerance and quality-of-life considerations. For example, an elderly patient with significant comorbidities and a life expectancy of 7 years may have a very different perception of the risk reduction associated with RT in addition to surgery compared with a young patient without comorbidities and a life expectancy of 37 years. It is therefore important to evaluate the risks of future breast events in the context of age- and comorbidity-related risk of dying from a cause other than breast cancer.

Finally, it is critical to emphasize that the perception and interpretation of an absolute risk estimate are highly personal. There are numerous competing risks in every patient's life. Whether the personal and financial costs of reducing a specific risk through RT justifies the discomfort, costs, and potential harms varies widely by individual. Therefore, the assessment of trade-offs of risks and benefits is ultimately up to the patient and their individual risk tolerance. A truly informed decision can only be made if the numeric risk estimates are communicated effectively, placed into context, and incorporated in the personal decision-making process.

In conclusion, high-quality, long-term outcome data such as that provided here by Muhsen and colleagues are essential to informing a path of rational de-escalation of treatment for low-risk DCIS patients by helping to better understand the trade-offs of treatment. Prospective clinical trials of lumpectomy alone or active surveillance for DCIS will provide further evidence regarding the long-term risks and benefits of a less intensive approach to this diagnosis.

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