Accelerated Partial Breast Irradiation for Early-stage, Low-risk Breast Cancer

a report by
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Breast-conserving therapy (BCT; tumor excision with adequate margins with axillary nodes dissection followed by external beam radiation therapy (EBRT)) has become the standard of care treatment for women with stage I/II breast cancer. The overall goal of radiation therapy is to eliminate microscopic foci of cancer remaining after surgery. Standard therapy after lumpectomy is six to seven weeks of EBRT to the whole breast. Unfortunately, fewer than 50% of American women choose BCT over mastectomy, even though there is more than 20 years' excellent scientific data showing that breast conservation is equivalent to mastectomy for disease control and survival, with much better cosmetic and psychologic outcomes. The reason that so few women choose BCT is largely due to the inconvenience of attending six to seven weeks of daily radiation treatments (RT). Often women, especially in the heartland of America, are many hours away from the nearest radiation facility, and many do not have the ability to take time away from employment or family commitments to attend such therapy. Many employers simply cannot afford extended time away for protracted therapy as a healthcare benefit. Reducing time from six or seven weeks to four or five days can change this pattern. Accelerated partial breast irradiation (APBI) delivery of RT to the tumor bed in four to five days allows not only for shortening of treatment time but also limits the dose to non-involved normal tissues such as the skin, heart, lungs and chest wall, and potentially reduces both the acute and chronic toxicity of RT, which would lead to improved quality of life for patients. Also, APBI may eliminate scheduling problems regarding systemic chemotherapy when indicated. The goals of this article are to review APBI techniques and discuss indications, follow-up results, and future research for this therapy.

There are two types of APBI: EBRT (intraoperative electron beam radiation therapy and intensity modulated radiation therapy) and brachytherapy (BT; interstitial and intracavitary). In EBRT, APBI source of radiation is external to the patient, while in BT it is placed inside or near the tumor. All these techniques will be studied and compared with each other and standard whole breast irradiation in an upcoming National Surgical Adjuvant Breast and Bowel Project (NSAPB) Radiation Therapy Oncology Group (RTOG) study. All APBI techniques allow definition of the highest risk area of the breast and delivery of highly focused radiation to this smaller, more precise area of the breast. The advantage of APBI is greater specificity of the delivered dose, which allows for optimizing the cosmetic appearance of the breast and avoids potentially painful fibrosis and necrosis. The scientific rationale for APBI is based on the finding that the vast majority of recurrences after lumpectomy occur in the tumor bed region, with only 1% to 6% incidence of remote (far away or elsewhere in the breast) failures, therefore whole breast radiation therapy may not be needed in appropriately selected patients. However, as the breast is attached to the chest wall, the target area in the breast can be subject to motion related to respiration. This can have the unwanted side effect of making it necessary to identify an even larger area before treatment, and therefore losing some of the advantage of these APBI over the standard whole breast radiation.

Three-dimensional (3-D) conformal EBRT is a type of computerized radiation that uses computer-generated images to show the size, localization, and shape of the tumor. Beams enter and exit specific breast points from different angles. Some beams may be filtered to adjust the intensity of radiation delivered (intensity-modulated radiation therapy (IMRT)). This adjustment allows concentration of the radiation in the region of the cancer, and minimizes the dose to the surrounding normal organs. Intraoperative radiation therapy (IORT) utilizes an advanced computer similar to 3-D IMRT planning system, but delivers a single high dose of radiation during surgery to the area from which a tumor has just been removed.

APBI BT offers some important advantages over EBRT. BT delivers radiation dose within millimeters of the isotope, and the source can be placed in or on tumors. There are both permanent and temporary forms of BT. There can be variable dose rates, energies, and shielding needs. APBI BT allows very conformal radiation therapy to cover the lumpectomy cavity inside-out with a 2–3cm additional margin. BT also has the radiobiologic advantage of increasing the dose to the central potentially hypoxic region of the tumor. However, there are hazards related to radiation exposure. For the low dose rate partial breast radiation, patients have to be hospitalized and isolated in specially designed radiation protection rooms.

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Figure 1: CAT Scan of Breast Showing Position of Needles for Interstitial BT with Isodose Lines

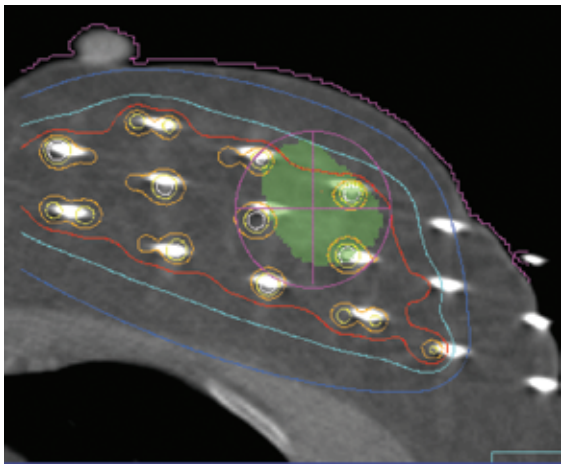
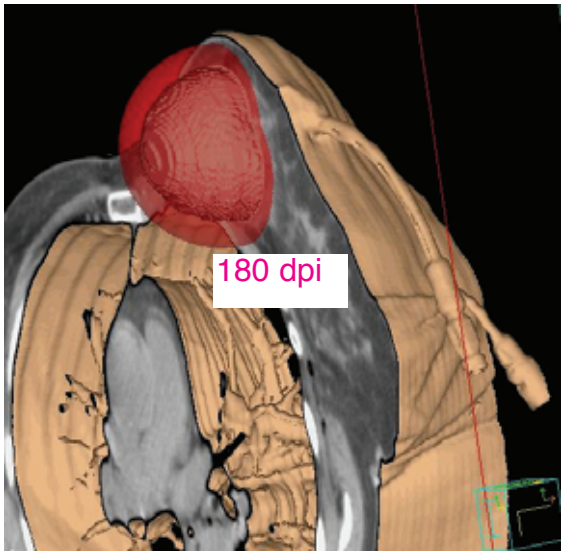


Figure 2: CAT Reconstruction of Intracavitary BT with Isodose Cloud



There is a potential disadvantage to not irradiating a larger area in the breast, in that there could be occult cancer cells that remain untreated.

Interstitial BT (see *Figure 1*) achieves irradiation by delivering radioactive sources through 12–16 plastic catheters (guided by a template placed over that part of the breast) inserted through the skin of the breast into the area surrounding the tumor cavity. The radiation is then prescribed to a volume of breast tissue corresponding to where the tumor was with an additional 1–2cm margin. It is often done in conjunction with a surgeon and/or intervential radiologist for ultrasound or guidance. It is not commonly practiced at this time.

Intracavitary BT (see *Figure 2*) achieves the same goal by delivering a radioactive source through a single catheter inserted into the tumor cavity. This catheter has an inflatable balloon that is inflated with water to conform to the tissue of the edge of the tumor cavity and may be placed either at the time of lumpectomy or afterwards under ultrasound guidance by the intervential radiologist. It is much simpler to perform and no template is needed. Since the US Food and Drug Administration (FDA)-approved MammoSite System (which is the only available single catheter product in the US) in 2002, there was a relatively rapid dissemination of its application. It is likely to become common as it becomes more available and partial breast BT becomes more in demand.

The earliest study from England randomized 708 women to receive either whole breast irradiation or APBI with external beam electrons. This study did not select for risk factors, which leads to relatively poor study results. When this patient group was re-analyzed to account for adverse risk factors, the low risk subgroup had a very small incidence of local and regional failures. American APBI studies employing approximately 16 small-gauge plastic catheters passed through the skin of the breast into the region of the tumor bed showed excellent long-term results. Earlier phases of these studies involved continuously in-dwelling radioactive isotopes known as low dose rate (LDR) BT. This was delivered as in-patient care with the patient isolated in a radiation protection room for approximately four to five days. Later studies have included high dose rate (HDR) BT, remote after-loading, and computer-optimized BT where the patient has catheters implanted and receives two treatments a day as an out-patient, but otherwise is able to carry on a normal life without the need of isolation in a radiation protection room as an in-patient in the hospital.

As mentioned above, selecting patients is vital for the success of any therapy. Selection criteria need to identify patients with minimal risk of multicentric disease, and with a low probability of microscopic extension of the cancer beyond 1–2cm from the primary tumor. Patients with pure ductal carcinoma *in situ* tumors with infiltrating lobular histology or with extensive intraductal components, and with final pathologic margins of resection less than 3cm, are excluded. Lymph node sampling should reveal no cancer cells and there should be no residual calcifications on post-surgical mammogram. The irradiation should happen within eight weeks of the final breast surgery. Patients under 40 may have a greater risk of local recurrence and are excluded. Patients whose breast shape is not technically suitable for partial breast therapy are also excluded. A matched pair analysis by Vicini et al. comparing traditionally treated patients with interstitial BT patients showed that there was no statistical differences between the two groups in failure, rate of distant metastasis, disease-free survival, overall survival, and cause-specific survival at four years. A collaborative group study RTOG performed a phase I/II trial to evaluate BT

in this group. The results at almost four years demonstrate that APBI BT yields excellent tumor control.

Overall, APBI techniques offer potential advantages of convenience and decreased radiation dose to healthy breast tissues. However, longer follow-up data is needed to resolve several outcome concerns, e.g. recurrence rate and location, and to compare the effectiveness of partial versus whole breast irradiation. Each year in professional meetings, the pros and cons are aired in debate format, but the unifying message from these debates is that patient care will always be paramount. ■