An Argument Against Routine Use of Radiotherapy for Ductal Carcinoma In Situ

By D. Lawrence Wickerham, MD

In his article, Dr. Silverstein reviews the changing incidence of ductal carcinoma in situ (DCIS) in the United States over the past 25 years, discusses the results of various clinical trials evaluating treatment options for the disease, and, using the Van Nuys Prognostic Index (VNPI), identifies a subgroup of DCIS patients treated by lumpectomy who, he feels, may be able to avoid breast irradiation. During several presentations at national meetings, I have had the opportunity to debate Dr. Silverstein on this topic. He is a powerful and articulate proponent of the idea that certain DCIS patients could be exempted from radiation therapy without consequences.

Diagnosis and Treatment

Dr. Silverstein correctly points out that DCIS was once an uncommon, if not rare, form of breast cancer, but now, with routine use of screening mammograms, will account for more than 20% of new cases of breast cancer diagnosed in the United States this year. The treatment of this disease has also evolved rapidly. Before the mid-1970s, DCIS was routinely treated by radical mastectomy. In 2003, the majority of women with DCIS will be offered a breast-conserving procedure, and many of them will be candidates for tamoxifen, which the Food and Drug Administration has approved as adjuvant treatment for these patients. These changes in treatment are largely the result of clinical trials and should be credited to the women who participated in those studies. Dr. Silverstein references three large randomized trials that compared lumpectomy plus radiation therapy with lumpectomy alone in patients with DCIS.[1-3] All three trials demonstrated a significant reduction in the incidence of ipsilateral breast tumor recurrence (IBTR) in the surgery-plus-radiation-therapy arm compared to the surgery-alone arm, with relative reductions in IBTR of approximately 50%. This reduction in IBTR is an overall reduction, and Dr. Silverstein suggests that there may be subgroups of DCIS patients in whom the benefit from radiation therapy is so small that they could be treated with excision alone.

Van Nuys Prognostic Index

Dr. Silverstein's basis for judging the risk of breast cancer recurrence in DCIS patients is the VNPI.[4] This index, which was developed by Dr. Silverstein and others using data from a nonrandomized group of patients, uses pathologic classifications (nuclear grade and comedo necrosis), tumor size, and margin width to predict the risk of local recurrence. Each of these factors is given equal weight, and a cumulative score is determined. When this index was introduced, it was both provocative and appealing. The individual components appear to be relatively straightforward, but Dr. Silverstein and his associates are capable of meticulous processing and evaluation of individual specimens that exceeds what is possible in most centers. This makes the reproducibility of the VNPI between centers difficult. Although margin width was one of the three independent, equally weighted factors in the VNPI, a subsequent evaluation suggested that, by itself, it was a satisfactory predictor of local recurrence.[5] However, margin width can be difficult to determine precisely; for example, inadequate sampling alone can result in its overestimation. I believe that the pitfalls associated with the VNPI data stem from its basis on nonrandomized data. The patients' patients and their treatments were likely to have been selected in a biased manner, resulting in a flawed evaluation. While investigators would agree that small, low-grade DCIS lesions that are widely excised have a low risk of recurring, in the randomized data from the National Surgical Adjuvant Breast and Bowel Project (NSABP) B-17 trial, for example, no subset of patients could be identified that did not benefit from breast irradiation.[6]

Survival Benefit Controversy

Page 1 of 3
Dr. Silverstein repeatedly points out that no survival benefit has been associated with the use of radiation treatment in any of the trials. Although it is important to note that none of the trials was designed to detect a survival benefit, I would be willing to concede that any difference in survival that may occur is likely to be small. However, there is more to breast cancer than dying from the disease. As my friend Dr. Terry Mamounas says, "Patients do not like to hear from their cancers again, even if their survival is not affected." If, through radiation treatment, we can reduce the risk of IBTR and the resultant need for a mastectomy by even a small amount, many women would opt for such therapy. Some women, fully advised of the risks, benefits, toxicities, and costs of radiation therapy, may make an informed choice to avoid the treatment, but that choice should not be made based on the misconception that radiation therapy has been conclusively proven to be of no value.

**Current and Future DCIS Trials**

The take-home message from this article should be that substantial progress has been made in the treatment of DCIS, but additional issues remain to be resolved. Several trials that may affect the treatment of DCIS are accruing patients or have completed accrual and are in the followup phase. The Radiation Therapy Oncology Group study 9804 is entering patients with tumors ≤ 2.5 cm, of low or intermediate nuclear grade, and with margins ≥ 3 mm. Patients are assigned to radiation therapy or observation, with or without tamoxifen, with the goal of determining how effective radiation therapy is in decreasing local treatment failures in this "good-risk" group. The Eastern Cooperative Oncology Group study E-5195 is also evaluating good-risk patients with low- or intermediate-grade lesions ≤ 2.5 cm, or high-grade lesions ≤ 1 cm in diameter, all with margins of 3 mm or greater. This study has completed accrual and will examine local recurrence rates and risk factors for recurrence. The Dana-Farber Cancer Center has completed accrual to a similar study in 157 patients with grade 1 and 2 lesions ≤ 2.5 cm, all with a 1-cm margin. The NSABP is contemplating a study that would compare partial-breast irradiation to conventional wholebreast irradiation. The design includes the entry of patients with DCIS, and, in addition to assessing the incidence of IBTR, would evaluate costs, toxicities, and quality of life. Another NSABP study (B-35) is currently enrolling patients. This study, which opened in January 2003, includes postmenopausal women with estrogen- or progesterone-receptor-positive DCIS who had undergone lumpectomy with clear margins. Patients are assigned to receive, in a double-blind fashion, either tamoxifen at 20 mg/d or anastrozole at 1 mg/d for a 5-year period plus radiation therapy. In addition to the breast cancer end point, quality of life will be evaluated. The accrual goal is 3,000 patients, who will be drawn from more than 200 NSABP centers throughout the United States, Canada, and Puerto Rico. Non-NSABP members will have access to the trial through the Clinical Trials Support Unit of the National Cancer Institute (1-800-823-5923). A similar trial, The second International Breast Cancer Intervention Study (IBIS II), is already under way in Europe, Australia, and New Zealand. **Conclusions**

As Dr. Silverstein points out, we live in an era of evidence-based medicine, and the advances in the treatment of DCIS that have occurred over the past decade are a reflection of that approach. There is still room for improvement in the therapeutic options offered to women with this disease, and studies are already under way or are about to begin that we hope will expand these options. Physicians and their patients should be strongly encouraged to consider participation in clinical trials as a first choice, not merely as a last resort.

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