

# Intraoperative Radiotherapy for Breast Cancer

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**W**ith one million new cases each year worldwide, breast cancer is the most common malignancy in women. Constituting 18% of all cancers in woman, breast cancer also accounts for approximately 30% of all malignancies diagnosed in the United States. Breast-conserving therapy is widely accepted as an effective treatment option for patients with early-stage carcinomas of the breast [1,2].

The conventional treatment for early breast cancer includes wide local excision, sentinel lymph node biopsy or axillary lymph node dissection, adjuvant medical treatment and radiotherapy to the whole breast. Pathological and clinical data suggest that about 90% of the recurrences of cancer in the ipsilateral breast are in the vicinity of the index lesion and that remote recurrences are uncommon – whether or not whole-breast radiotherapy is delivered.

The proportion of patients who have recurrence in a portion of the breast that would not be covered by partial-breast irradiation is the same as that for patients given whole-breast irradiation. Thus, the necessity of whole-breast radiotherapy has been questioned, and the idea of partial-breast irradiation became a reasonable alternative. Moreover, whole-breast radiotherapy is usually delivered daily over 5–7 weeks. The logistic barriers to this treatment, especially time and travel, lead to a situation where only 30–50% of patients who are candidates for breast conservation treatment actually receive it [1,3–5].

The first accelerated partial-breast irradiation technique that was developed, and is associated with the most mature data, is that of multicatheter interstitial brachytherapy. This method was first implemented several decades ago; it was performed at the time of lumpectomy and was used to boost whole-breast

irradiation. The technique and its indications have progressed substantially, and thus accelerated APBI can be used as the main treatment after lumpectomy [4].

The concept of PBI is still under investigation since long-term results are not yet available. There are various methods of PBI. Intraoperative radiotherapy is the delivery of a single high dose of irradiation directly to the tumor bed during surgery immediately following surgical resection of the tumor.

## THE TECHNIQUE

Older IORT devices were technically cumbersome or required custom-built operating rooms. Some institutions performed IORT by transporting the patient from the operating room to the radiotherapy unit during surgery. These limitations have hampered the widespread adoption of IORT. The technology of miniaturization that has permeated the modern world has enabled the development of mobile IORT devices.

IORT can be delivered using a mobile linear accelerator or using a mini-electron beam low energy X-ray source. The method for using a linear accelerator involves resection of the primary tumor plus a 1 cm margin of normal tissue based on intraoperative evaluation, placement of an aluminum-lead disk just above the pectoralis muscle to minimize thoracic radiation exposure, complete retraction of the skin away from the radiation applicator, mobilization of the deep aspect of the breast above the pectoralis muscle for 5–10 cm around the tumor bed, and delivery of IORT using a mobile dedicated linear accelerator device. The total dose of 21 Gy is approximately biologically equivalent to 60 Gy given over 5 weeks.

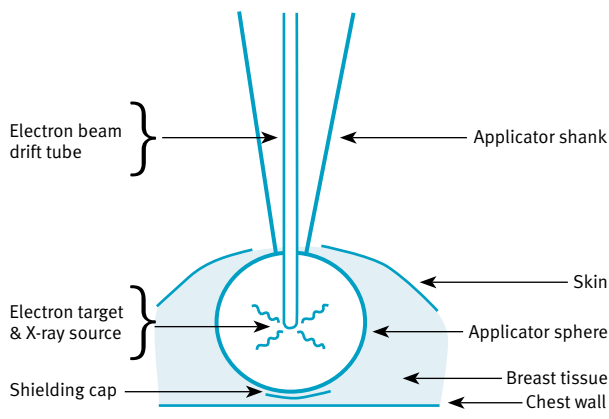
With the advent of low energy X-rays, IORT can now be delivered utilizing a mini-electron beam-driven X-ray source called Intrabeam™ (Zeiss, Germany). Low energy X-rays (50 kV maximum) are emitted from the tip of a 10 cm x 3.2 mm diameter probe that is enclosed in a spherical applicator that in turn is inserted into the tumor bed, as depicted in Figure 1.

**Compared with postoperative external beam radiotherapy, intraoperative radiotherapy has several important advantages**

**According to ongoing trials regarding intraoperative radiotherapy for breast cancer, this technique appears to be safe and effective**

APBI = accelerated partial-breast irradiation  
PBI = partial-breast irradiation  
IORT = intraoperative radiotherapy

**Figure 1.** IORT technique applied to the tumor bed [10]



IORT is delivered for about 30–50 minutes. The prescribed doses at 1 cm and 0.2 cm are 6 Gy and 20 Gy, respectively. The dose rate depends on the diameter of the applicator and the energy of the beam, both of which may be varied to optimize the radiation treatment. During the procedure, tissue is kept at a distance from the source by spherical applicators to give a more uniform dose. Tungsten-impregnated rubber sheets are placed on the chest wall to protect the heart and lungs and over the wound to block stray radiation. The quick attenuation of the radiation minimizes the need for radiation protection for the operating personnel. The operating team usually leaves the room during the irradiation, but the radiation team and anyone else interested in observing the procedure sit behind a mobile lead shield to prevent exposure [6-10].

**PATIENT SELECTION**

Previous pathological findings and the results of prospective clinical studies have demonstrated the importance of identifying a low risk subset of breast cancer patients, for whom tumor bed radiotherapy might be sufficient treatment after breast-conserving surgery. According to these findings, there are several populations that are not good candidates for IORT, such as patients with invasive lobular carcinomas due to the multifocality and diffuse spread of this lesion, patients with EIC (extensive intraductal component), patients with ductal carcinoma in situ since a large proportion of these tumors are widely spread in the breast, patients with involved margins of resection, and patients with clinically involved lymph nodes [11-13].

In 2009, The American Society for Radiation Oncology (ASTRO) convened a task force of experts in the field of breast cancer to develop a consensus statement regarding patient selection criteria and best practices for the use of PBI, outside the context of a clinical trial. According to the consensus statement, all patients considered for PBI should be candidates for breast-conserving therapy (no prior radiotherapy, no history of certain collagen vascular diseases, and not pregnant), and they should be committed to long-term follow-up for evaluation

**Table 1.** Inclusion criteria for APBI, ASTRO consensus:

Factor	Criterion
<b>Patient factors</b>	
Age	≥ 60 yrs
BRCA 1/2 mutation	Not present
<b>Pathological factors</b>	
Tumor size	≤ 2 cm
T stage	T1
Margins	Negative by ≤ 2 mm
Grade	Any
LVSI	No
ER status	Positive
Multicentricity	Unicentric only
Multifocality	Clinically unifocal with total size ≤ 2 cm
Histology	Invasive ductal or other favorable subtypes
Pure DCIS	Not allowed
EIC	Not allowed
Associated LCIS	Allowed
<b>Nodal factors</b>	
N stage	N0
Nodal surgery	SN Bx or ALND
<b>Treatment factors</b>	
Neoadjuvant therapy	Not allowed

APBI = accelerated partial-breast irradiation, LVSI = lymph-vascular space invasion, ER = estrogen receptor, DCIS = ductal carcinoma in situ, EIC = extensive intraductal component, LCIS = lobular carcinoma in situ, SN Bx = sentinel lymph node biopsy, ALND = axillary lymph node dissection

**Table 2.** Exclusion criteria for APBI, ASTRO consensus:

Factor	Criterion
<b>Patient factors</b>	
Age	< 50 yrs
BRCA 1/2 mutation	Present
<b>Pathological factors</b>	
Tumor size	3 cm
T stage	T3-4
Margins	Positive
LVSI	Extensive
Multicentricity	Present
Multifocality	If microscopically multifocal > 3 cm in total size or if clinically multifocal
Pure DCIS	If > 3 cm in size
EIC	If > 3 cm in size
<b>Nodal factors</b>	
N stage	N1-3
Nodal surgery	None performed
<b>Treatment factors</b>	
Neoadjuvant therapy	If used

of recurrence, second primary cancers, and treatment toxicity. Tables 1 and 2 present the task force’s consensus regarding “suitable” and “unsuitable” groups for whom treatment with PBI is considered acceptable and not acceptable outside of a clinical trial, respectively [14-16]:

**TRIALS**

Many studies have discussed the option of accelerated partial breast irradiation after lumpectomy, but there are only a few

published trials about IORT specifically [17,18]. One of the most important IORT trials to date is the TARGIT trial conducted by Vaidya et al. [7], which uses the technique of single-dose targeted IORT with IntraBeam. In this study, 1113 patients were randomly allocated to targeted intraoperative radiotherapy and 1119 were allocated to external beam radiotherapy. At 4 years, there were six local recurrences in the intraoperative radiotherapy group and five in the external beam radiotherapy group. The Kaplan-Meier estimate of local recurrence in the conserved breast at 4 years was 1.20% (95% confidence interval 0.53–2.71) in the targeted IORT and 0.95% (0.39–2.31) in the external beam radiotherapy group (difference between groups 0.25%, -1.04 to 1.54,  $P = 0.41$ ). The frequency of any complications and major toxicity was similar in the two groups: for major toxicity, 37 (3.3%) of 1113 targeted IORT vs. 44 (3.9%) of 1119 external beam radiotherapy,  $P = 0.44$ . Radiotherapy toxicity (Radiation Therapy Oncology Group grade 3) was lower in the targeted IORT group (6 patients, 0.5%) than in the external beam radiotherapy group (23 patients, 2.1%,  $P = 0.002$ ). The follow-up will continue for another 5 years [19,20].

Another important IORT trial is the ELIOT trial conducted by Veronesi and co-researchers [17]. In this study, 590 patients affected by unifocal breast carcinoma up to a diameter of 2.5 cm received wide resection of the breast followed by IORT with electrons. Ninety-seven percent of the patients in this study had IORT as the sole radiation treatment modality. After a follow-up from 4 to 57 months (mean 24 months, median 20), 19 patients (3.2%) developed breast fibrosis – mild in 18, severe in 1 – which resolved within 24 months. Local recurrences developed in three patients (0.5%), ipsilateral carcinomas in other quadrants in three patients and contralateral breast carcinoma in five. One patient (0.2%) died of distant metastases [21].

## DISCUSSION

Compared to postoperative external beam radiotherapy, IORT has several advantages: shorter treatment duration, which improves patient convenience; normal tissue sparing; fewer adverse effects on the lung, heart, and contralateral breast through marked dose attenuation; less chance of seeding of tumor cells; reduced skin damage leading to a satisfactory breast reconstruction and better cosmetic outcomes; and virtually no delay between surgery and the irradiation of any residual cancer cells. In addition, IORT enables a woman to have breast-conserving therapy in the future – if a new tumor appears in another area of the breast. These advantages could result in more women being offered, and subscribing to, breast-conserving treatment [1,6,22].

The results of the trials mentioned here are very good regarding the safety and effectiveness of single-dose targeted IORT. If

the final results of the ongoing IORT trials are consistent with the current findings, IORT should be considered as a preferable alternative for whole-breast irradiation in a selected low risk breast cancer population. We have begun practicing IORT in our institution as a substitute for whole-breast irradiation in selected patients. So far the outcome is promising.

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### References

- Reitsamer R, Sedlmayer F, Kopp M, et al. Concepts and techniques of intraoperative radiotherapy for breast cancer. *Breast Cancer* 2008; 15: 40-6.
- Bitterman A, Bleicher RJ, Cabot MC, et al. Sentinel lymphadenectomy: a new alternative for managing early breast cancer. *IMAJ Isr Med Assoc J* 2002; 4: 803-9.
- Clarke M, Collins R, Darby S, et al. Early Breast Cancer Trialists' Collaborative Group (EBCTCG). Effects of radiotherapy and of differences in the extent of surgery for early breast cancer on local recurrence and 15-year survival: an overview of the randomized trials. *Lancet* 2005; 336: 2087-106.
- Patel RR, Das RK. Image-guided breast brachytherapy: an alternative to whole-breast radiotherapy. *Lancet Oncol* 2006; 7: 407-15.
- Mikeljevic JS, Haward R, Johnston C, et al. Trends in postoperative radiotherapy delay and the effect on survival in breast cancer patients treated with conservation surgery. *Br J Cancer* 2004; 90: 1343-8.
- Fisher ER, Anderson S, Redmond C, et al. Ipsilateral breast tumor recurrence and survival following lumpectomy and irradiation: pathological findings from NSABP Protocol B-06. *Semin Surg Oncol* 1992; 8: 161-6.
- Vaidya JS, Tobias JS, Baum M, et al. TARGIT: an innovative approach to partial-breast irradiation. *Semin Radiat Oncol* 2005; 15: 84-91.
- Vaidya JS, Tobias JS, Baum M, et al. Intraoperative radiotherapy for breast cancer. *Lancet Oncol* 2004; 5: 165-73.
- Vaidya J. Targeted intra-operative radiotherapy (Targit): an innovative method of treatment for early breast cancer. *Ann Oncol* 2001; 12: 1075-80.
- Kuerer HM, Julian TB, Strom EA, et al. Accelerated partial breast irradiation after conservative surgery for breast cancer. *Ann Surg* 2004; 239: 338-51.
- Polgar C, Fodor J, Major T, et al. Radiotherapy confined to the tumor bed following breast conserving surgery: current status, controversies, and future prospects. *Strahlenther Onkol* 2002; 178: 597-606.
- Lagios MD. Pathologic features related to local recurrence following lumpectomy and irradiation. *Semin Surg Oncol* 1992; 8: 122-8.
- Krishnan L, Jewell WR, Tawfik OW, et al. Breast conservation therapy with tumor bed irradiation alone in a selected group of patients with stage I breast cancer. *Breast J* 2001; 7: 91-6.
- Smith BD, Arthur DW, Buchholz TA, et al. Accelerated partial breast irradiation consensus statement from the American Society For Radiation Oncology (ASTRO) – Consensus Statement. *Int J Radiat Oncol Biol Phys* 2009; 74: 987-1001.
- Arthur DW, Vicini FA, Kuske RR, et al. Accelerated partial breast irradiation: an updated report from the American Brachytherapy Society. *Brachytherapy* 2003; 2: 124-30.
- Bartelink H, Horiot JC, Poortmans P, et al. Recurrence rates after treatment of breast cancer with standard radiotherapy with or without additional radiation. *N Engl J Med* 2001; 345: 1378-87.
- Intra M, Gatti G, Luini A, et al. Surgical technique of intraoperative radiotherapy in conservative treatment of limited-stage breast cancer. *Arch Surg* 2002; 137: 737-40.

18. Mussari S, Sabino della Sala W, Busana L, et al. Full-dose intraoperative radiotherapy with electrons in breast cancer: first report on late toxicity and cosmetic results from a single-institution experience. *Strahlenther Onkol* 2006; 182: 589-95.
19. Vaidya JS, Joseph DJ, Tobias JS, et al. Targeted intraoperative radiotherapy versus whole breast radiotherapy for breast cancer (TARGIT-A trial): an international, prospective, randomised, non-inferiority phase 3 trial. *Lancet* 2010; 376: 91-102.
20. Holmes DR, Baum M, Joseph D. The TARGIT trial: targeted intraoperative radiation therapy versus conventional postoperative whole-breast radiotherapy after breast-conserving surgery for the management of early-stage invasive breast cancer (a trial update). *Am J Surg* 2007; 194: 507-10.
21. Veronesi U, Orecchia R, Luini A. Full-dose intraoperative radiotherapy with electrons during breast-conserving surgery experience with 590 cases. *Ann Surg* 2005; 242: 101-6.
22. Cuncins-Hearn A, Saunders C, Walsh D, et al. A systematic review of intraoperative radiotherapy in early breast cancer. *Breast Cancer Res Treat* 2004; 85: 271-80.