**Editorial**

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# Partial-Breast Irradiation - Current Situation with Evidence

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The implementation of breast-conserving surgery in the management of early breast cancer is one of the most important successes of the modern treatments in the field. Numerous randomized clinical trials initiated more than 30 years ago have reported 20-year durable results documenting that survival is equivalent to mastectomy when the breast is conserved by removal of the index cancer with wide excision followed by whole-breast radiotherapy (1-4). Nearly simultaneously with the initial trials studying breast conservation instead of mastectomy, investigators began to study alternative approaches that could achieve comparable cancer outcomes while reducing the burden of care imposed by the 4–6 weeks of daily radiotherapy delivery post lumpectomy. Administration of radiation to the breast tissue that is adjacent to the surgical cavity, i.e., partial-breast irradiation is one of the treatment alternatives studied. The first trials in this approach were initiated nearly as early as breast-conserving surgery trials. Multiple influences have since contributed to the development and success of accelerated partial-breast irradiation and made it one of many effective approaches for radiotherapy following lumpectomy in selected early-stage breast cancer patients. In this editorial, we decided to touch on the historical advances of partial-breast irradiation.

**The rationale of alternatives to whole-breast irradiation**

Since the 1980s, it has been well-recognized that breast-conserving therapy is a safe alternative to mastectomy for selected early-stage breast cancer patients. In those trials and similar trials searching for relapse patterns after breast-conserving surgery, it was reported that the majority of the local relapses (87-90%) were in or around the primary tumor foci (5-10). The local recurrences outside the primary foci were less than 1% in the group of patients who were treated with whole-breast irradiation and around 1.5-3.5% in the group of patients who were observed after surgery. In any case, those numbers were fewer than the number of recurrences around the primary foci in the group of patients who were observed after surgery (4.1-22%).

**Historical advances in partial-breast irradiation**

The initial trials comparing partial-breast irradiation with whole-breast irradiation were done using external beam radiotherapy techniques. The first trial came from England (Christie Hospital) where the increased number of patients for whole-breast irradiation due to breast-conserving surgery became troublesome. This trial was initiated as early as the trials comparing mastectomy with breast-conserving surgery and was comparing partial-breast irradiation performed with electrons with whole-breast irradiation after breast-conserving surgery with no intervention to axilla (11). The in-breast recurrence rates in the first 37 months of this trial were 8% vs 4%; these rates were reported to be 19.6% vs 11% after 7 years of follow-up. The majority of the patients experiencing a local failure were the ones with invasive lobular histology. Although there were no differences in overall survival rates, fibrosis and telangiectasia were reported to be more pronounced in the partial-breast irradiation arm.

The second trial again came from England (Yorkshire Breast Cancer Group) (12). Although patients included in this trial were highly selected in terms of standardized treatments as breast-conserving surgery with axillar dissection, appropriate systemic treatments the number of the planned patients could not be reached. The technique of the partial-breast irradiation was left to the clinic so as to be performed in the form of electrons, photons or direct cobalt field. After 8 years of median follow-up, the local and regional recurrences were reported to be higher in the partial-breast irradiation group (24% vs 9%). There were no differences in distant relapse or overall survival rates. The majority of the local recurrences (70%) in the partial-breast irradiated group were in or around the primary foci.

The brachytherapy period came right after this. Most of these trials were non-randomized, single arm, retrospective or prospective series, which included small number of patients. The patient selection criteria in these studies had major differences among each other in terms of

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clinical and pathologic factors, situation of surgical margins (13-15). The rates of in-breast recurrences in these studies were unacceptably high (15.4 – 37%).

Three major important lessons were learned from these initial studies; thus, more modern studies came to be designed in a more detailed way. The first one of those lessons was to perform the surgery in appropriate way and proper staging of the tumor. Although more recent studies evaluating partial-breast irradiation included patients operated with modern standards and appropriate pathological staging is performed the first studies was far from this. The poor outcomes reported in those studies may be the results of this inferior surgical staging. The second lesson learned was the proper selection of the patients for partial-breast irradiation. The inclusion of the patients with bad prognostic factors for local recurrence such as invasive lobular histology, young age, high grade and axillary metastases was another factor for high recurrence rates. It is important to point out that none of these early attempts at partial-breast irradiation reported estrogen/progesterone receptor presence and HER2 Neu presence/amplification used standardly in current clinical practice as biomarkers for prognosis classification. Lastly, the technical factors played a major role in explaining the high rate of local recurrences in these studies. The target volume definition and proper treatment planning strategies for good dose coverage were missing in the majority of the early studies. Today, it is easier to make good treatment plans for partial-breast irradiation with the high imaging technologies and computer based planning systems.

After the lessons learned as explained above, the first of the next-generation studies investigating partial-breast irradiation was done with brachytherapy. Although they were non-randomized, most of them were match-pair studies. These studies are characterized by having well-controlled surgery methods, systemic therapy, patient selection, and consistent targeting and dose delivery for partial-breast irradiation (16-18). The local relapse rates reported in those trials are around 5% in five years, which seemed quite similar to whole-breast irradiation.

The next set of investigations determined if the success with APBI within a single institution could be translated to the multi-institution setting. Three important studies investigated the feasibility and standardization of this procedure: the Radiation Therapy Oncology Group (RTOG) 9517 brachytherapy trial (100 patients were included), single-entry balloon brachytherapy device (MammoSite®) study (70 patients were included) and the RTOG 0319 external beam 3D conformal radiotherapy study (58 patients were included) (19-21). These phase II trials among others established a foundation for experience with accelerated partial-breast irradiation, which helped launch several large phase III randomized trials that are powered to determine if APBI could yield local control equivalent to standard whole-breast irradiation post-lumpectomy. Most of these studies are still ongoing and accruing patients or closed for accrual and pending for maturation (Table 1).

Table 1. Ongoing phase III trials of accelerated partial-breast irradiation

| Clinical Trial | Status | Target Patient Number | APBI Technique | Inclusion Criteria |
|---|---|---|---|---|
| NSABP B-39/ RTOG 0413 (29) | Closed 2013 | 4214 | 3DCRT | >18 y, stage 0-II, < 3 cm, pN-0 – N-1 (<3 LN+), (-) margins |
| GEC-ESTRO (30) | Closed 2009 | 1300 | Brachytherapy | ≥40 y, stage 0–II, <3 cm, pN0 –N mic, (-) margins (2 mm) |
| RAPID OCOG (31) | Closed 2012 | 2135 | 3-DCRT | ≥40 y, stage 0–II, < 3 cm, pN-0, (-) margins, no lobular histology |
| IMPORT Low MRC (32) | Closed 2011 | 1935 | IMRT/3D | ≥50 y, stage I–II, < 3 cm, pN-0 – N-1 (<3 LN+), (-) margins (2 mm), no lobular histology |
| IRMA (33) | Open | 3302 | 3DCRT | ≥49 y, stage I–II, < 3 cm, pN-0 – N-1 (<3 LN+), (-) margins (2 mm) |
| SHARE (34) | Open | 2796 | 3DCRT | ≥50 y, stage 1, < 2 cm, p N0-N i+ (-) margins (2 mm) |

APBI: accelerated partial-breast irradiation; 3-DCRT: 3-dimensional conformal radiotherapy; IMRT: intensity modulated radiation therapy

**Intraoperative Radiotherapy**

Intraoperative radiotherapy is shown to be a safe and effective treatment after breast-conserving surgery for early stage breast cancer. Intraoperative radiotherapy in breast cancer can be applied with different techniques but roughly it is the application of single high dose radiation to the lumpectomy cavity mostly right after the surgical excision of the tumor; very rarely it can be performed as a second procedure after surgery and pathological examination. Intraoperative radiotherapy is a special application of partial-breast irradiation and it needs special and dedicated treatment devices and needs training and expertise. There are different intraoperative radiotherapy platforms that are commercially available.

There are 2 phase III randomized trials investigating the efficacy of intraoperative radiotherapy compared with whole breast radiation. The first one is TARGIT-A study and the second one is ELIOT study (22-24).

The TARGIT-A study compared standard whole-breast radiation to single-dose intraoperative radiotherapy using the Zeiss Intrabeam technology. The trial enrolled 3451 patients from 33 sites in 10 countries between 2000 and 2012 using a non-inferiority statistical design. The study employed a risk-adapted design that anticipated the possibility of finding adverse pathologic features on the final pathology and mandated whole-breast radiation after intraoperative radiotherapy when such features were present. The study pre-specified two strata for intraoperative radiotherapy during the lumpectomy (pre-pathology) or as a second procedure after the initial surgery (post-pathology). The eligible patients for this trial were women with unifocal invasive ductal cancer older than 45 years of age, who had breast-conserving surgery with (-) surgical margins. Three adverse features mandating whole-breast irradiation after intraoperative radiotherapy on the experimental arm were specified in the core protocol: final excision margins <1 mm, extensive in-situ component, or invasive lobular carcinoma histology. The majority of the patients included in this trial had early-stage, hormone receptor (+), low-grade disease without any axillary lymph node metastasis. After a median follow-up of 2.5 years, the ipsilateral

breast cancer recurrence rates were reported as 1.3% vs 3.3%, which was within the pre specified non-inferiority margin of 2.5 %. In the post-pathology stratum, these rates were 1.7 % for whole breast radiotherapy and 5.4 % for intraoperative radiation. The investigators suggest that the pre-pathology timing is thus the preferred option. In the overall sense, the number of deaths was lower in the TARGIT arm (3.9 %) compared to the EBRT arm (5.3 %).

ELIOT study on the other hand was a single-site (Institute Milan) randomized study which included 1305 patients. The patients were randomized either to whole-breast radiotherapy or single-session electron beam radiotherapy performed after the lumpectomy in the operating room. To be eligible for the ELIOT trial, women had to have a stage I-II invasive breast cancer aged 48–75 years with a maximum tumor diameter of 2.5 cm suitable for breast-conserving surgery. There weren't any additional whole-breast radiation and other exclusion criteria; nor was there any adaptation of treatment for any adverse pathologic features on the final pathology. The majority of the patients included in this trial had tumors with good prognostic features (ER+, Her2- without axillary lymph node metastasis). At a median follow-up of 5.8 years, the in-breast recurrence occurred in 0.4 % in the external beam radiotherapy arm and in 4.4 % in the intraoperative radiotherapy arm, which was within the pre specified equivalence margin, and with no difference in 5-year overall survival (96.8 % and 96.9 %, respectively). All the skin-related side effects significantly favored the intraoperative radiotherapy group, while a higher incidence of fat necrosis was seen after intraoperative radiotherapy than after whole-breast radiation. There were no differences in breast fibrosis, retraction, pain, or burning. The investigators suggest that the in-breast recurrence rate could be improved with stricter selection criteria and potentially through the use of additional external beam radiation in selected patients. According to their analyses, the risk factors for local recurrence with intraoperative radiotherapy included tumor size >2 cm, high grade, four or more positive nodes, and triple negative histology.

**Controversies and unanswered questions regarding partial-breast irradiation**

Although some of the problems are unsolved and questions are unanswered about partial-breast irradiation, it is widely used outside of a clinical trial during routine treatments. Several groups have developed consensus statements and guidelines regarding optimal patient selection for post-lumpectomy APBI to be referred to until more robust pieces of evidence become available from the pending randomized controlled trials. This has included the American Brachytherapy Society (ABS) (25), American Society of Breast Surgeons (ASBS) (26), American Society of Radiation Oncology (ASTRO) (27) and Groupe Européen de Curiethérapie-European Society for Therapeutic Radiology and Oncology (GEC-ESTRO) (28). The ASTRO guidelines were updated very recently with the addition of intraoperative radiotherapy (35).

Partial-breast irradiation is a new treatment technique to substitute whole-breast radiotherapy in early-stage breast cancer. It is especially more convenient for high-volume radiation centers with long waiting lists and for patients who live far away from the radiotherapy centers. However, one of the most important considerations is to select the most appropriate patient population for this treatment strategy and this should be performed in experienced and trained hands. There are many ongoing trials and while we are waiting for them to mature, we have to be very careful when we are offering this treatment strategy for our daily routine.

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