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Novel and Highly Compressed Schedules for the Treatment of Breast Cancer

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Our thinking about radiotherapy (RT) for early-stage breast cancer has evolved considerably over the last several years. Increasingly patients and physicians together are making the decision to use altered fractionation rather than standard 6-7 weeks of conventional whole breast treatment plus lumpectomy bed boost. Adjuvant hypofractionated whole breast irradiation is now viewed as a preferred strategy for many eligible women, and can be completed in 3-4 weeks. Adjuvant accelerated partial breast irradiation is another alternative that is typically delivered in 8-10 fractions over 4-5 days. With improvements in delivery techniques, there has been renewed interest in shortening treatment times even further, with novel intraoperative approaches and ultrashort courses of external beam RT. This article provides a summary of the status and future directions in intraoperative and ultrashort course RT schedules used in the treatment of breast cancer. Outlined are the benefits as well as the drawbacks of these techniques for abbreviated breast RT.
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Compressed Schedules of Accelerated Partial Breast Irradiation

A remarkable shift in the paradigm of postlumpectomy radiotherapy (RT) has been the use and acceptance of accelerated partial breast irradiation (APBI) over the last decade, thus offering women a shorter and more convenient method of adjuvant treatment. APBI can be delivered with the following techniques: multicatheter interstitial brachytherapy, balloon brachytherapy, 3-dimensional (3D) conformal external beam RT (EBRT), and intraoperative radiation treatment (IORT). All of these approaches allow for the treatment of the lumpectomy bed with a 1-2-cm margin, substantially reducing the amount of normal breast tissue within the treatment volume. Multiple reports have shown that APBI is equivalent to whole breast irradiation (WBI) when safety, efficacy, and breast cosmesis are compared in well-selected patient populations.[1-6] Most recently, there has been significant interest with emerging data from randomized trials and institutional studies using extremely short courses of APBI. These novel approaches may offer us a glimpse into the intermediate-term future of breast RT, although one should simultaneously maintain a healthy level of skepticism and caution as these data mature. We sequentially discuss these approaches, dividing them into preoperative, intraoperative, and postoperative methods.

Preoperative Stereotactic APBI

Accelerated preoperative partial breast irradiation involves a stereotactic, image-guided RT delivered before lumpectomy in either single or multiple fractions. There are many potential conveniences of such an approach, including potentially completing treatment in a single fraction similar to intraoperative RT (IORT). Furthermore, one can target an in vivo lesion with an image-guided approach, thus eliminating the issue of volume reconstruction during postoperative APBI planning. Preoperative target volumes are potentially smaller and there may be radiobiological advantages to treating a well-vascularized tumor. In addition, this treatment offers the chance to study tumor response to large fraction sizes. Perhaps most excitingly, this treatment sequence allows for the study of radiation response, and perhaps in future studies, the study of candidate drugs that modify radiation response.

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Bondiau et al[7,8] in Nice reported results from their institutional pilot trial of preoperative hypofractionated APBI. The intent of this trial was to add a short course of preoperative RT to patients receiving neoadjuvant chemotherapy. Before treatment planning computed tomography (CT) scan, 4 fiducial markers were placed under ultrasound guidance to help localize the tumor. A magnetic resonance imaging (MRI) was also performed to help in target volume delineation, although it was performed prone while treatment planning CT scan was in the supine position. A breast radiologist performed gross tumor volume (GTV) delineation; 5-mm clinical target volume (CTV) and 2-mm planning target volume (PTV) expansions were used. Patients underwent radiation treatment during the 2nd of 6 planned cycles of chemotherapy. In all, 5 dose levels were tested in 1 Gy per fraction increments starting at 5.5 Gy × 3 (ie, then progressing to 6.5 Gy × 3 then 7.5 Gy × 3). The final dose level was 10.5 Gy × 3. A robotic stereotactic radiosurgery system was used to deliver the treatment. Surgery was performed 4-8 weeks after chemotherapy as per standard of care and postoperative RT was delivered to 50 Gy in 2 Gy fractions.

A total of 25 patients were enrolled in a standard 3 + 3 phase I design. There was only 1 dose-limiting toxicity at the 9.5 Gy × 3 dose level. A pathologically complete response was seen in 36% of patients (9 of 25). Skin toxicity as measured at multiple time points by clinical examination, calorimetry, dermoscopy, and thickening on ultrasound revealed minimal levels. This study demonstrated that high-fraction EBRT to the breast was feasible and associated with acceptable early toxicity.

Horton et al[9] at Duke recently reported early outcomes from their institutional, prospective, dose-escalation phase I trial of single-fraction APBI. The study included women with low-risk, cT1N0-invasive ductal carcinoma, or ductal carcinoma in situ less than 2 cm. All the patients underwent a treatment planning MRI. Most patients were scanned in the prone position with arms up and a titanium clip was placed in the tumor as a protocol requirement (2 patients were scanned supine). Both T1 contrast—enhanced and T2 (for postbiopsy changes) MR images were reviewed with a breast radiologist. Titanium clip and surrounding soft tissues were used or manual rigid registration of MR image fusion to treatment planning CT was used. After GTV delineation, 1.5-cm CTV and 0.3-cm PTV expansions were applied. Intensity-modulated radiation therapy (IMRT) treatment plans were generated and on-board kV and cone-beam CT imaging was performed before treatment delivery. Radiation treatment was prescribed to a dose of 15, 18, or 21 Gy to cohorts of 8 patients to find the maximum tolerated dose. Patients underwent lumpectomy within 10 days of radiation treatment. Response to radiation treatment was assessed on MRI as well as paraffin-embedded samples.

The authors enrolled a total of 32 patients. Only 3 women underwent additional WBI after lumpectomy. After a median follow-up of 23 months, no dose-limiting toxicities were observed. The authors saw dose-dependent correlations with postradiation vascular permeability on MRI as well as induction of an inflammatory gene signature in a 27-gene set. Patients who were treated with single-fraction RT had good or excellent cosmesis. Conversely, the 3 patients who had additional WBI had worse outcomes, with 1 patient developing 2 grade 3 toxicities, 1 with a wound infection, and with fair or poor cosmetic outcome in all 3.

Additional experiences in preoperative APBI have been reported from a Danish group[10] and as well as similar study currently open at the University of Maryland (NCT01014715). These 2 studies are not elaborated in this review, as they are not shortened compared to conventional APBI. Unlike IORT, preoperative APBI allows for image guidance and more sophisticated treatment planning such as IMRT. This novel approach, however, has its own set of considerations. Primarily, accurate GTV delineation of branching intraductal components on CT images can be problematic, even with fiducial placement. Given the large fraction sizes used in this approach, the seriousness of accurate target localization is obvious. Although MRI fusions may be helpful, MRIs are typically acquired in the prone position, thus requiring complex deformable image fusion techniques to blend CTs that may be acquired in the supine position. A potential solution would be dedicated MRI-based treatment planning. One could thus invoke the principles of intracranial stereotactic radiosurgery and the rigorous image-guidance principles of stereotaxis employed in that context. However, the breast is a deformable and mobile organ; hence, accounting for the inherent differences (and limitations) of fixation and registration compared with intracranial techniques would need to be understood.

Proponents of preoperative APBI claim that this technique offers patients a treatment that is highly convenient and simple. However, preoperative APBI would likely require complex immobilization techniques for supine treatment plans, routine MRI simulation, or complex soft tissue deformable fusion of MRI and CT images, target delineation with the aid of a breast radiologist, pretreatment image verification with cone-beam or other 3D imaging, and multibeam stereotactic treatment planning with robotic tumor tracking. With changes in the health care system on the horizon, these considerations may not integrate well into a cost conscious system and seem almost impossible for resource-limited economies. Finally, similar to IORT, the preoperative approach still has to resolve the question of "remedial treatment" in the face of higher-risk findings discovered on final pathology (ie, positive nodes).

Intraoperative Radiation Treatment

Targeted Intraoperative Radiotherapy

Intraoperative radiation is perhaps the purest of short-course RT techniques with adjuvant treatment bundled and completed on the day of resection. The targeted intraoperative radiotherapy (TARGIT)-A trial is the largest reported experience of IORT with a novel approach. This technique involves the use of a spherical applicator (Intrabeam device, Carl Zeiss, Oberkochen, Germany) delivering a single 20-Gy fraction of radiation intraoperatively, prescribed to the applicator surface using 50 kV x-rays. The surface dose attenuates to 5 Gy at 1 cm from the applicator surface.[11] The authors of this trial justify an intraoperative approach as follows: (1) although there