Radiotherapy to the Conserved Breast: Is It Avoidable if the Cancer Is Small?

Richard D. Gelber, Aron Goldhirsch*

After limited surgical removal of macroscopic tumor, irradiation to the conserved breast tissue is delivered to cause neoplastic cell kill. Tumor recurrence is hypothesized to be due to the persistence of foci of cancer cells, even in patients with small carcinomas (1-5). Recurrent disease in the conserved breast has devastating psychological effects on the patient, although its impact on survival is likely to be small (6).

The efficacy of radiation therapy to decrease the risk of relapse in the conserved breast was demonstrated beyond any doubt in several randomized trials (7-11) (Table 1). Nevertheless, some attempts have been made to limit the use of radiation therapy to the breast by selecting patients for whom surgery alone is sufficient. Radiation therapy might have early and especially late side effects that will have a negative impact on quality of life and serve to offset the positive effects of local disease control. The burden for the patient of undergoing daily treatment for up to 6 weeks during a period of difficult coping with recent events (i.e., diagnosis, surgery, and rehabilitation) increases the negative attitude toward this treatment modality. Furthermore, the economical costs of radiation therapy to all patients are high. Demonstrating that the use of radiation therapy may be spared for a well-defined patient population is therefore an important task from the viewpoint of individual patient care and of public health.

To its credit, in 1981 the Uppsala-Orebro Breast Cancer Study Group started a randomized trial to investigate how to select patients for local treatment that may not include radiation therapy (11). The trial was performed on 381 assessable patients with tumors 20 mm or smaller; 45.4% of these patients had tumors detected by screening mammography [Table 1 (11)]. The patients were treated with a strictly standardized surgical technique followed by a meticulous examination of the specimen to confirm a complete excision of neoplastic tissue. They were randomly assigned to complete the breast conservation with radiation therapy to the breast or to receive no further local treatment after breast-conserving surgery. The first report of this study was published in 1990, at which time the median follow-up was 29 months (12).

The updated report by Liljegren et al. (11) in this issue of the Journal illustrates what the vast majority of readers already understood in 1990—that the follow-up time in the initial report was too short to evaluate outcomes for a lymph node-negative breast cancer population with primary tumors 20 mm or smaller. Furthermore, it shows that it was incorrect to interpret the initial  P value of .063 (12) as proof of no difference in local control. The report also focuses on the results within the first 5 years of follow-up and indicates that more than 80% of the patients in the no-radiation-therapy group remain free of breast recurrence. As follow-up continues beyond 5 years, breast recurrence will exceed 20% in that group, thus decreasing the proportion of patients classified as “overtreated” if they receive radiation therapy. On the other hand, late side effects of treatment might appear after additional follow-up, an event that would tip the balance back away from radiation therapy. A trade-off analysis that weighs all factors related to costs and benefits of radiation therapy and corrects for elapsed follow-up time should be considered.

The investigators of the Uppsala-Orebro Breast Cancer Study Group are puzzled by the fact that they found a higher than expected breast recurrence rate. They attribute this poor outcome to improper adherence to the protocol-prescribed selection and treatment criteria. The participating surgeons apparently accepted the paradigm that incomplete removal of microscopic disease may not be detrimental.

Thus, the following two factors must be taken into account when applying the results of this important trial to clinical practice: 1) More breast relapses will appear after 5 years of follow-up and should be included in a more realistic cost-benefit equation, and 2) the lax adherence to recommendations regarding surgery (and pathologic work-up of the specimen for identification of adverse factors) in a non-research environment makes it difficult to accept data and recommendations based on retrospective analyses of patients who did not receive radiation therapy (13,14).

Based on the randomized trials cited in Table 1, as well as on other studies of patients undergoing breast conservation procedures (15-17), certain characteristics of patients and neoplasia were found to be associated with an increased risk of relapse in the conserved breast. They are as follows:

1) Residual breast cancer cells: multifocality and multicentricity
2) Lymph node metastases and vessel invasion
3) Large size of the tumor
4) Lobular carcinoma
5) Extensive intraductal component
6) Inflammatory reaction
7) Tumor necrosis
8) Low estrogen receptor concentration in the primary tumor

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<table>
<thead>
<tr>
<th>Trial (ref. No.)</th>
<th>Years of patient entry</th>
<th>Follow-up time reported</th>
<th>No. of patients</th>
<th>Tumor size and node (N) status</th>
<th>Type of surgery of primary tumor</th>
<th>Results and comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>NSABP B-06 (7)</td>
<td>1976-1984</td>
<td>9 y</td>
<td>1140</td>
<td>≤4 cm; N+; N-</td>
<td>Lumpectomy</td>
<td>Breast relapses in the RT group = 12%; in the lumpectomy-alone group = 43%. Difference also for small tumors</td>
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<tr>
<td>Ontario (8)</td>
<td>1984-1989</td>
<td>43 mo</td>
<td>837</td>
<td>≤4 cm; N-</td>
<td>Lumpectomy</td>
<td>Breast relapses in the RT group = 5.5%; in the lumpectomy-alone group = 25.7%</td>
</tr>
<tr>
<td>Scottish Trials (9)</td>
<td>1983-1989</td>
<td>Up to 5 y</td>
<td>556</td>
<td>≤4 cm, premenopausal, N-; postmenopausal, N+ and N-</td>
<td>Wide excision (lumpectomy)</td>
<td>For estrogen receptor levels ≥20 fmol/mg cytosol protein or unknown, breast relapses in the RT vs. no-RT group = 8% vs. 27%. For estrogen receptor levels &lt;20 fmol/mg cytosol protein, breast relapses in the RT vs. no-RT group = 3% vs. 10%</td>
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<tr>
<td>Milan Trial III (10)*</td>
<td>1987-1989</td>
<td>39 mo</td>
<td>567</td>
<td>≤2.5 cm; N+; N-</td>
<td>Quadrantectomy</td>
<td>Breast relapses or new ipsilateral breast tumors in the RT group = 0.3%; in the lumpectomy-alone group = 10%. Difference also for small tumors (&lt;1 cm)</td>
</tr>
<tr>
<td>Uppsala-Orebro Trial (11)</td>
<td>1981-1988</td>
<td>5 y</td>
<td>381</td>
<td>≤2.0 cm, N-</td>
<td>Sector resection</td>
<td>Breast relapses or new ipsilateral breast tumors in the RT group = 2.3%; in the lumpectomy-alone group = 18.4%</td>
</tr>
</tbody>
</table>

*The Milan Trial III data show a lower incidence of breast recurrences when compared with the figures of all other trials. The Milan series are single-institution figures, thus involving specific selection criteria that influence local control. Furthermore, the surgical approach in Milan included the quadrantectomy that involves the removal of one quarter of the breast and the overlying skin, a much more “radical” tissue removal that might reduce the chance of missing multifocal disease.

9) High proliferation rates of the tumor cells (high proportion of cells in S phase)
10) Younger age of the patient

The importance of intraductal components of the primary tumor was investigated in several studies (18,19). A recent trial (20) for patients with localized ductal carcinoma in situ compared radiation therapy to the breast after a lump excision with no radiation therapy to the breast after a lump excision. The study showed that, within 5 years, the incidence of invasive breast relapse in the radiation-therapy group was reduced by a factor of four, while noninvasive neoplastic recurrence was reduced by a factor of two.

Considering the features listed above, one may therefore conclude that a postmenopausal patient with a small tumor (<2 cm), classified by the pathologist as radically excised, with no vessel invasion, with no metastases to the axillary lymph nodes, with no ductal carcinoma in situ component, and with demonstrated absence of multicentric disease, may be offered a clinical trial of additional radiation therapy compared with no radiotherapy to the breast. This trial should incorporate utility measures (21) in a Q-TWIST analysis (22) to provide a quality-of-life evaluation of early discomfort and cost of treatment, late toxicity, and effects of devastating reappearance of breast disease.

The issue of whether or not to deliver radiation therapy to the conserved breast cannot be addressed in isolation from other aspects related to the care of breast cancer patients. Some of the features listed above that were found to be associated with increased risk of relapse in the conserved breast are also associated with an increased breast relapse after radiation therapy. For patients who present with these features, surgery followed by radiation therapy may not be the best treatment available, and alternative options should be investigated. The role of more effective systemic therapies to reduce the risk of breast recurrence, the timing of radiation treatment with respect to surgery, and issues related to the combination of radiation therapy and systemic treatment all require proper investigation. Also relevant is the question of whether or not tamoxifen and radiation therapy may be administered concurrently without any concern (23,24).

References


Notes

Editor's note: This paper cites one or more National Surgical Adjuvant Breast and Bowel Project (NSABP) clinical trials, to which some falsified data were submitted. Insofar as we are able to determine, impeached data do not alter the conclusions of any of the studies. Reanalyses of data from several of the trials are available through the National Cancer Institute's CancerFax and CancerNet.

To access CancerFax, call 301-402-5874 from the telephone on your fax machine, and when prompted for the six-digit code, enter 400027 (for trial B-06) and/or cn-400027 (for trial B-07) and/or cn-400028 (for trials B-13/B-14). Follow the voice prompts to receive the information. To access CancerNet, send an electronic mail message to cancernet@icicb.nci.nih.gov with cn-400027 (for trial B-06) and or cn-400028 (for trials B-13/B-14) in the body of the message (if requesting both, enter the codes on separate lines). The items will be returned to you via electronic mail, usually within 10 minutes.

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This editorial is dedicated to the memory of Philip A. Gelber, who died on March 9, 1994.