

Partial-Breast Irradiation: Is it the Time for Prime Time?

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A few decades ago several prospective randomized studies (NSABP-06, Milan 1, NCI, Gustave Rousy, EORTC 1081 and DBCG-82) evaluated the role of breast-conserving therapy compared to mastectomy in early-stage breast cancer patients. They all concluded that there were no differences between BCT (lumpectomy and breast irradiation) and mastectomy in terms of local control and overall survival in all patients independent of lymph node involvement and young age. Moreover, in triple negative (estrogen/progesterone receptors and HER-2 negative) breast cancer patients, an advantage of BCT over mastectomy was recently reported [1]. Whole-breast irradiation following breast-conserving surgery, with or without systemic therapy, is mandatory. The recurrence (loco-regional or distant) in the BCS group alone was 35.0% compared to 19.3% in BCS and radiotherapy (BCT), and the overall survival was 25.2% and 21.4% respectively, according to the Early Breast Cancer Trialists' Collaborative Group meta-analysis study [2]. The advantage was also confirmed in older patients [3], although in this subgroup of patients the survival advantage was of marginal value due to the contribution of comorbidities to overall mortality. Consequently, the need for whole-breast irradiation was revisited, and the concept

BCT = breast-conserving therapy
BCS = breast-conserving surgery

of partial-breast irradiation to the tumor bed was evaluated. The rationale for such an assumption was based on the finding that most of the recurrences were at the tumor bed. Moreover, the duration of the treatment was also reassessed. A period of 5–7 weeks, 5 times a week (conventional radiotherapy), might be replaced by an accelerated regimen such as high daily dose, once or twice a day, delivered over 5–8 days. The term of accelerated partial-breast irradiation was then formulated. Until now APBI has been implemented in several ways, including:

- Three-dimensional external beam accelerated hypofractionation regimen
- An intra-operative technique that is well reviewed by Bitterman and co-authors in this issue of *IMAJ* [4]. With this technique the tumor site is exposed by the surgeon and is irradiated during the actual surgery
- Deposition of a balloon
- Insertion of catheters into the tumor site

These last two devices are usually loaded several days after completion of surgery and are therefore called after-load brachytherapy. These four techniques of delivering APBI were based on several radiobiological principles driven from the linear quadratic equation of predicting tumor and normal tissue response to irradiation. Based on this linear quadratic model, the tumor, presumably a rapidly responding tissue, would be more efficiently damaged if the daily dose were increased and the treatment duration reduced over the conventional fractionation (1.8–2.0 Gray a day 5 times a week for 5–7 weeks). Special attention should be given to development of late toxicity

APBI = accelerated partial-breast irradiation

in slow-responding normal tissue. Based on this equation, late toxicity is entirely dependent on the daily dose, i.e., a higher daily dose will initiate more grade 3–4 toxicity. Indeed, multiple APBI studies have reported a non-inferiority outcome over conventional treatment. The RTOG study 95-17 [5] revealed that when multi-catheter interstitial partial-breast irradiation was used, local recurrence was 4% and regional lymph node recurrence 3% during a median follow-up of 80 months. Using a balloon (Mammosite[®], USA), Vicini et al. [6] reported on 1249 invasive and 194 non-invasive (ductal carcinoma in situ) breast cancer patients who had an in-breast recurrence of 3.9% and 3.4% during a period of 53 months. The same author [7] reported on the RTOG 0319 study in which the external beam irradiation technique (3.85 Gy twice a day for 5 days) was used and in-breast recurrence was 6% in 4.5 years.

During the years 2004–2006 three prospective randomized studies were initiated: NSABP B39/RTOG 0413 (external beam, multi-catheter and balloon techniques), GEC-ESTRO (multi-catheter technique), and RAPID OCOG (external beam technique) to explore this type of treatment. The results are expected in the near future. Despite the lack of a prospective randomized study, the American Society of (Targeted) Radiation Oncology ASTRO [8] and the European counterpart [9] recommended that certain patients be treated with APBI outside of a clinical trial. Nevertheless, these modalities should not be considered as the standard of care until the above mentioned prospective randomized studies are completed. Indeed, during the last 2 years several small single-institution studies have reported an excessive late toxicity (grade 3–4 of 10%) and poor

cosmesis (18–22%) using the external beam technique of APBI [10,11]. These studies as well as others led the NSABP/RTOG group to disclose prematurely the toxicity results of the B39/0413 study [12]. They reported that of 1094 patients who were followed for 3 years, none had grade 4 fibrosis-cosmesis toxicity, 3% had grade 3 and 12% had grade 2. They concluded that APBI is safe and enrollment of patients should be continued.

The main advantages of APBI are its short duration of treatment, which reduces the workload of busy radiation oncology institutions, and its greater convenience for patients who have to commute. However, these advantages should not compromise the treatment. As indicated by international guidelines and as applied at Rambam Health Care Campus, at present, APBI cannot safely replace the conventional approach and should be applied in selected low risk patients only.

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References

1. Abdulkarim BS, Cuartero J, Hanson J, Deschènes J, Lesniak D, Sabri S. Increased risk of locoregional recurrence for women with T1-2N0 triple-negative breast cancer treated with modified radical mastectomy without adjuvant radiation. *J Clin Oncol* 2011; 29: 2852-8.
2. Darby S, McGale P, Correa C, et al., for Early Breast Cancer Trialists' Collaborative Group (EBCTCG). Effect of radiotherapy after breast-conserving surgery on 10-year recurrence and 15-year breast cancer death: meta-analysis of individual patient data for 10,801 women in 17 randomised trials. *Lancet* 2011; 378: 1707-16.
3. Smith BD, Gross CP, Smith GL, Galusha DH, Bekelman JE. Effectiveness of radiation therapy for older women with early breast cancer. *J Natl Cancer Inst* 2006; 98: 681-90.
4. Bitterman A, Kessner R, Goldman L, Shiloni E, Steiner M. Intraoperative radiotherapy for breast cancer [Review]. *IMAJ Isr Med Assoc J* 2012; 14: 256-9.
5. Arthur DW, Winter K, Kuske RR, et al. A phase II trial of brachytherapy alone after lumpectomy for select breast cancer: tumor control and survival outcomes of RTOG 95-17. *Int J Radiat Oncol Biol Phys* 2008; 72: 467-73.
6. Vicini F, Arthur D, Wazer D, et al. Limitations of the American Society of Therapeutic Radiology and Oncology Consensus Panel Guidelines on the use of accelerated partial breast. *Int J Radiat Oncol Biol Phys* 2011; 79: 808-17.
7. Vicini F, Winter K, Wong J, et al. Initial efficacy results of RTOG 0319: three-dimensional conformal radiation therapy (3D-CRT) confined to the region of the lumpectomy cavity for stage I/II breast carcinoma. *Int J Radiat Oncol Biol Phys* 2010; 77: 531-6.
8. Smith BD, Arthur DW, Buchholz TA, et al. Accelerated partial breast irradiation consensus statement from the American Society for Radiation Oncology (ASTRO). *Int J Radiat Oncol Biol Phys* 2009; 74: 987-1001.
9. Polgar C, Van Limbergen E, Potter R, et al., for GEC-ESTRO breast cancer working group. GEC-ESTRO Recommendations: Patient selection for accelerated partial-breast irradiation (APBI) after breast-conserving surgery. Recommendations of the Groupe Européen de Curietherapie-European Society for Therapeutic Radiology and Oncology (GEC-ESTRO) breast cancer working group based on clinical evidence (2009). *Radiother Oncol* 2010; 94: 264-73.
10. Leonard KL, Hepel JT, Hiatt JR, Price LL, DiPetrillo TA, Wazer DE. Updated toxicity results of three-dimensional conformal accelerated partial breast irradiation. *Int J Radiat Oncol Biol Phys* 2011; 81 (Suppl): S7-8.
11. Jagsi R, Ben-David MA, Moran JM, et al. Unacceptable cosmesis in a protocol investigating intensity-modulated radiotherapy with active breathing control for accelerated partial-breast irradiation. *Int J Radiat Oncol Biol Phys* 2010; 76: 71-8.
12. Julian TB, Costantino JP, Vicini FA, et al. Early toxicity results with 3-D conformal external beam therapy (CEBT) from the NSABP B-39/RTOG 0413 accelerated partial breast irradiation (APBI) Trial. *Int J Radiat Oncol Biol Phys* 2011; 81 (Suppl): S7.