Commentary

Commentary on the GEC-ESTRO trial: is partial breast irradiation ready for prime time?

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In the era of personalized oncology, a multidisciplinary approach has been utilized involving surgery, radiation, and systemic therapy in the management of patients with breast cancer. Recent advances in adjuvant systemic therapy have reduced the risk of distant metastases and local recurrences as well; improvements in imaging technology and radiation therapy have also contributed to the same. Given these factors, a "less is more" approach has been gradually accepted in surgical oncology. In patients with early stage of breast cancer, breast-conserving therapy (BCT) is suggested instead of mastectomy. BCT has proved the "less is more" concept because compared with mastectomy patients undergoing BCT have shown a higher survival rate (1). BCT comprises breast-conserving surgery (BCS) with adjuvant radiation therapy and axillary management. A less-invasive procedure has been attempted for each element. In axillary management, the safe omission of axillary clearance can be extended from patients with a negative sentinel-node to being positive for metastasis (2,3). In BCS, a wider clear margin is not related to a reduction in the risk of ipsilateral breast tumor recurrence (IBTR), and "no ink on tumor" has introduced the standard adequate margin (4). In adjuvant radiotherapy, traditionally, whole breast irradiation (WBI) requires daily for up to 5 weeks or longer. In addition, hypofractionated radiotherapy for approximately 3 weeks is performed (5,6). However, this lengthy duration is burdensome to patients, and the radiation to the entire breast exposes the surrounding organs especially the coronary artery thereby increasing the risk of ischemic heart disease (7). Partial breast irradiation (PBI) is a more convenient and limited-field radiotherapy that can be performed in five days or less. Because WBI after performing BCS reduces the risk of IBTR and mortality due to breast cancer (8), PBI should be carefully introduced as an alternative procedure to WBI based on evidence from well-designed clinical trials.

Multicatheter brachytherapy (MCB) was the earliest technique developed for PBI as a boost treatment following WBI (9). In the 1990's, MCB had been introduced as adjuvant radiotherapy, and the earliest data on PBI was obtained by this technique, which includes a relatively small randomized study conducted by a single institution in Hungary. This trial compared patients undergoing PBI primarily with MCB with conventional WBI. At a median follow-up of 10.2 years, the equivalent local recurrence rate (5.1% and 5.9% in PBI and WBI, respectively; P=0.77) and favorable cosmetic outcomes (81% and 63% in PBI and WBI, respectively; P<0.01) were reported (10). However, their sample size of 258 patients was insufficient to support MCB-PBI as an alternative to WBI. After that, there were several types of PBI techniques developed: (I) intraoperative radiation therapy (IORT) delivered with an electron and a low-energy X-ray source; (II) external beam radiation therapy (EBRT) including three-dimensional conformal radiation therapy (3D-CRT) and intensity-modulated radiation therapy (IMRT); and (III) interstitial brachytherapy using intracavity devices (e.g., single-entry applicators and multilumen and strut-based devices). The earliest reported large randomized clinical trials in

more than 1,000 patients were developed using the IORT technique. In the targeted intraoperative radiotherapy [(TARGIT)-A] trial, IORT was performed using 50 kV photons (11). Moreover, in the electron intraoperative therapy (ELIOT) trial, large electrons were used (12). In these two non-inferiority designed trials, there were small absolute differences in IBTR rates favoring WBI (3.3% and 1.3% for TARGIT, and 4.4% and 0.4% for ELIOT). However, the follow-up period of the TARGIT-A trial (median: 2.4 years) was too short to prove non-inferiority. In both trials, the IBTR rate using IORT was almost three times higher than that of WBI thereby fueling the doubt whether radiation therapy is effective in reducing IBTR, because adjuvant radiotherapy after BCS was expected to halve the IBTR rate. Therefore, suitable patients should be identified for IORT. EBRT is another promising PBI delivery method, because it is already available and can avoid an additional invasive procedure. The indication of PBI can also be decided after confirmation of the final pathology. Although it only had a small sample size of 520 patients, the randomized trial comparing PBI using IMRT with WBI found no differences in the IBTR after the 5-year follow-up period (1.5% and 1.5% in PBI and WBI, respectively; P=0.86) (13).

The Groupe European de Curietherapie-European Society for Therapeutic Radiology and Oncology (GEC-ESTRO) conducted a large randomized phase 3, non-inferiority trial to compare the efficacy of MCB-PBI with WBI to a tumor bed boost after BCS. Their primary endpoint was the IBTR rate. In The *Lancet*, Strnad and colleagues showed 5-year results of the trial in 1,184 patients with low-risk breast cancer from 16 European centers (14). The median follow-up time was 6.6 years. The cumulative local recurrence rate with MCB-PBI and WBI was 1.44% and 0.92%, respectively. Of these, a 0.52% difference [95% confidence interval (CI): 0.72–1.75; P=0.42] was below the non-inferiority margin of three percentage points. Acute and late toxicities were also equivalent between techniques. Therefore, based on mature and valid data from large datasets, MCB-PBI has been shown to be an efficient technique than WBI, which can be a standard option for patients with low-risk breast cancer. At the same time, the pooled registry of multicatheter interstitial sites (PROMIS) study supported the results of the GEC-ESTRO trial (15). Although it was a retrospective cohort study, it revealed long-term follow-up outcomes from more than 1,000 patients with a variety of backgrounds. The 5- and 10-year local recurrence rate was 3.8% and 7.6%, respectively, which are quite similar to the 10-year risk of IBTR of 10% in the EBCTCG meta-analysis. Regarding cosmetic outcomes, 84% of patients achieved excellent or good cosmesis, similar to the GEC-ESTRO trial.

The aforementioned two studies developed evidence about MCB-PBI as an adjuvant radiotherapy after BCS. To standardize MCB-PBI, we should generalize this technique by comparing it with the other methods, and develop optimal patient selection criteria by further analysis. To achieve a successful PBI, obtaining the correct dose distribution curve is relevant, delineating a clinical target of the surrounding lumpectomy cavity with less exposure to the organs at risk. IORT can cover only the spherical dose distribution around lumpectomy cavity. However, PBI using EBRT or MCB can provide individualized detailed planning targeting volume (PTV) depending on breast size, tumor size, and the location of the tumor. However, PTV in EBRT should be larger than in MCB-PBI to account for the set-up error and patients' movement, which may cause higher rates of late toxicities and worse cosmetic outcomes. A randomized trial of accelerated PBI using 3D-CRT (Rapid) reported worse cosmetic outcomes due to these late toxicities (16). IMRT is another promising PBI technique with initial results showing good cosmetic outcome, although further follow-up is warranted (13,17). The technique of MCB-PBI can produce an ideal dose distribution curve with a high level of skill. There are two different approaches to insert catheters for delivering radiation therapy with brachytherapy: open cavity and closed cavity implants. The breast cancer working group of GEC-ESTRO developed a guideline for both of these techniques to achieve an appropriate delineation of PTV (18,19). Although the open cavity implant may be an easier technique than the closed cavity implant, skill is required to delineate appropriate PTV, especially for patients with large breasts. The introduction of intracavity devices may be a good option to achieve a reproducible PTV to reduce the learning curve. Patient selection is the other important factor. The patients' criteria before the GEC-ESTRO trial were made by many societies using traditional clinico-pathological risk factors for IBTR (e.g., age, tumor size, and histology) based on data of BCT with WBI. However, IBTR was not associated with age in the GEC-ESTRO trial or the PROMIS study. To identify suitable patients and extend the candidates for MCB-PBI, molecular subtypes and genomic profiling should be considered to evaluate the individual risk of recurrence. Ideal PBI techniques and patient selection criteria should be continuously discussed by an ongoing

national study, the National Surgical Adjuvant Breast and Bowel Project (NSABP) B-39/Radiation Therapy Oncology Group (RTOG) 0413, comparing various types of PBI with WBI in more than 4,000 patients.

While choosing a radiation technique, the additional benefits of PBI should also be taken into account, such as the reduction in radiation burden as well as that the normal tissues are not exposed to unnecessary radiation. Although further evidence is still required, there were fewer non-breast cancer-related deaths in patients undergoing PBI than WBI (20), which supports the "less is more" concept. Is PBI ready for prime time? The answer is "Yes". There is no doubt that MCB-PBI should be offered as the new standard option based on skilled PBI techniques and optimal patient selection. Adjuvant radiotherapy for BCT can be personalized by the following trade-offs: no radiotherapy, PBI, WBI, WBI with boost, and WBI with regional irradiation. At this point, when PBI is chosen, the MCB technique should be offered as a new strategy for radiation options in BCT.

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Footnote

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