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EDITORIAL

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Early complications after intraoperative radiotherapy revisited

Intraoperative Radiotherapy (IORT) has emerged as a comparable alternative to conventional fractionated whole breast irradiation (WBI) for administration of adjuvant breast radiotherapy following breast conserving surgery (BCS). As a strategy for delivering accelerated partial breast radiation (APBI), the principal appeal of IORT to the patient is the option to receive her entire course of therapeutic breast radiation in a single fraction at the time of tumor resection. **Targ**eted **I**ntraoperative Radio**T**herapy (TARGIT) is one of several major methods of delivering IORT that has been adopted globally because of its ease of use and affordability. The efficacy of TARGIT was evaluated in the TARGIT-A Trial, an international prospective randomized controlled trial in 3451 patients comparing TARGIT to post-operative 6-week fractionated WBI. Equivalent local control was demonstrated among women with clinically node negative, T1-2 invasive breast cancer receiving TARGIT at the time of BCS (5-year local recurrence rate 2.1% for TARGIT vs. 1.1% for WBI, $P = 0.31$).[1] At 6 months following completion of radiotherapy, the TARGIT-A trial also demonstrated low rates of acute adverse events in both TARGIT and WBI recipients with no significant difference in the rate of major toxicity.

In *Short-Term Complications of Intra-Operative Radiotherapy for Early Breast Cancer* (*Journal of Surgical Oncology 2016;113:370-373*), Zur et al. reported the results of a clinical registry review of 395 patients at a single center to characterize complications occurring within one year of administering TARGIT at the time of BCS. The study's key finding was an alarming 27.3% overall complication rate among TARGIT recipients, including an 8.1% incidence of wound dehiscence, a 10.8% infection rate, and a 10.1% seroma rate. The high complication rate reported by Zur et al. should raise concerns regarding the authors' surgical technique and assessment of complications. The following commentary will address the major issues raised by the study and discuss strategies that may be used to minimize adverse events following TARGIT.

Study Design. For a proper analysis of the publication by Zur et al., it would have been valuable for the authors to have reported their baseline or contemporary complication rate in patients treated with BCS followed by WBI even if the data were not randomized to TARGIT. Furthermore, since IORT is a relatively new procedure among general and breast surgeons, it would be instructive to understand how complication rates differ between surgeons with different levels of experience with the TARGIT procedure. With any new surgical procedure requiring a modest learning curve, one would expect reduced complications rates with time as surgical volume increases and as surgical techniques become standardized.

Surgical Technique. TARGIT is administered using the Intrabeam System (Carl Zeiss Meditec, Oberkochen, Germany) which emits radiation in the form of low-energy X-ray photons (maximum 50 kilovolts) in an isotropic distribution for uniform dose delivery. The Intrabeam System is supplied with reusable sterilizable spherical applicators ranging in diameter from 1.5-5.0 cm, which are mounted onto the miniature accelerator to conform the surgical margins to the radiation point source. Unlike the high-dose rate mega-voltage IORT systems (e.g, Liac, Novac7, and Mobetron) where the use of a protective internal chest wall shield is mandatory to minimize radiation exposure of the ribs, lung, and heart, internal shielding has been proved unnecessary in most TARGIT cases where attenuation of the low kilovoltage X-rays by breast tissue and chest muscles results in a steep radiation dose fall-off from 20 Gy at the surgical margins to 5-7 Gy at a distance of 1 cm.

The technique most commonly employed with TARGIT is to perform a standard tumor resection creating a spheroid surgical cavity into which the spherical radiation applicator can be positioned. The surgeon may use purse-string sutures placed within the breast superficial and deep to the applicator to conform the surgical margins to the surface of the spherical applicator. Undermining the breast from the chest wall in the retromammary plane creates a space into which a radiation shield can be positioned, if needed, and also facilitates purse-string approximation of the deep surgical margins.

A major shortcoming of the publication by Zur et al. is its failure to describe the surgical techniques utilized by their surgeons performing BCS and TARGIT. However, some aspects of their surgical technique can be inferred, and may suggest that excessive tissue dissection could have been employed by many surgeons. For example, the fact that the largest applicators (4.5 and 5 cm) were utilized in 87% of patients indicates that the surgical resection specimens were unusually large despite the predominance of tumors under 2 cm. In contrast, the average applicator diameter used in the TARGIT-A trial was 3.5-4 cm even with a mean tumor size that was similar to that reported by Zur et al. Similarly, the 3.5 and 4.0 cm applicators were used in 58% of patients in the TARGIT Retrospective Registry, a U.S. retrospective registry of 935 TARGIT recipients.[2] In addition, in a personal series of 100 recent TARGIT cases, the mean applicator diameter was 3.78 cm. Another indication by Zur et al. of excessive dissection, specifically excessive tissue undermining, is that a chest wall radiation shield was used in 32.8% of patients in spite of early findings of the TARGIT-A trial that an internal radiation shield was unnecessary due to the rapid dose attenuation of low-kilovoltage X-rays. Absent a discussion of surgical technique, readers are unable to assess precisely how the

surgeons' approach might have contributed to complications. However, limiting the surgical cavity size, minimizing tissue mobilization, and standardizing effective surgical techniques across surgeons would likely go a long way to reducing surgical complications.

Wound Dehiscence. In their results, Zur et al. reported an 8.1% rate of wound dehiscence, the highest rate reported in the APBI literature. In contrast, wound dehiscence was reported in only 2.8% of patients in the TARGIT-A trial's TARGIT arm, statistically identical to the 1.9% rate observed in the WBI arm (p = 0.155), and was not reported at all in the TARGIT Retrospective Registry. While Zur et al. did not report the precautions taken by surgeons to ensure adequate applicator-to-skin distance, technical factors that might have increased the risk of wound dehiscence are excessive radiation skin dose when the applicator is positioned <5 mm from the skin, and tissue ischemia resulting from excessive skin undermining. To assess applicator-to-skin proximity prior to irradiation, many surgeons perform ultrasound of the breast with the applicator in place within the surgical cavity to confirm applicator-to-skin distance >5 mm, while also assessing the conformity of the surgical margins to the applicator surface. Inadequate skin distance can be managed by several surgical techniques including resection of thin skin flaps adjacent to the applicator, retraction of the skin edges away from the applicator, or placement of a superficial purse-string suture to displace the skin away from the applicator.

Infection. The 10.8% rate of infection reported by Zur et al. is consistent with overall rates of infection commonly reported after breast conserving therapy. For example, a Medicare database review of women treated with BCS between 2008 and 2009 reported a 12.0% infection rate among patients receiving brachytherapy (all related CPT codes) vs. a 10.2% rate among those receiving WBI (p = 0.004).[3] The experience by Zur el al. is also identical to the 10.8% rate of infection reported in the Mammosite Registry.[4] With respect to *severe* infections, the 3.3% rate of infection requiring intravenous antibiotics report by Zur et al. was also comparable to rates of severe infection reported in the TARGIT-A Trial (1.8% TARGIT vs. 1.3% WBI, p = 0.292), TARGIT Retrospective Registry (2.8%), and the Medicare database review (1.0% brachytherapy vs. 1.4% WBI, p = 0.09).

Additionally, the authors also described a non-specific pattern of skin erythema which they sometimes misinterpreted as a breast infection. The more likely explanation for this finding is radiation dermatitis, an inflammatory response in the epidermis and dermis caused by radiation-induced tissue injury. Some measure of radiation dermatitis is a nearly universal feature of WBI, which is administered transdermally. However, this should occur far less often after intracavitary administration of TARGIT when appropriate precautions are taken. Potential causes of radiation dermatitis include inadequate applicator-to-skin distance (i.e., <5 mm) and radiation backscatter caused by reflection of radiation by the external radiation shield commonly placed on the surface of the breast during IORT to reduce radiation scatter in the operating room. Backscatter results in the skin receiving a double dose of radiation—initially from X-rays leaving the breast and then a second dose from X-rays reflecting off the external radiation barrier. Backscatter may be particularly pronounced when the applicator is situated close to the skin. To minimize backscatter, surgeons must take care to buffer the surface of the breast by placing a thick layer of moistened gauze between the skin surface and the external radiation barrier to further attenuate emitted radiation.

Seroma. Increased rates of both asymptomatic and symptomatic seromas have been consistently associated with all forms of APBI, including IORT. In the TARGIT-A trial symptomatic seromas requiring more than three aspirations were infrequent but significantly more common in the TARGIT arm compared to the WBI arm (2.1% vs 0.8%, p = 0.012). At first glance, the 10.1% incidence of seroma was the second highest adverse event reported by the Zur et al. However, the authors made no distinction between grade I (asymptomatic) and grade II (requiring ≤1 aspiration) seromas. In fact, the authors reported not a single instance of a grade III seroma (requiring multiple aspirations). Using the more liberal threshold of "at least one aspiration required", in the published literature, the incidence of symptomatic seromas following TARGIT ranges from 4% after TARGIT alone to 33% following WBI with TARGIT boost. These rates are comparable to the 12%-23% rates of symptomatic seromas associated with a variety of catheter-based brachytherapy techniques.[5]

Perspective and Conclusion. With the exception of their unusually high rate of wound dehiscence (which can likely be eliminated with adjustments in their surgical technique), the overall complication rate reported by Zur et al. is comparable in character and magnitude to adverse events commonly reported after breast conserving therapy, whether or not IORT is involved. However, a cautionary note is in order. As health plans and Medicare agencies increasingly refuse to pay for treatment of preventable complications, physicians should be wary about classifying expected asymptomatic side effects of BCS and radiation therapy as complications. Throughout the entire breast conservation era, surgeons have considered a seroma a "friend" because it transiently helps to maintain breast cosmesis following tumor resection. To reclassify all seromas now as complications seems inappropriate. Seroma formation is to be expected after surgery, much like induration and ecchymosis, and should only be deemed to be a complication if it alters surgical recovery or leads to additional interventions. Having observed no documented grade III seromas, it is likely that most of the seromas reported by Zur et al. were asymptomatic events that would have resolved naturally over time as do the majority of seromas that develop after breast conserving therapy.

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