Commentary

Accelerated partial breast irradiation: the case for current use

Martin E Keisch

Mount Sinai Comprehensive Cancer Center, Miami Beach, Florida, USA

Corresponding author: Martin E Keisch, mkeisch@salick.com

Published: 5 April 2005
This article is online at http://breast-cancer-research.com/content/7/3/106

Breast Cancer Research 2005, **7:**106-109 (DOI 10.1186/bcr992)

See related commentary by Ross, page 110 [http://breast-cancer-research.com/content/7/3/110]

Abstract

The treatment of early stage breast cancer is evolving from traditional breast conservation techniques, employing conventionally fractionated whole breast irradiation, to techniques in which partial breast irradiation is used in an accelerated fractionation scheme. A growing body of evidence exists, including favorable findings. Additional studies are under way that may ultimately prove equivalence. The logic behind this approach is reviewed, and the currently available data are presented to support the current use of carefully applied partial breast irradiation techniques in appropriately selected and informed patients.

Introduction

Over the past decade there has been growing interest in decreasing the volumes of radiotherapeutic treatment post-lumpectomy in breast conservation therapy (BCT). Historically, we have demonstrated the need for post-lumpectomy radiation to optimize local control. Currently, no subset of patients can be successfully identified in whom radiotherapeutic treatment can be eliminated when local control and breast preservation are used as end-points [1]. More recently, we have demonstrated the effectiveness of accelerated partial breast irradiation (APBI) in maintaining excellent local control in select subsets of patients [2]. The methods of APBI have evolved to highly reproducible techniques with excellent quality assurance [3]. Although continued study is important, APBI can be offered as an option to patients who desire an alternative to standard whole breast irradiation. To convince the reader, we examine the history of BCT, the evolution of techniques employed in APBI, the rationale supporting use of APBI, and the growing data pool showing equivalence in properly selected, properly treated patients. In addition, arguments against APBI are examined and critiqued. In defending this advance in treatment, appropriate selection criteria are reviewed, published guidelines discussed, and ongoing research reviewed.

Thoughtful consideration of the history and status of BCT drives the need for better BCT options. Just as it was the perception of a handful of institutions that led away from the one size fits all, mastectomy for everyone dogma, it is a questioning of the status quo of BCT that has led to a more tailored approach. The concept that some patients could undergo lumpectomy plus whole breast irradiation to maintain an acceptable rate of local control and minimize morbidity is evolving into further limitation in the volume treated in select patients. Despite the demonstrated efficacy of BCT, many women are still treated with mastectomy for a variety of reasons, including time commitment, inconvenience, fear of radiation, and treating physician bias [4,5]. Additionally, a growing number of women are avoiding radiation post-lumpectomy despite markedly reduced local control, probably for similar reasons to those that lead to high mastectomy rates [6]. Current Surveillance, Epidemiology, and End Results (SEER) data from the USA demonstrate mastectomy rates of 40–60% nationally, and lumpectomy alone rates of 46% in patients with ductal carcinoma *in situ* who are potential BCT candidates [7]. If our goal is to minimize local therapy on a more individualized basis while maintaining a high breast conservation rate, then a need exists for another treatment option such as APBI, which addresses patients' and physicians' concerns over treatment duration and side effects. Shorter treatment courses with more focal side effects may allay issues leading to high rates of mastectomy and/or high rates of lumpectomy alone.

APBI techniques have evolved over time. In the USA brachytherapy is the most commonly employed method, whereas in Europe both brachytherapy and intraoperative electron and photon beam techniques are used. Initially, the US techniques were interstitial catheter based with low-dose rate sources [8], but they have since evolved toward nearly exclusively high-dose rate, image-guided techniques [3]. Data exist that show outstanding target coverage and homogeneity for these techniques [3]. Additionally, a balloon-based interstitial catheter (MammoSite™, Proxima Therapeutics, Alpharetta, Georgia, USA) has been cleared by the US Food and Drug Administration and is now the most widely used

APBI = accelerated partial breast irradiation; BCT = breast conservation therapy.

form of APBI worldwide [9]. The evolution of the techniques has led to high-quality implants with excellent target coverage and reproducible homogeneity. The most common treatment scheme is 34 Gy in 10 fractions given twice daily, over 5 treatment days to a volume covering the lumpectomy cavity with a margin of 1–2 cm. More recently, US centers have begun exploring three-dimensional external beam techniques as a noninvasive option, despite the requirements for a larger margin and a subsequent higher integral dose to surrounding tissues [10]. The European experience with APBI has included similar brachytherapy based methods but has focused more on single, high-dose intraoperative treatments with either photons or electrons, with the treatment delivered at the time of lumpectomy [11,12]. Techniques performed at the time of lumpectomy have been of less interest in the USA because of lack of knowledge of final pathologic suitability for treatment, unclear radiobiology, and lack of dosimetric quality assurance.

Arguments

Regardless of the technique employed, an APBI approach must maintain equivalence in results in critical end-points including local control, breast preservation, cosmesis, and patient acceptability. Local control and breast preservation rates are obviously linked, and the supporting data for APBI include pathologic studies, historical BCT studies that show a lack of benefit elsewhere in the breast, and a growing single institution database with promising results. First, we examine the pathologic data supporting APBI.

Data from Holland and coworkers [13] have been used to suggest the necessity of whole breast irradiation, but these data are probably not valid in the modern era because of large tumor size, high percentage of palpable lesions, and suboptimal methodology, including simulated tumor excisions, in those series. Studies that are more valid exist that demonstrate a relatively small distance of extension of disease from the main lesion to the pathologically identifiable edge of the lesion. Careful specimen evaluation, as in the studies by Imamura [14], Ohtake [15], and Goldstein [16] and their coworkers, demonstrates tumor extension at distances that are generally quite small and typically covered by the margin of current APBI techniques. These modern series include smaller tumors, more mammographically detected tumors, and more realistic techniques for determining tumor extent. The microscopic extent is typically in the range of 5–15 mm, skip lesions are rare, and extent appears to be age related.

A second argument in favor of APBI is the lack of evidence demonstrating the effectiveness of whole breast irradiation in preventing either local recurrence of the primary tumor outside the tumor bed or the occurrence of future tumors [1,17–20]. Data from both large randomized trials and single institutional series show that 'elsewhere recurrences' occur at essentially the same rate as new tumors in the contralateral breast, suggesting that they in fact are new primary tumors (Table 1) [1,17,18,21]. Because whole breast irradiation does not affect new primary tumors, treating only the site of most local recurrences seems logical.

Table 1

Incidence of elsewhere failures from published randomized trials

Study	Follow up (months)	Surgery (%)	Surgery + radiation (%)
NSABP B06 [21]	144	2.7	3.8
Milan III [1]	39	1.5	0
Ontario [17]	91	3.6	1
Uppsala-Orebro [18]	65	3.7	–

NSABP, National Surgical Adjuvant Breast and Bowel Project.

Table 2

Results of published accelerated partial breast irradiation studies with median follow up of 5 years

Institution	Number of patient	Follow up (months)	Local recurrence (%)
William Beaumont Hospital [2]	199	65	1.2
Ochsner Clinic [31]	45	75	2.0
National Institute of Oncology [22]	51	60	4.4

Finally, giving further support to the use of APBI is the growing body of data from multiple institutions that demonstrates promising local control and cosmesis in properly selected and properly treated patients (Table 2) [2,23,31]. In a matched pair analysis, Vicini and coworkers [2] recently demonstrated equivalence of APBI to whole breast irradiation. Local recurrence, elsewhere failures, cosmesis, and survival were all identical with a median follow up of 5 years. More than 8 years of follow up in 62 patients revealed no deterioration in outcomes (Vicini F, personal communication). Additionally, the Radiation Therapy Oncology Group study 95-17 [23] demonstrated the ability of multiple institutions to effectively perform similar interstitial catheter-based implants. The results to date with balloon-based brachytherapy have been equivalent, with good tolerance, cosmesis, and no local failures in the initial trial of 43 patients, now with a median follow up of 3 years.

Rebuttal of counter arguments

Opponents of APBI decry the treatment based on multiple arguments, including survival concerns, selection bias, and lack of adequate studies proving efficacy. Although these concerns are natural for any new treatment paradigm, the arguments appear to be overstated and in some cases contradictory.

Table 3

Three trials reporting negative experiences with partial breast irradiation

				Local recurrence	
Trial	Technique	Selection criteria	Quality assurance	Whole breast	Partial breast
Christies Hospital [25]	Electron beam quadrant	No margin, stage, or histologic criteria	No image guidance or verification of coverage	8%	34%
Guys Hospital [26]	Cs137 MDR, 45 Gy	Positive margins, nodes, EIC	Dose, targeting, and volume issues	NA	20%
London Regional [28]	Ir192 HDR	Positive nodes, EIC	Small volume implants	NA	16%

EIC, extensive intraductal component; HDR, high-dose rate; MDR, medium-dose rate.

Table 4

Published national professional society recommendations for accelerated partial breast irradiation

	American Brachytherapy Society recommendations 1 [27]	American Society of Breast Surgeons recommendations 2 [29]
Age (years)	>45	>50
Diagnosis	Unifocal, invasive ductal carcinoma	Invasive ductal carcinoma or ductal carcinoma *in situ*
Tumor size	<3 cm	<2 cm
Surgical margin	Negative microscopic surgical margins of excision	Negative microscopic surgical margins of at least 2 mm in all directions
Node status	N0	N0

First, arguments concerning survival are directly contradictory to those of selection bias and over-treatment of patients who could be observed. The survival argument is based solely on an as yet unpublished meta-analysis of multiple randomized trials of lumpectomy with or without radiation [24]. Using a meta-analysis as sole support for any argument is risky due to methodological concerns. Using a meta-analysis with an arm receiving no radiotherapy as an argument against APBI is clearly flawed. Although absolute equivalence of APBI to standard whole breast irradiation remains to be demonstrated, it would be difficult to deny reasonable efficacy, making a survival disadvantage highly unlikely.

The contradictory argument, that of over-selection of those patients who do not actually need treatment, cannot be supported by the literature. Even well selected quadrantectomy trials show an advantage of radiotherapy [1]. The growing data pool supports treatment of the correct subset of patients (Table 2). The importance of patient selection and careful treatment delivery cannot be over-emphasized. Three negative experiences with partial breast irradiation exist in the literature and all support, by their failure, the concept of careful selection and treatment quality assurance [25,26,28]. The trials used different techniques, including electron beam, iridium, and cesium needle brachytherapy. The details are summarized in Table 3. The studies share a lack of careful attention to patient selection and/or technique, which would be considered substandard by today's guidelines. In general, if a patient is not a good candidate for breast conservation because of their tumor characteristics, then they are not candidates for APBI. In addition, after selection, treatment must be performed with care given to defining and treating the target adequately; otherwise, both local control and toxicity results suffer. Modern image-guided brachytherapy performed with high dose rate remote afterloaders leads to well defined, highly assured dose delivery.

Although additional study is warranted both to demonstrate equivalence and further refine selection criteria, two professional societies have published guidelines for APBI with useful selection criteria (Table 4) [28,29]. The guidelines are conservative and represent our current state of knowledge of appropriate selection. Both societies recommend enrollment in clinical trials if possible and adequate informed consent in all cases. The process of acquiring informed consent, as discussed by Arthur [30], should include providing the prospective patient with information regarding the status of the evidence supporting APBI.

Conclusion

APBI is gaining acceptance in the management of early breast cancers, and this is related to both improved delivery techniques and from multiple single institutions reporting positive experiences. Studies are ongoing and include an upcoming phase III trial sponsored by the National Surgical Adjuvant Breast and Bowel Project/Radiation Therapy

Oncology Group. Hopefully, this trial will offer a definitive answer regarding equivalency and additional guidelines for patient selection. In the 10 years before the data are mature, physicians will need to examine the currently available data and determine whether their patients are appropriate candidates for APBI.

Competing interests

The author is a technical consultant for Proxima Therapeutics.

References

1. Veronesi U, Marubini E, Mariani L, Galimberti V, Luini A, Veronesi P, Salvadori B, Zucali R: **Radiotherapy after breast-conserving surgery in small breast carcinoma: Long-term results of randomized trial.** *Ann Oncol* 2001, **12:**997-1003.
2. Vicini FA, Kestin L, Chen P, Benitez P, Goldstein NS, Martinez A: **Limited-field radiation therapy in the management of early-stage breast cancer.** *J Natl Cancer Inst* 2003, **95:**1205-1211.
3. Cuttino LW, Arthur DW, Todor DA, *et al.*: **CT- guided multi-catheter insertion technique for partial breast brachytherapy (PBB): Reliable target coverage and dose homogeneity.** *Brachytherapy* 2003, **2:**41-68.
4. Hebert-Croteau N, Brisson J, Latreille J, Blanchette C, Deschenes L: **Compliance with consensus recommendation for the treatment of early stage breast carcinoma elderly women.** *Cancer* 1999, **85:**1104-1113.
5. Athas WF, Adams-Cameron M, Hunt WC, Amir-Fazli A, Key CR: **Travel distance to radiation therapy and receipt of radiotherapy following breast conserving surgery.** *J Natl Cancer Inst* 2000, **92:**269-271.
6. Nattinger AB, Hoffmann RG, Kneusel RT, Schapira MM: **Relation between appropriateness of primary therapy for early-stage breast carcinoma and increased use of breast conserving surgery.** *Lancet* 2000, **356:**1148-1153.
7. Baxter NN, Virnig BA, Durham SB, Tuttle TM: **Trends in the treatment of ductal carcinoma in situ of the breast.** *J Natl Cancer Inst* 2004, **96:**443-448.
8. Vicini FA, Baglan KL, Kestin LL, Mitchell C, Chen PY, Frazier RC, Edmundson G, Goldstein NS, Benitez P, Huang RR, *et al.*: **Accelerated treatment of breast cancer.** *J Clin Oncol* 2001, **19:** 1993-2001.
9. Keisch M, Vicini F, Kuske RR, Hebert M, White J, Quiet C, Arthur D, Scroggins T, Streeter O: **Initial clinical experience with the MammoSite breast brachytherapy applicator in women with early stage breast cancer treated with breast conserving therapy.** *Int J Radiat Oncol Biol Phys* 2003, **55:**289-293.
10. Baglan KL, Sharpe MB, Jaffray D, Frazier RC, Fayad J, Kestin LL, Remouchamps V, Martinez AA, Wong J, Vicini FA: **Accelerated partial breast irradiation using 3D conformal radiation therapy (3D-CRT).** *Int J Radiat Oncol Biol Phys* 2003, **55:**302-311.
11. Vaidya JS, Baum M, Tobias JS, D'Souza DP, Naidu SV, Morgan S, Metaxas M, Harte KJ, Sliski AP, Thomson E: **Targeted intra-operative radiotherapy (Targit): an innovative method of treatment for early breast cancer.** *Ann Oncol* 2001, **12:**1075-1080.
12. Veronesi U, Orecchia R, Luini A, Gatti G, Intra M, Zurrida S, Ivaldi G, Tosi G, Ciocca M, Tosoni A, *et al.*: **A preliminary report of intraoperative radiotherapy (IORT) in limited-stage breast cancers that are conservatively treated.** *Eur J Cancer* 2001, **37:** 2178-2183.
13. Holland R, Veling SHJ, Mravunac M, Hendriks JH: **Histologic multifocality of Tis, T1-2 breast carcinomas: Implications for clinical trials of breast-conserving surgery.** *Cancer* 1985, **56:**979-990.
14. Imamura H, Haga S, Shimizu T, Watanabe O, Kinoshita J, Nagumo H, Kajiwara T, Aiba M: **Relationship between morphological and biological characteristics of intraductal components accompanying invasive ductal breast carcinoma and patient age.** *Breast Cancer Res Treat* 2000, **62:**177-184.
15. Ohtake T, Abe R, Kimijima I, Fukushima T, Tsuchiya A, Hoshi K, Wakasa H: **Intraductal extension of primary invasive breast carcinoma treated by breast-conservative surgery.** *Cancer* 1995, **76:**32-45.
16. Goldstein NS, Kestin L, Vicini FV: **Factors associated with ipsilateral breast failure and distant metastasis in patients with invasive breast carcinoma treated with breast conservation therapy.** *Am J Clin Pathol* 2003, **120:**485-488.
17. Clark RM, McCulloch PB, Levine MN, Lipa M, Wilkinson RH, Mahoney LJ, Basrur VR, Nair BD, McDermot RS, Wong CS, *et al.*: **Randomized clinical trial to assess the effectiveness of breast irradiation following lumpectomy and axillary dissection for node-negative breast cancer.** *J Natl Cancer Inst* 1992, **84:**683-689.
18. Uppsala-Oreboro Breast Cancer Study Group: **Sector resection with or without postoperative radiotherapy stage I breast cancer: a randomized trial.** *J Natl Cancer Inst* 1990, **82:**277-282.
19. Fisher B, Anderson S: **Conservative surgery for the management of invasive and noninvasive carcinoma of the breast: NSABP trials.** *World J Surg* 1994, **18:**63-69.
20. Holli K, Saaristo R, Isola J, Joensuu H, Hakama M: **Lumpectomy with or without postoperative radiotherapy for breast cancer with favourable prognostic features: Results of a randomized study.** *Br J Cancer* 2001, **84:**164-169.
21. Fisher B, Anderson S, Bryant J, Margolese RG, Deutsch M, Fisher ER, Jeong JH, Wolmark N: **Twenty-year follow-up of a randomized trial comparing total mastectomy, lumpectomy, and lumpectomy plus irradiation for the treatment of invasive breast cancer.** *N Engl J Med* 2002, **347:**1233-1241.
22. Polgar C, Sulyok Z, Fodor J, Orosz Z, Major T, Takacsi-Nagy Z, Mangel LC, Somogyi A, Kasler M, Nemeth G: **Sole brachytherapy of the tumor bed after conservative surgery for T1 breast cancer: five-year results of a phase I-II study and initial findings of a randomized phase III trial.** *J Surg Oncol* 2002, **80:** 121-128.
23. Kuske RR, Bolton JS: *A Phase I/II Trail to Evaluate Brachytherapy as the Sole Method of Radiation Therapy for Stage I and II Breast Carcinoma. Radiation Therapy Oncology Group Publication no. 1055.* Philadelphia, PA: Radiation Therapy Oncology Group; 1995.
24. Storme G, Van de Steene J, Vinh-Hung V, for the Open Meta-Analysis Project; Oncologisch Centrum, AZ-VUB, Brussels, Belgium: **Radiation after lumpectomy for breast cancer improves survival: Lack of evidence was not lack of an effect [abstract 332].** *Proc Am Soc Clin Oncol* 2003, **22:**83.
25. Ribeiro GG, Magee B, Swindell R, Harris M, Banerjee SS: **The Christie Hospital breast conservation trial: an update at 8 years from inception.** *Clin Oncol (R Coll Radiol)* 1993, **5:**278-283.
26. Fentiman IS, Deshame V, Tong D, Winter J, Mayles H, Chaudary MA: **Caesium (137) implant as sole radiation therapy for operable breast cancer: a phase II trial.** *Radiother Oncol* 2004, **71:** 281-285.
27. Arthur DW, Vicini FA, Kuske RR, Wazer DE, Nag S; American Brachytherapy Society: **Accelerated partial breast irradiation: an updated report from the American Brachytherapy Society.** *Brachytherapy* 2002, **1:**184-190.
28. Perera F, Yu E, Engel J, Holliday R, Scott L, Chisela F, Venkatesan V: **Patterns of breast reoccurrence in a pilot study of Brachytherapy confined to the lumpectomy site for early breast cancer with six years' minimum follow up.** *Int J Radiat Oncol Biol Phys* 2003, **57:**1239-1246.
29. American Society of Breast Surgeons: *Consensus Statement for Accelerated Partial Breast Irradiation from the American Society of Breast Surgeons* [http://www.breastsurgeons.org/officialstmts/officialstmt3.shtml]
30. Arthur D: **Accelerated partial breast irradiation: a change in treatment paradigm for early breast cancer.** *J Surg Oncol* 2003, **84:**185-191.
31. King TA, Bolton JS, Kuske RR, Fuhrman GM, Scroggins TG, Jiang XZ: **Long-term results of wide-field brachytherapy as the sole method of radiation therapy after segmental mastectomy for Tis,1,2 breast cancer.** *Ann J Surg* 2000, **180:**299-304.