Re: Trends in the Treatment of Ductal Carcinoma in Situ of the Breast

Baxter et al. (1) report that about half the women undergoing lumpectomy for ductal carcinoma in situ do not get radiotherapy. The authors consider this to be undertreatment, because several studies have shown that radiotherapy reduces the risk of local recurrence and of invasive cancer. But the effect on mortality is not encouraging (2), and I believe the 50–50 split reflects the considerable uncertainty about what to do with carcinoma in situ.

What the authors found most likely represents overtreatment. More than anything else, people with cancer want to increase their chance of survival. Radiotherapy causes adverse cardiovascular effects, and in a large meta-analysis, it was predicted that radiotherapy treatment of women at low risk, such as those who have their cancers identified at screening, will increase overall mortality (2).

Women with carcinoma in situ are at exceptionally low risk of dying from breast cancer, and it is therefore very likely that radiotherapy will increase overall mortality by even more than predicted in the meta-analysis. Tumor recurrence is sometimes used as a surrogate marker for mortality in cancer trials, but it is obviously a very misleading marker in this case. The studies on tumor recurrence that Baxter et al. cite do not have sufficient power to address overall mortality because very few women died. The best evidence we have is, therefore, the meta-analysis, which makes me seriously question the wisdom of treating women with carcinoma in situ with radiotherapy rather than using a wait-and-see approach.

There is also substantial surgical overtreatment because practically all patients were treated surgically; in 1999, 28% of women got a mastectomy (1), despite the fact that less than half of these cell changes ever develop into cancer.

Not only the treatment but also the diagnosis of carcinoma in situ seems out of control. It is detected by mammography, but although breast cancer is very rare among women 18–39 years of age and mammography screening is not recommended, 4.8% of the cases of carcinoma in situ were found in this age group (1). Furthermore, 18.0% of the cases were found in women aged 70–79 years, and 5.7% of the cases were found in women aged 80 years and older. These age groups are generally not screened in Europe because we doubt whether the possible benefits outweigh the harms. In fact, because screening leads to about 30% overdiagnosis and overtreatment, even for invasive cancers (3), this doubt can be raised for any age group. For example, the group that did a meta-analysis for the U.S. Preventive Services Task Force expressed concern whether, across all age groups, the magnitude of benefit is sufficient to outweigh the harms (4).

It seems to me that the harms of screening for cancer need to be much better understood, acknowledged, and honestly communicated, both in scientific papers and in the information materials directed to women, which currently are very misleading (5–7).

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Baxter et al. (1) bring to light a number of issues about the diagnosis and management of ductal carcinoma in situ (DCIS) of the breast. It is interesting that the proportion of comedo histology decreased during the period from 1992 through 1999, that less than 50% of lesions had a reported grade, and that tumor size was not reported in one-third of cases.

The National Breast Cancer Centre (NBCC) in Australia commissioned a population-based study (2) that reviewed the epidemiology and pathology of DCIS reported to the cancer registry in one large Australian state from 1995 through 2000. The study identified a number of trends in important areas of reporting and management. First, about 65% of all cases over the 6-year period were identified through initial contact with the national population-based screening program, BreastScreen Australia. Second, fewer cases of DCIS were identified with comedo histology from 1998 through 2000 than from 1995 through 1997 (10% versus 26%, respectively). Finally, pathology reports of DCIS from 1998 through 2000 were more complete than earlier reports. For instance, the joint reporting of both size and grade were not recorded in 27% of reports from 1995 through 1997 but had decreased to only 9% of reports from 1998 through 2000.

The NBCC report found that surgical management changed during the study period. Approximately two-thirds of women underwent breast-conserving therapy alone from 1995 through 1997, compared with about three-fourths of women from 1998 through 2000. This change was mainly because of a twofold decrease in the proportion of women undergoing mastectomy alone. The rates of axillary surgery remained stable over the period. We compare salient differences between the two studies in Table 1.

The importance of accurate pathology reporting of DCIS is critical in determining treatment for women diagnosed with this disease and may provide information for the future definition of more tailored treatment regimes. In Australia, guidelines on the handling, description, and reporting of breast cancer specimens (including invasive breast cancer and DCIS) were developed in 2001 (3), and then recommendations about the clinical management of DCIS were released in 2003 (4). These recommendations are important to clinicians and to the increasing number of women diagnosed with DCIS considering management options for a disease that, although preinvasive, has the potential to recur as a life-threatening disease. The uncertainties about DCIS are well recognized. However, they do not negate the need to provide clinical guidance through evidence-based recommendations and to highlight areas in which evidence is not currently available.

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We wish to comment on the article by Baxter et al. (1), an epidemiologic analysis of treatment trends for ductal carcinoma in situ (DCIS) in the United States. Changes in practice for DCIS that Baxter et al. describe preceded the publication of the results of the earliest randomized trial of radiation therapy for DCIS, namely, NSABP trial B-17 in 1993 (2). These changes included the introduction of breast conservation, the use of adequate excision alone without radiation therapy, and the avoidance of axillary lymph node dissection for this disease. These changes in treatment were the result of prospective observational studies, none of which were cited in the article or the editorial (3–5).

It is true that pathologic features cannot be used to predict which patients with DCIS will later develop invasive disease. Similarly, we cannot predict which patients with T1b, N0, low-grade invasive ductal carcinomas may develop distant metastases. However, this inability to predict outcome for an individual patient does not vitiate the utility of microscopic prognostic features for treatment planning. The use of pathologic prognostic features for DCIS permits the identification of subsets with different risks of local recurrence, whether of DCIS alone or as invasive carcinoma. Such microscopic features have been defined and standards for examination established in several consensus conferences (6,7). It is these substantial observational studies that have permitted the identification of DCIS patient subsets for whom radiation therapy provides no clinical benefit and that account for the fact that those DCIS patients treated by breast conservation alone avoid the cost and morbidity of radiation therapy.

The randomized trials for DCIS cited by the authors use pathology practices.
that would not currently be acceptable for the examination of any image-directed biopsy, let alone a resection for DCIS. Current pathologic standards for image-detected abnormalities including DCIS, which include mammographic pathologic correlation, specimen radiography, inking of margins, and thorough histologic examination, were not required by the protocols of the trials. Data from these randomized trials do not permit identification of low-risk subsets because such pathologic data cannot be generated retrospectively.

We are confident that the results of these observational studies will be validated, and the changes in practice that they initiated will continue to benefit patients perhaps until the predictive gene signature for an individual patient provides a more precise assessment of risk. Meanwhile, we vehemently object to the pejorative description of complete excision without radiation therapy for DCIS as “undertreatment.” We, among others, have monitored patients who have undergone breast conservation without radiation therapy for up to 20 years without witnessing recurrence, either as DCIS or as invasive cancer, in a substantial majority of these patients.

Finally, and most importantly, because there is essentially no difference in the most important end point of treatment, namely overall and breast cancer–specific survival, no matter how patients with DCIS are treated (mastectomy, excision plus radiation therapy, or excision alone), why not strive for the least aggressive treatment (excision alone) whenever it is appropriate? Those who advocate more aggressive treatments should be forced to justify them from this perspective. Under the same premise that the authors considered excision alone as “undertreatment,” how often is more than that “overtreatment?”

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RESPONSE

Women with ductal carcinoma in situ (DCIS) who receive treatment are at a low risk of dying from breast cancer, and certainly this fact should temper all treatment approaches in this population (1). However, as in invasive breast cancer, the goal of radiation after lumpectomy for DCIS is not to improve survival but rather to improve local control of disease. Local recurrence after lumpectomy is associated with substantial psychological morbidity, generally necessitates mastectomy, and in DCIS will result in a diagnosis of invasive breast cancer in 50% of cases (1). Local recurrence is considered a primary end point (not a surrogate marker for mortality) in DCIS trials because local control is important. On the basis of the best evidence available (from three randomized trials) (2–4), radiation therapy after lumpectomy is effective in reducing local recurrence and the development of invasive breast cancer. Of course, consistent with the nature of adjuvant treatment, if radiation therapy after lumpectomy is given to all women with DCIS, many women will be treated unnecessarily. The relatively low rate of radiation after lumpectomy found in our study may reflect community equipoise with respect to the value of radiation therapy, particularly in women at low risk of recurrence (although in 1999, 33% of women with a predicted high risk of local recurrence, those with comedo histology, did not undergo radiation therapy after lumpectomy). Dr. Silverstein’s group has certainly provided hypothesis-generating data that are based on their experience with a single cohort (5); their results may lead to improvements in patient selection for radiation therapy in the future. However, given that other centers using current pathologic standards have had less success in selecting women at low risk of local disease recurrence after lumpectomy alone (6–7), the need for evidence from a randomized trial before widespread adoption of such practice is clear.

I share Dr. Getzsche’s concerns regarding the need to balance the benefits and harms of breast cancer screening and agree that the potential harms of screening are rarely communicated as effectively or understood as well as the potential benefits. However, when a patient is diagnosed with DCIS, it is not currently possible to determine whether the disease is “real” or is a case of overdiagnosis. Similarly, it is not currently possible to determine which individual patient with DCIS is overtreated, which patient is undertreated, and which patient receives only the precise care necessary. Although we treat our patients without the benefit of a crystal ball, we should treat our patients with the benefit of evidence from randomized studies. For women at a low risk of DCIS recurrence, the need for randomized evidence must be addressed. Given the dramatic increase in the incidence of DCIS, demonstrated in our study, at least one barrier to such trials is gone.

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