VIEWPOINT

Targeted Intraoperative Radiation Therapy—A Promising Option for Accelerated Partial Breast Irradiation

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Accelerated partial breast irradiation (APBI) has been established as an alternative to whole breast irradiation (WBI) following breast-conserving surgery for select patients with early-stage breast cancer. In addition to lending greater patient convenience and a significant reduction in treatment time, APBI promotes normal tissue sparing and has demonstrated equivalent ipsilateral breast tumor recurrence (IBTR) and long-term toxic effects rates in selected patients.[1] Whereas older trials comparing WBI with APBI used multicatheter brachytherapy, more recent phase 3 clinical trials have used alternative radiation therapy (RT) modalities, including 3-dimensional conformal radiation therapy (3D-CRT), intensity-modulated radiation therapy (IMRT), and intraoperative radiation therapy (IORT) using low-energy photons or electrons. Of these alternative modalities, IORT yields the greatest reduction in treatment time—compared with standard external beam radiation therapy (EBRT) spanning several weeks, IORT may be completed in minutes during breast-conserving surgery. In addition, IORT has been shown to be significantly less costly than EBRT while producing similar quality-adjusted life years.[2] Unfortunately, IORT has often been overlooked as a treatment option, and many clinicians remain skeptical of its efficacy even in the face of encouraging results.

The recently performed Targeted Intraoperative Radiotherapy (TARGIT-A) phase 3 clinical trial comparing EBRT-based WBI with IORT-based APBI using photons has led some clinicians to believe that IORT is associated with a higher risk of IBTR than EBRT following breast-conserving surgery based on the new ASTRO consensus statement on APBI.[3,4] The TARGIT-A trial (n = 3451) compared IORT to EBRT using a risk-adapted approach with 2 distinct strata (prepathology and postpathology) depending on whether IORT was performed during lumpectomy or after lumpectomy as a delayed procedure with reoperation and reopening of the initial excision, respectively.[2] Importantly, the prepathology stratum (n = 2298) was associated with a local recurrence rate that was noninferior to the local recurrence rate for EBRT (2.1%, 95% CI, 1.1%-4.2%) vs 1.1%; 95% CI, 0.5%-2.5%; *P* = .31). It was only when prepathology cases were combined with postpathology that the overall local recurrence rate for all patients receiving IORT (n = 3451) increased to 3.3% (95% CI, 2.1%-5.1%) vs 1.3% (95% CI, 0.7%-2.5%) for patients receiving EBRT (*P* = .04).[2,5] Recommendations for IORT should interpret the recurrence rate of the prepathology stratum separately because placing an undue emphasis on the combined recurrence rate for prepathology and postpathology IORT cases may skew clinically meaningful interpretation of this treatment.[2]

Vaidya et al[2] conducted the TARGIT-A clinical trial with the hypothesis that postlumpectomy radiation could be restricted to the tumor bed, and results from the prepathology stratum demonstrate that this is both feasible and noninferior to EBRT. Reasons for reduced efficacy of TARGIT delivery in the postpathology stratum include increased trauma secondary to wound reopening, reduced precision of applicator placement, radiation delivery to scar tissue, and missing the critical temporal window for radiation delivery (the median time to delivery of radiation following surgery in the postpathology stratum was 37 days).[2] Further analysis by Vaidya et al[2] determined that the super-selected subset of patients assigned to receive TARGIT alone in the postpathology stratum—which had a much better prognosis than patients in the prepathology stratum based on tumor size and grade, lymph node status, and breast cancer survival—still had a 5-year local recurrence rate far greater than the local recurrence rate for prepathology cases alone (5.9% vs 2.7%).[2] Therefore, these data demonstrate that the accurate delivery of radiation in the appropriate timeframe is truly the rationale for the different results between the prepathology and postpathology strata and serve as evidence for a clinically meaningful distinction in methodology. As a result of these analyses, use of IORT in the United States is generally restricted to treatment in the prepathology setting.

In addition to the aforementioned equivalent results for patients in the prepathology stratum, a planned subanalysis revealing that progesterone receptor (PR) status was the sole predictor of outcome further determined that patients with PR-positive disease had a similar 5-year local recurrence when receiving IORT vs EBRT (1.4%; 95% CI, 0.5%-3.9% vs 1.2%; 95% CI, 0.5%-2.9%; *P* = .77).[2] With regard to overall survival, there was a 3.1% improvement in survival for patients receiving IORT trending toward significance (3.3%; 95% CI, 1.8%-6.0% vs 6.4%; 95% CI, 4.3%-9.6%; *P* = .08).[2] Whereas the ASTRO consensus guidelines previously used a post hoc analysis of a small subgroup (n = 294) of patients in the Electron Intraoperative Radiation Therapy (ELIOT) trial as support for the use of electron beam IORT,[4] neither the present subanalysis for PR-positive patients in TARGIT-A with over 5 times the patients (n = 1625) nor the prepathology stratum with nearly 8 times the patients (n = 2298) were acknowledged in the new ASTRO consensus statement regarding low-energy photon IORT.[2] Based on these results from TARGIT-A, IORT

using low-energy photons truly merits recognition as a treatment option for patients with good risk disease.

Going a step further, with regard to the TARGIT-A study follow-up, the median follow-up period initially reported in the trial was 2 years and 5 months based on the most recently enrolled cohort of patients, which is sufficient time for discerning the effect of radiation given that the effect of radiation on locoregional recurrence tends to manifest in the first 2 to 3 years following treatment.[2,4] However, even for the 636 patients comprising the mature cohort with a median follow-up of 5 years, there was still no evidence of delayed recurrences.[2,4] Overall, IORT has been found to confer a possible survival benefit and carry less grade 3 to 4 toxic effects. Patients receiving IORT experienced fewer deaths related to causes outside of their cancer, such as cardiovascular-related deaths or other malignant diseases (1.3%; 95% CI, 0.7%-2.8% vs 4.4%; 95% CI, 2.8%-6.9%; $P = .02$).[5] Moreover, although the rates of complications and toxic effects were similar between the 2 treatment groups, TARGIT-A found that toxic effects secondary to RT and grade 3 to 4 skin toxic effects were significantly reduced with IORT (0.5% vs 2.1%; $P = .002$ and 4 of 1720 vs 13 of 1731; $P = .03$, respectively).[2]

In spite of the great popularity of mammosite balloon brachytherapy for APBI when the US Food and Drug Administration first approved its use in 2002—with sparse data immediately available to support its use at the time—IORT has conversely been the subject of constant criticism in spite of its established efficacy for good risk patients. Along with demonstrating noninferior local recurrence and overall survival rates—with improved mortality for non-breast cancer-related causes—IORT remains a convenient and less expensive option for necessary adjuvant local therapy for a disease in which patients are underirradiated. A recently published article[6] in the *International Journal of Radiation Oncology, Biology, and Physics* analyzing radiation noncompliance (defined as 2 or more absences from scheduled radiation appointments) found that 21.7% of patients were noncompliant, which resulted in inferior recurrence-free survival and overall survival.

Intraoperative radiation therapy has been used in over 250 centers across the world and has been introduced into treatment guidelines in Europe and Asia. Intraoperative radiation therapy has been shown to be significantly less costly than EBRT while producing similar quality-adjusted life years, and increasing attention to IORT may lead to a better understanding of its role in APBI while reducing treatment time and minimizing treatment costs. As we await the results of ongoing prospective randomized clinical trials assessing APBI, it is critical that IORT be recognized as a good option for good-risk patients.

ARTICLE INFORMATION

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