Contradictory treatment recommendations for ductal carcinoma in situ (DCIS).

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The vast majority of women with DCIS are told that in addition to surgical excision, radiation therapy and tamoxifen (or an aromatase inhibitor in postmenopausal patients) will be required for local control of their disease in program of breast conservation. Yet, half of US women with DCIS who elect breast conservation forgo radiation therapy, an option recognized by the NCCN and others. These competing recommendations sow much confusion and anxiety in patients. This problem reflects the contrast between the historical, but limited results of the randomized trials of radiation therapy for DCIS, and modern prospective studies which have utilized a different approach.

Beginning in 1985, a series of randomized trials of radiation therapy for DCIS were begun. These include the NSABP B17, EORTC 10,853, UK/ANZ, and SWE DCIS. All confirmed the benefit of radiation therapy compared with patients who were treated with surgery alone, and all clearly demonstrated an approximate 50% reduction in the frequency of local in-breast recurrence.

However these trials employed pathology protocols for tissue examination, which were modeled after those for invasive breast cancers dating from the 1970s and 1980s. The tissue sampling employed in these protocols did not permit exclusion of invasive disease, particularly microinvasion, nor accurate assessment of margin involvement and margin width, nor tumor size. In the quarter century since the advent of these studies, much has been learned about the biology of DCIS, and also about optimizing tissue examination for this disease. The changes in pathology practice, generated by the necessity of examining and detecting minute foci of disease in a large resection, were dramatic and culminated in a new set of formal guidelines by the American College of Pathology in 2009 (Lester et al 2009). The new guidelines required serial, sequential tissue processing of the entire specimen, minimizing the likelihood of missing microinvasion, and permitting accurate assessment of size and margin width. The serial subgross technique had been an integral part of prospective nonrandomized studies (Lagios et al 1982, Lagios et al 1989, Lagios 1990, Silverstein et al 1996, Silverstein 2002, Silverstein and Lagios 2010) for some time, and had been validated in a formal registration trial by Hughes et al (2009). Arguments against this approach were that it was too costly and/or too cumbersome, and not "randomized" but have not hindered widespread acceptance of the new guidelines..

The studies of Silverstein, in particular, which established the Van Nuys Prognostic Index, now permit a patient whose breast resection has been examined within the new guidelines to determine what the likely risk of local recurrence and what the benefit of irradiation would be for the same time frame. Let us take a specific patient as an example. She is 49 years old, underwent a carefully conducted needle localized segmental resection for DCIS, which had been previously confirmed by a stereotactic core biopsy. Review of the needle-localized resection demonstrated 21 mm of disease, but all margins were at least 10 mm. Her carcinoma in situ had been graded, and was established as nuclear grade I without necrosis (low grade). A VNPI score can be calculated as follows: Grade - 1, size - 2, margin status - 1, age - 2, total score 6.

The Van Nuys database can project a likely local recurrence rate at 12 years with and without irradiation for this specific patient, approximately 5.5% and 2.5%, respectively. However, the

same information cannot be used to interrogate the randomized trials. They are not empowered; i.e., they lack the technical capacity to establish the size or extent of the DCIS, to evaluate all margins, and to exclude microinvasion. The randomized trials cannot perform subset analysis, so the patient is simply told what the average relapse-free survival is in the current followup period. In the case of NSABP B17, current followup published by Wapner et al 2011 indicates a 20% local recurrence rate in the ipsilateral breast with irradiation therapy, and a 35% rate without radiation therapy. These figures exclude locoregional and distant recurrences, which marginally increase the numbers. The 35% local recurrence rate at 15 years is approximately 6.5 times the recurrence rate for the same patient projected by the Van Nuys Prognostic Index.

While radiation therapy clearly provides an established benefit for duct carcinoma in situ in terms of local control, reducing the local recurrence rate by half, the same cannot be said for the use of tamoxifen. Two randomized trials examined the use of tamoxifen as an adjuvant agent in patients with DCIS, who were treated by breast conservation. The UK/ANZ trial showed no significant benefit whatever. This trial contained more than 1000 patients. The NSABP-B24 trial, which was modeled after B17 and begun the following year, showed an extraordinary finding. Whereas all studies of DCIS treated by breast conservation have shown that local recurrences are essentially 50% invasive and 50% in situ, in B24 there was no impact of tamoxifen on noninvasive recurrence in the treated breast. There was a small benefit for preventing invasive cancer of 1.7%, for which other explanations can be offered.

It is understandable that patients would be confused by the information and misinformation, but the fact remains that radiation therapy for DCIS has a limited role, and that tamoxifen has no certain role at all.

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