Accelerated Partial Breast Irradiation After Conservative Surgery for Breast Cancer

To the Editor:

We read with interest the article by Kuerer et al in the March 2004 issue of *Annals of Surgery*.[1] This is an excellent review of actual modern radiation methods to the breast. However, we have some comments on the intraoperative radiation therapy (IORT) section of this review because our group is cited in this article.

Kuerer et al state that IORT complications at the skin, chest wall, and ribs are of major concern and limit the IORT dose. This is not right; skin complications are not a concern of IORT because the skin is totally retracted from any radiation. This is one of the advantages of IORT with electrons, the technique used by the Salzburg group[2] and the Milan group, compared with all the other methods as the MammoSite system, conventional brachytherapy (high dose rate [HDR] and low dose rate [LDR]), or the intrabeam system, and especially the intensity modulated radiation therapy (IMRT) with the largest dose to the skin.

A justifiable concern is the radiation dose to the chest wall and the ribs. We observed 2 rib necroses in our first series of patients with IORT, but after precise depth measurement of the target volume and exact depth dose prescription and a limited dose of 5 Gy to the rib surface, we could not observe any further rib necrosis in more than 500 patients with IORT. Furthermore, a shielding of the thoracic wall as used by the Milan group can optimally reduce radiation to the thoracic wall and the ribs. In other words, from all the mentioned methods of modern radiotherapy, IORT with electrons is the simplest method to precisely place the radiation dose to the target volume.

A second comment deals with the question of partial breast irradiation or whole breast irradiation. We recently published the follow-up data of the Salzburg model of IORT[3] (9 Gy plus postoperative irradiation to the whole breast of 51–56.1 Gy). In this sequential study of 378 patients, we compared 188 patients (group1) who received conventional radiation after breast-conserving surgery (51–56.1 Gy to the whole breast plus an electron boost of 12 Gy) with 190 patients (group 2) who received IORT (9 Gy directly to the tumor bed intraoperatively plus 51–56.1 Gy to the whole breast).

An update of the data with a median follow up of 68.7 months in group 1 and 37.5 months in group 2 revealed 10 local recurrences (5.3%) in group 1 and no local recurrence in group 2 ($P = 0.04$). The 5-year actuarial rates of local recurrence were 5.3% (95% confidence interval [CI], 1.8–8.2%) and 0% (95% CI, 0.0–1.9%), respectively. With this analysis, we could demonstrate that immediate IORT boost yields excellent local control, and a further reduction of local failure rates is possible compared with standard radiation schemes.

Assuming that local failure is responsible for the decrease in survival for patients with breast cancer treated with conservative surgery and postoperative radiotherapy as proposed by some authors,[4,5] our intent should be to further reduce local recurrence rates whenever possible.

Currently, only the Salzburg model of IORT considers this fact. All the other models of (accelerated) partial breast irradiation run the risk of an increase in local failure rates associated with the risk of the decrease in overall survival.

In this context, one should consider the data provided by Perera et al[6] in which 5-year actuarial rates of ipsilateral breast recurrence was 16.2% in patients who received HDR brachytherapy to the lumpectomy site as the sole radiation. If one discusses the reasons for this high local failure rate, one should bear in mind the risks of partial breast irradiation if not appropriately performed. The reduction of radiation time is extremely attractive from the patient's point of view (not having to be irradiated for approximately 6 weeks looks alluring at first sigh, but is not true, because the previously mentioned methods (MammoSite, conventional brachytherapy, or IMRT) need at least 1 week of therapy. The IORT (Milan model) and the intrabeam system are the only 2 systems that apply the radiation dose intraoperatively as a single dose and do not require postoperative radiation. As mentioned by Kuerer et al, 3.3% of patients would develop local failure after partial breast irradiation in the nonirradiated breast tissue. With the estimated 211,300 new cases of invasive breast cancer in 2003 in the United States and an estimated breast-conserving surgery rate of 70%, approximately 4881 cases of unnecessary local failures per year could be expected in the United States.

The Austrian Health System covers irradiation for all patients with breast cancer, and distances to radiation facilities within Austria are below 2 hours of travel time for nearly all patients. Therefore, the main goal of the Salzburg model was not to reduce radiation time (which is reduced by 7–10 days), but the main goal was to reduce local failure rates. The nonavailability of radiation facilities in the near distance to the patients may play a crucial role in other healthcare systems and, therefore, may play a role in the approach to the problem if a patient decides on mastectomy instead of breast-conserving surgery for this reason. Also, the balancing between higher and lower local failure rate has to be evaluated in this context and the question of costs. The longest experience with partial breast irradiation is documented with brachytherapy. Nevertheless, this method is somehow medieval to interlard the breast with multiple catheters, and there is no evidence that the proposed MammoSite system, although U.S. Food and Drug Administra-

tion-approved, can produce the same results. Another problem is that only 20% to 25% of patients undergoing breast-conserving surgery are eligible for the MammoSite procedure.[7] The data for MammoSite have to be collected and it will need years until results will be available. This applies analogously to the Milan model and the intrabeam system. Unless these data are available, it is not yet the time to abandon whole breast irradiation after breast-conserving surgery.

Roland Reitsamer, MD
Florentia Peintinger, MD
Felix Sedlmayer, MD
Michael Kopp, MD
Walter Cimpoca, MD
Christian Menzel, MD
University Hospital Salzburg
Salzburg, Austria
r.reitsamer@iks.at

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In Reply:

There is no question that our goal as oncologists is to give every possible chance to cure our patients of cancer while minimizing risks. The concept that local failure after breast cancer surgery causes distant failure or whether local failure is a marker of aggressive biologic capacity, and thus is associated with distant metastases, is a matter of ongoing unresolved controversy. NSABP B-06 had addressed this very notion in its concept. At 20 years of follow up, the addition of whole breast irradiation after lumpectomy only marginally altered overall survival when compared with lumpectomy only.[1] The Reitsamer group appears to be concerned that the estimates of approximately 3% to 4% of women treated with breast conservation would be expected to potentially develop an ipsilateral breast cancer outside of the initially treated area. We feel that an equally or more relevant theoretical concern is the fact that 96% to 97% of women ordinarily will receive potentially unnecessary therapy in the form of whole breast radiation after breast-conserving surgery. Furthermore, the 3% to 4% risk of elsewhere in the breast failures is similar whether the patient receives or does not receive whole breast radiation.

At the present time, in the absence data from randomized, controlled trials, it is uncertain which technique of accelerated partial breast irradiation (APBI) will yield the most optimal results both in terms of local control as well as long-term toxicity. With respect to the former, to ultimately establish if APBI is efficacious, it will be necessary to correlate the dose of radiation delivered to the clinical target volume (CTV) with the anatomic location of the local recurrence. Unfortunately, we are not aware of any published clinical dosimetric analysis of patients treated with any of the IORT systems currently in use. Therefore, we are not certain that the efficacy of APBI using IORT can ever be conclusively proven. This is not a trivial point. One cannot simply conclude that because the human eye "aims" the radiation to the target that a uniform, comprehensive, and tumoricidal dose was delivered. We have previously demonstrated with our long-term brachytherapy experience that more precise, quality control is needed to target radiation than simply using one's clinical impression.[2] The lack of accurately demonstrating CTV coverage is what doomed Perera's group to the results they obtained.[3] We caution those involved in the use of IORT not to make these same errors and to apply modern, 3-dimensional dosimetric techniques to the application of their method of APBI.[4]

We also caution those involved in the use of large, single fractions of IORT to small volumes that there is a limit as to what dose breast tissue can safely tolerate long term. Wazer et al have clearly shown this in their dosimetric analysis of patients who developed fat necrosis after interstitial brachytherapy.[5] The methods of APBI primarily used in the United States (MammoSite, interstitial brachytherapy, and 3-dimensional conformal external beam radiation therapy) have all set upper limits on the volume of tissue receiving these large doses to prevent this troubling late effect.[6–8] In addition, we now have long-term data using these techniques and fraction sizes in patients treated with these methods of APBI demonstrating their safety.[9] We are seriously concerned that the doses used with IORT may ultimately be proven dangerous in some cases and therefore, efforts should now be made to systematically apply formal methods of dosimetric analysis to these IORT techniques and patients irradiated. We have learned from our mistakes by applying these formal methods of dosimetric evaluation to our APBI techniques. We hope those involved with IORT do the same.

At this time, there is no call to abandon whole breast irradiation. However, this is the time to formulate a well-designed, large-scale randomized phase III trial comparing whole breast irradiation to the techniques of partial

breast irradiation for equivalency of outcome and safety. The National Cancer Institute is sponsoring such a trial through the NSABP and RTOG.

Henry M. Kuerer, MD, PhD, FACS
Thomas Julian, MD, FACS
Frank Vicini, MD
University of Texas
M. D. Anderson Cancer Center
Houston, TX
hkurer@midanderson.org

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