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Accelerated partial breast irradiation (APBI): Options and new horizons

After completing this activity, the participant should be better able to:

- Determine good candidates for hypofractioned whole-breast irradiation and accelerated partial-breast irradiation
- Differentiate between the various modalities of partial-breast irradiation
- Describe newer modalities and technology currently under investigation for partial-breast irradiation

Breast cancer is the second most common cancer diagnosed in women. (Skin cancer is the most common.) With better screening modalities such as annual mammography and MRI, more women are diagnosed with breast cancer at earlier stages. Depending on the location of the tumor and patient breast size, breast conservation therapy is usually an option for many women instead of mastectomy. Several randomized trials have demonstrated that breast irradiation substantially reduces the risk of local recurrence and prevents the need for subsequent mastectomy in patients with invasive breast cancer.[1-5]

Breast conservation therapy typically requires lumpectomy surgery with or without nodal evaluation and whole-breast radiation treatments. Whole-breast radiation treatments have historically required 6-6.5 weeks of treatment (30-33 fractions). Hypofractionated whole-breast radiation (involving a higher dose of radiation per fraction, with fewer total fractions), has become another option for early-stage breast cancer, constituting 42.5 Gy in 16 fractions of radiation therapy.[6] Whelan et al., in their phase III randomized trial, compared standard fractionation to hypofractionated whole-breast irradiation and found similar local control and cosmetic results at 10 years. However, hypofractionated whole-breast radiation is not an option for every candidate for breast conservation therapy as ASTRO consensus guidelines require favorable dosimetric parameters that usually rely on breast size, T1 or T2N0 disease, age >/= 50 years old, and no prior chemotherapy.[7]

Over the years, it has been discovered that 15-30% of women fail to complete whole-breast radiation therapy treatments as part of their breast conservation therapy (BCT).[8-9] Contributing factors for this high incompletion percentage include inaccessibility to a nearby radiation facility, development of toxicity, and/or the inconvenience of 6.5 weeks of daily radiation treatments. Common early toxicities include fatigue, edema, and skin erythema or blistering, all of which can have an impact on quality of life.

Clinical trials evaluating the role of breast irradiation following breast-conserving surgery suggest that if local recurrences occur, they are most likely (70-80% of cases) to develop at the site of the primary tumor with or without radiation therapy. The risk of recurrence in the breast away from the primary tumor site is only 1.5-3.5%.[10-11] These observations have led to the hypothesis that limiting radiation therapy to the primary tumor site—a technique called accelerated partial-breast irradiation (APBI)—rather than treating the whole breast may result in potentially less morbidity and shorter overall treatments in early-stage breast cancer.

Partial-breast radiation therapy allows for completion of radiation in a faster time frame, thus allowing a more convenient treatment for women. Larger doses per fraction are used while limiting the volume of normal breast tissue exposed to radiation. The lumpectomy cavity is treated with a 1-2.5 cm margin, depending on the technique of APBI used. Even though the standard of care is still whole-breast radiation, the frequency of partial-breast radiation in breast conservation therapy has increased due to promising clinical data and perceived patient convenience.

Several consensus guidelines outline the ideal candidate for partial-breast radiation outside of a clinical trial setting. As more institutions have started implementing PBI techniques in their practices, different medical societies have published guidelines—among them the American Society for Radiation Oncology (ASTRO), Groupe Européen de Curietherapie-European Society of Therapeutic Radiation Oncology (GEC-ESTRO), American Society of Breast Surgeons (ASBS), and American Brachytherapy Society (ABS). There are minor variations among the different societies regarding the definition of a suitable candidate. Briefly, these include early-stage, low-risk breast cancer: T1 or T2 invasive ductal breast carcinoma less than 3 cm; estrogen positive; age greater than 60; and node negative12 (see Table 1 for ASTRO consensus guidelines).

Treatment options

Partial-breast radiation can be delivered via several different modalities, including interstitial brachytherapy, intracavitary brachytherapy (SAVI, Contura, or Mammosite), intraoperative radiation and 3-D external beam radiation therapy. Brachytherapy and conventional 3-D external beam radiation therapy treatments are usually given over a five-day period twice per day while intraoperative radiation is delivered at the time of surgery in the operating room in a single fraction.

Interstitial brachytherapy is the oldest technique for APBI. This technique uses multiple interstitial catheters that are placed in the breast with either a template or free-hand and usually with some image guidance (ultrasound or CT scan). This technique is very operator-dependent and requires an experienced physician to produce an implant of excellent quality. The catheters can be loaded with either low dose rate (LDR) or high dose rate (HDR) sources. HDR is the most common because iridium-192 sources can be used on an outpatient basis.

Intracavitary balloon (Mammosite and Contura) or strut-based brachytherapy (SAVI) are another modality of breast brachytherapy. These devices come in different sizes, have single or multiple lumens (strut-based or balloon-based catheters), and the entire device is placed into the lumpectomy cavity. The lumens are then connected to an HDR unit, and treatments are given twice daily for five days to a dose of 34 Gy in 10 fractions. This treatment is invasive, and the device stays within the lumpectomy cavity for the duration of the radiation treatments (five to seven days, typically). The ASBS registry trial has reported 1,449 patients treated with balloon-based brachytherapy with a median follow-up of 53.3 months. The five-year actuarial rate of ipsilateral breast tumor recurrence is only 2.59%.[13]

Intraoperative radiation (IORT) is a single high-dose fraction of radiation delivered to the lumpectomy cavity at the time of surgery. This can be done with either megavoltage electrons or 50KV photons prescribed to 20-21 Gy. The advantage of this technique is that radiation treatment can be completed at the time of surgery, tissues can be physically displaced out of the radiation beam as needed, and radiation can be delivered theoretically before residual tumor cells have time to proliferate postoperatively. One disadvantage is that some women will still require whole-breast radiation after IORT when unexpected findings are found on the final pathology report because final pathology results are not available at the time of surgery.

Figure A

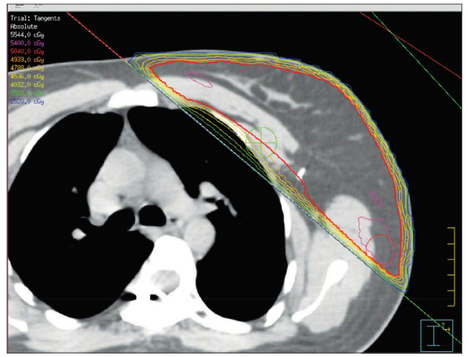
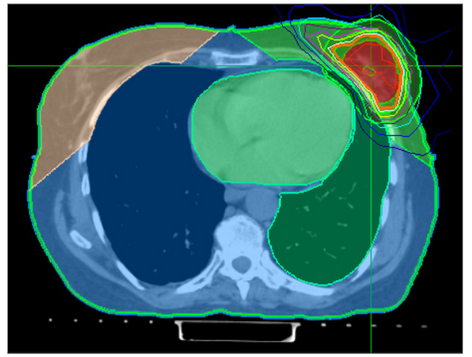


Figure B



Tangential whole-breast radiation (Fig. A) versus CyberKnife stereotactic partial-breast radiation (Fig. B).

Clinical evidence for partial-breast irradiation

The TARGIT, a phase III non-inferiority trial, compared single-dose targeted intraoperative radiotherapy (TARGIT) versus fractionated external beam radiotherapy (EBRT) for breast cancer.[14] From 2000-2012, a total of 3,451 patients were randomized between APBI and whole-breast radiation in 33 centers in 11 countries. Fifteen percent of women in the APBI arm were treated with additional EBRT due to adverse pathological features. With a median follow-up of two years and five months for the whole cohort, the five-year risk of local recurrence was 3.3% with TARGIT and 1.3% with the WBRT, (p=0.04). The ELIOT trial using megavoltage electrons has a median follow-up of 5.8 years.[15] The five-year risk of ipsilateral breast recurrence was 4.4% with IORT and 0.4% with the standard WBRT (p<0.0001). The overall mortality was not different between both groups, with a five-year survival rate around 97%.

Initial phase II trials have reported low rates of local recurrences and acceptable rates of cosmesis (with at least 80% good-to-excellent cosmesis outcomes) following APBI with 3DCRT. Currently, the largest U.S. randomized control trial (RTOG 0413 / NSABP 39) comparing whole-breast radiation to partial-breast radiation has finished accruing, and we are awaiting final results. More than 4,000 women participated in this trial nationwide. PBI treatments were delivered via interstitial brachytherapy, intracavitary brachytherapy, or 3-D external beam radiation at the discretion of the treating

radiation oncologist. The clinical target volume (CTV) and planning target volume (PTV) (with expansions to cover potential microscopic disease and set-up error, including chest wall movement with respiratory variation, respectively), included a total expansion of 2.5 cm from the lumpectomy cavity. Patients treated with 3-D CRT were treated to 38.5 Gy in 10 fractions (treatments given twice daily over five days).

Meanwhile, the Canadian RAPID trial has reported cosmesis outcomes with a median follow-up of 36 months.[16] This phase III trial involved 2,135 women randomized to whole-breast irradiation and 3-D conventional external beam partial-breast radiation (CRT) with CTV and PTV expansions from the lumpectomy cavity totaling 2.0 cm. Adverse cosmesis at three years was increased among those treated with APBI compared with WBI as assessed by trained nurses (29% v 17%; p=.001), by patients (26% v 18%; p=0.002), and by physicians reviewing digital photographs (35% v 17%; p=.001). In this trial, 3D-CRT APBI was associated with increased rates of adverse cosmesis and late radiation toxicity compared to standard WBI. This publication cautioned physicians and patients against the use of 3-D APBI outside of a clinical trial.[16] One factor that potentially contributed to these adverse cosmetic outcomes was the 3-D CRT technique that was used. Not only were there a limited number of beams, but the margins used to create the PTV were large, allowing a large volume of normal breast tissue to receive the prescription dose.

Future directions

At UT Southwestern Medical Center, we have pioneered a new modality for PBI utilizing stereotactic body radiation therapy (SBRT, also known as stereotactic ablative radiotherapy or SABR). Currently, a robotic stereotactic system is being utilized in a phase I institutional dose escalation trial of PBI, decreasing the total number of fractions from 10 to five fractions while escalating the dose of radiation. Sixty-eight women have been reported thus far, and early cosmetic results seem promising. Physicians have scored cosmesis post-SBRT as excellent or good at baseline, 6, 12, and 24 months in 94.9%, 100%, 97.7%, and 100% of patients, respectively (p=0.28), while patients scored the same periods as 82.7%, 96.2%, 95.4%, and 92.8% (p=0.04) (results presented at ASCO Chicago 2015).

The benefit of using the robotic stereotactic system is that the respiratory cycle is continuously tracked, allowing total lumpectomy cavity expansions to be minimized because there is no need to account for major variations in chest wall movement during the respiratory cycle. This reduces the volume of breast tissue being irradiated, which we hope will translate to better long-term cosmetic outcomes. In comparison to interstitial and balloon brachytherapy, this treatment is noninvasive and is given in five daily fractions rather than 10 twice-daily fractions. This ongoing phase I dose-escalation trial demonstrates that a dedicated stereotactic unit —or in fact simply a stereotactic radiation technique—can be implemented and used for APBI. This technique also is less operator-dependent compared to brachytherapy procedures.

Further on the horizon is the development of dedicated stereotactic external beam radiation technology to treat breast cancer. UT Southwestern soon will be one of five centers worldwide to obtain a device called the GammaPod™ (Xcision Medical Systems LLC, Columbia, Maryland). The design goal of the GammaPod™ is to deliver ablative doses with sharp gradients under stereotactic image guidance. Highly focused radiation is achieved at the isocenter due to the cross-firing from 36 radiation arcs generated by 36 rotating individual cobalt-60 beams while using vacuum-assisted breast cups for immobilization of the breasts.

Currently, APBI still is an investigational treatment for breast cancer; however, preliminary data seem promising, and we are all awaiting the final results of the several large phase III trials comparing whole-breast radiation therapy to partial-breast radiation.

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Table 1 ASTRO Consensus Guidelines for APBI

Patients are "suitable" for APBI if all criteria are present

Factors	Criterion
Age	>/= 60 years
BRCA1/2 mutation	Not present
Tumor size	</= 2 cm
T stage	T1
Margins	Negative by at least 2 mm
Grade	Any
LVSI	No
ER status	+
Multicentricity	Unicentric
Multifocality	Clinically unifocal
Histology	Invasive Ductal, mucinous Tubular, colloid
Pure DCIS	Not allowed
EIC	Not allowed
Associated LCIS	Allowed
N stage	N0 (i-,i+)
Nodal surgery	SN Bx or ALND
Neoadjuvant therapy	Not allowed