

ADVANCES IN ONCOLOGY

Current Developments in the Management of Solid Tumor Malignancies

Guest Section Editor: Ruth O'Regan, MD

Breast Cancer in Focus

Molecular Profiling for DCIS



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H&O What factors are currently used to guide treatment decisions about ductal carcinoma in situ (DCIS)?

CR The initial decision is whether a woman will undergo a lumpectomy or mastectomy. Unfortunately, we do not have high-quality randomized trials to help us make that decision.

When we learned a couple of decades ago that women with invasive breast cancer could have a lumpectomy plus radiation instead of a mastectomy without affecting their survival, we did not have the answer to that question about DCIS—which left us with a standard of care that was more aggressive for DCIS than for invasive breast cancer. Because we still do not have an answer, we make this decision in DCIS based on the clinical features of the cancer in combination with patient preference. We look at clinical factors such as the size of the DCIS—or at least the perception of the size on mammography—vs the size of the breast. If we need to remove so much breast tissue to get all the DCIS that the breast becomes very distorted, we often recommend a mastectomy.

H&O Do women with DCIS who have a lumpectomy always require radiation?

CR The study that addressed that was the NSABP (National Surgical Adjuvant Breast and Bowel Project) B-17 trial in the mid-1980s. For this trial, nearly 800 women with DCIS who were candidates for lumpectomy were randomly assigned to lumpectomy alone or lumpectomy plus radiation.

The trial initially showed that radiation therapy could halve the risk of a local recurrence in the same breast. Now we have 17-year follow-up, which was published in the *Journal of the National Cancer Institute* in 2011. These results showed that among women who had a lumpectomy alone, 20% had an invasive recurrence and 15% had an in situ recurrence. These numbers were approximately half that amount for women who received radiation. Does that mean that all these women needed radiation? The investigators tried to determine whether specific groups of patients did or did not benefit from radiation. The authors were not able to determine that, although they did find that younger women and those with higher-grade tumors seemed to be at increased risk for recurrence.

A major challenge with NSABP B-17 is that the risk of a recurrence in the same breast was extremely high, even in patients who received radiation. One of the reasons for the high recurrence rate is that the surgical margins were required to be negative, but otherwise were not controlled. If you have patients who do not get radiation therapy and 35% of them experience a local recurrence, that strongly suggests a problem with surgical local control.

H&O What other studies have looked at whether women with DCIS who have had a lumpectomy require radiation?

CR The E5194 (Eastern Cooperative Oncology Group 5194) study, which was published in the *Journal of Clinical Oncology* in 2009, looked at 711 women with DCIS who were candidates for lumpectomy. All of the women had either a low- or intermediate-grade tumor of less than 2.5 cm

or a high-grade tumor of less than 1 cm, plus good surgical margins: at least 3 mm of normal tissue around the DCIS.

What the study showed was that after 7 years of follow-up, the risk of cancer recurrence in the same breast was 10% for women with a low- or intermediate-grade tumor and 18% for women with a high-grade tumor. Women aged 45 years and younger were at elevated risk for recurrence, as were those who had larger tumors. The authors concluded that the ipsilateral breast event rate without radiation may be acceptable to patients with low- and intermediate-grade tumors, but unacceptably high for those with high-grade tumors.

H&O Why does the potential to use molecular profiling for DCIS hold such appeal?

CR We want to be able to figure out 2 things. First, we want to know the risk of local recurrence in a woman being treated for DCIS, and whether the recurrence will be in the form of invasive cancer. Once the cancer becomes invasive, there is a potential need for chemotherapy and/or prolonged estrogen blockade. Second, we want to know which tumors and patients will benefit most from radiation therapy.

The goal would be to use molecular assays to help us determine the answers to these questions.

H&O What are the markers of risk that have been identified in patients with DCIS?

CR With regard to molecular markers, gene expression profiling can be used to categorize both invasive breast cancer and DCIS into 4 subtypes: luminal A, luminal B, HER2, and triple-negative. Luminal A tumors are positive for estrogen and progesterone receptors (ER and PR) and negative for HER2. Luminal B tumors are positive for ER and PR and also for HER2. In the HER2 subtype, the tumor is negative for ER and PR and positive for HER2. Triple-negative tumors are negative for ER and PR as well as for HER2. These 4 categories were described in a study reported at the San Antonio Breast Cancer Symposium in 2012. The authors obtained 314 DCIS specimens from women who had participated in 3 different DCIS trials. The tumors were tested by immunohistochemistry and were then subdivided according to molecular phenotypes using ER, PR, and HER2. The authors found that immunohistochemical surrogates for these markers can be successfully used in DCIS to stratify patients into different molecular phenotypes, and that these phenotypes in DCIS can independently predict both overall and invasive recurrence.

H&O What other categorizations are used in DCIS?

CR Another type of subtyping involves the Oncotype DX breast cancer assay for DCIS from Genomic Health.

This assay involves looking at 12 genes, rather than the 21-gene assay used for patients with invasive breast cancer. The 12-gene assay was validated in a 2013 study in the *Journal of the National Cancer Institute* with Solin as the first author. The study was partially funded by Genomic Health to validate results using specimens from their internal database as well as specimens provided by a hospital in Northern California. It involved looking at tumor samples from 409 women who had participated in the E5194 trial, all of whom had undergone surgery. The E5194 trial was used because it was one of the few studies that rigorously controlled tumor margins.

A 10-year ipsilateral breast event (IBE) was found in 14.6% of patients with low- or intermediate-grade DCIS of less than 2.5 cm, and 19% in those with a high-grade DCIS of less than 1 cm. When evaluating the DCIS score as a continuous variable, the score was significantly associated with developing an IBE. In a multivariable analysis, factors significantly associated with developing an IBE were DCIS score, tumor size, and menopausal status. Using the DCIS score (low, intermediate, or high), the 10-year risk of developing an IBE was 10.6%, 26.7%, and 25.9%, respectively. The risk of an invasive IBE was 3.7%, 12.3%, and 19.2%, respectively. What this study showed is that even among patients with DCIS who seem to have a low risk of recurrence by tumor size and grade, some patients are actually at high risk.

H&O Does a woman with a 3.7% risk of invasive recurrence need radiation therapy?

CR Radiation therapy will reduce the risk of a recurrence by half at most. If a woman has a 3.7% chance of developing an invasive breast cancer and we can reduce that to 1.9%, is that worth going through 6 weeks of radiation? That is a decision that needs to be made by a patient and her doctor.

Are there patients for whom we can avoid radiation? For example, if we treat a patient with DCIS with a lumpectomy and no radiation and she later develops a recurrence of DCIS, we can then remove the second tumor and administer radiation, or we can perform a mastectomy. In contrast, someone who experiences a recurrence of DCIS in the same breast after receiving radiation is obligated to have a mastectomy. It would be meaningful to identify a group of women who do not need radiation, especially for women who are motivated to avoid a mastectomy.

Right now, molecular profiling is good for predicting who is at risk for developing a second cancer in the same breast: either DCIS or invasive cancer. We still need a study that answers the question of whether the Genomic Health DCIS score or molecular profiling of DCIS by other methods can predict the response to radiation.

H&O What other relevant studies are being conducted?

CR One study whose results I am waiting to see is one by Genomic Health; they put out a press release saying that they have validated their DCIS assay in a separate study but this study will not be reported until the 2014 San Antonio Breast Cancer Symposium.

A second study, which was presented this year as a poster at the annual American Society of Clinical Oncology meeting by Dr Michael Alvarado, looked at the impact of the DCIS score on treatment decisions. For this trial, researchers from 10 institutions enrolled a total of 115 women who were receiving a lumpectomy for DCIS. After the lumpectomy, the radiation therapist or surgeon made a recommendation about radiation therapy. After receiving the DCIS score, physicians were given the opportunity to reconsider their recommendation.

The researchers found that based on the initial information, the physician had recommended against radiation therapy in 27% of cases. After receiving the DCIS score, the physician recommended against radiation therapy in 41% of patients. Overall, getting the information changed the treatment recommendation in 31% of patients; the

doctors change their minds 31% of the time when they initially recommended no radiation therapy and 32% of the time when they initially recommended radiation therapy. Although this was a small study, the results are striking. What will really be interesting is to find out how treatment recommendations and decisions affect outcomes.

References

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