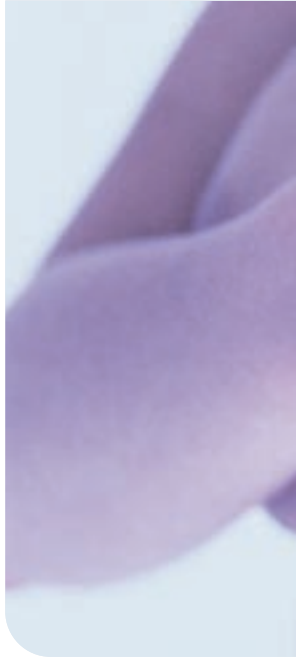

DEVELOPMENTS IN PARTIAL BREAST IRRADIATION

Its potential role in breast-conserving therapy for breast cancer

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Top-line summary

The advent of breast-conserving therapy — partial mastectomy followed by radiotherapy (RT) — for most patients with Stage 1–2 breast cancer has focused attention on how radiation should be delivered for optimal overall results. The need for whole-breast irradiation is being questioned and several new techniques for delivering partial breast irradiation (PBI) have been developed. Technologies and methodologies have advanced considerably in recent years, and appear to provide efficacy comparable to that of conventional whole-breast irradiation while offering much more convenient scheduling. This article reviews a variety of different techniques under investigation for partial breast irradiation.

Local management of early-stage breast cancer has evolved over the past 30 years from radical mastectomy to breast-conserving therapy (BCT) consisting of partial mastectomy followed by radiotherapy.

The efficacy of BCT has been studied systematically in thousands of patients. After randomized trials comparing mastectomy to BCT showed equivalent local control and survival the National Institutes of Health Consensus indicated in its 1990 statement on early-stage breast cancer that breast-conserving surgery followed by radiotherapy (RT) was an appropriate and preferable treatment for most women with Stage 1 and 2 diesease.[1-7] Two of the original trials, the NSABP B-06 and the study of the European Institute of Oncology, have since published long-term data that continue to demonstrate results equivalent to those obtained with mastectomy, further supporting the use of BCT.[8,9]

Although the routine use of RT after partial mastectomy has been challenged, so far no subgroup of patients has been identified which did not benefit from radiation in terms of tumour local control.[10-12] The impact on survival is less clear. In a review of randomized studies comparing adjuvant radiation to no radiation in early-stage cancer treated with breast-conserving surgery, Whelan et al found no difference in survival.[13] In contrast, a recent meta-analysis of 15 published randomized trials involving over 9000 patients found that omission of RT was associated with a small increased risk of death.[14]

ISSUES IN WHOLE-BREAST IRRADIATION

Standard BCT applies RT to the whole breast, with or without a boost to the tumour bed, using daily treatments 5 days per week over a period of 5 to 7 weeks. This prolonged regimen can create logistical problems especially for elderly patients, working women and those who live far from radiotherapy centres. Indeed, although increasing numbers of patients undergo breast-conserving surgery, data from the U.S. National Cancer Institute Surveillance, Epidemiology and End Results Registry reveal a rising rate of omission of breast irradiation after surgery since 1990.[15]

Shorter radiation treatment protocols may be more acceptable to patients. A Canadian randomized trial successfully piloted one such protocol. Hypofractionated accelerated whole-breast

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irradiation (WBI) consisting of 42.4 Gy in 16 treatments given over 3 weeks was compared to the conventional 50 Gy in 25 fractions over 5 weeks. With a median followup of 4.8 years, results in terms of both local control and adverse effects were equivalent, and this accelerated regimen has become an accepted alternative to the conventional regimen, for at least the subset of patients studied.[16]

Another important question is whether the entire breast needs to be treated. The routine use of WBI is supported by the finding of multicentric disease, as found in studies of mastectomy specimens.[17,18] With extensive pathologic evaluation, residual foci were found in 26% to 36% of tumours 4 cm or less. These studies were done many years ago, however, when most tumours were palpable and mammography was far less sensitive in detecting multicentric disease. Although more recent investigations have not fully evaluated the presence of disease elsewhere in the breast, some studies focusing on the extent of intraductal component beyond the initial tumour[19,20] have shown infrequent DCIS beyond 1 cm (8% in Faverly et al's review[19]). Moreover, this was mostly seen in patients younger than 40 years.

Despite the frequency of multicentric disease, reports of randomized trials investigating conservative surgery with or without WBI reveal that most local failures occur in the vicinity of the surgical bed.[21-23] Long-term followup data show low rates of new primaries or recurrences in regions of the breast distant from the site of the primary tumour whether or not patients had received RT (**Table 1**). In patients who received WBI, Veronesi et al reported a rate of 0.63 per 100 woman-years for ipsilateral recurrence, which approaches that for contralateral breast cancers, 0.66 per 100 woman-years. This suggests that WBI does not prevent new primaries — which likely make up a substantial proportion of distant in-breast failures, with or without WBI.[9] Although the evidence is indirect, these results support the hypothesis that whole-breast RT may be unnecessary.

POTENTIAL ADVANTAGES OF PARTIAL BREAST IRRADIATION

An attractive investigational treatment approach, partial breast irradiation (PBI) dramatically shortens the duration of adjuvant breast irradiation, directly addressing one of the major practical problems of the standard treatment plan for many women with breast cancer. It is given in a single intraoperative treatment or in an accelerated course over 4 or 5 days, covering the surgical bed with 1–2 cm margins.

Techniques developed for accelerated PBI include brachytherapy using multiple catheters, single balloon catheter brachytherapy, intraoperative radiation and 3-dimensional conformal external beam RT (**Figure 1**). Patient selection is the most critical issue when considering PBI. This is well demonstrated by earlier reports on brachytherapy or electron beam delivered to the tumour bed as a sole treatment in unselected patients (**Table 2**). The unacceptably high rate of local recurrence can be explained by the inclusion of patients with large tumour size, positive margins or lobular histology, and those in whom axillary lymph node dissection was not done.[27-29] In their 2003 report on accelerated PBI, the American Brachytherapy Society recommends strict selection criteria as outlined in **Table 3**.[30] The American Society of Breast Surgeons has defined similar standards.[31] Accepted exclusion criteria include the presence of extensive intraductal component, lobular histology and younger age, all factors associated with higher risk of local recurrence. Many practitioners also exclude patients with ductal carcinoma in situ (DCIS), often considered to be multifocal disease.

PBI TECHNIQUES

Brachytherapy

Interstitial brachytherapy with placement of multiple catheters covering the surgical bed has been used for many years, first as a boost following whole-breast treatment and more recently as sole treatment. Typically, image-guided

TABLE 1. Incidence of failure elsewhere in the ipsilateral breast

Author	No. of patients	Partial mastectomy	Partial mastectomy + WBI
Randomized studies			
Fisher et al[21]	1265	2.7%	3.8%
Veronesi et al[22]	579	2.8%	0.6%
Clark et al[23]	837	3.7%	1.0%
Non-randomized BCT studies			
Gage et al[24]	1628	-	2.8%
Pierquin et al[25]	245	-	6.0%
Huang et al[26]	1339	-	3.6%

techniques — ultrasound, computed tomography or fluoroscopy — are used to insert 14 to18 or more catheters, ensuring proper target coverage. Three-dimensional dosimetric planning assures dose homogeneity. Several recent studies that incorporated adequate brachytherapy quality assurance have published excellent results in terms of local control, with local recurrence rates of only 0% to 4.4% (**Table 4**). Side effects and cosmetic outcome appear to be acceptable.[32-38]

A trial by Perera et al with one of the longest followups (not included in Table 4) reports 16% local failure.[39] This small pilot study has been criticized because it included some patients not generally considered suitable for PBI, and for its small treatment volumes using minimal margins beyond the surgical cavity. The poor results underline the importance of attention to meticulous treatment technique and selection criteria, and highlight the need for long-term followup data. Another study not listed in Table 4 is the Radiation Therapy Oncology Group Phase I/II study (RTOG 95-17), a PBI trial using brachytherapy. Published only in abstract form, results to date demonstrate the feasibility and acceptable toxicity rate of this technique across multiple institutions.[40] A Hungarian Phase III trial comparing brachytherapy alone to whole-breast RT is ongoing, so we anticipate further information to define the utility of this approach.

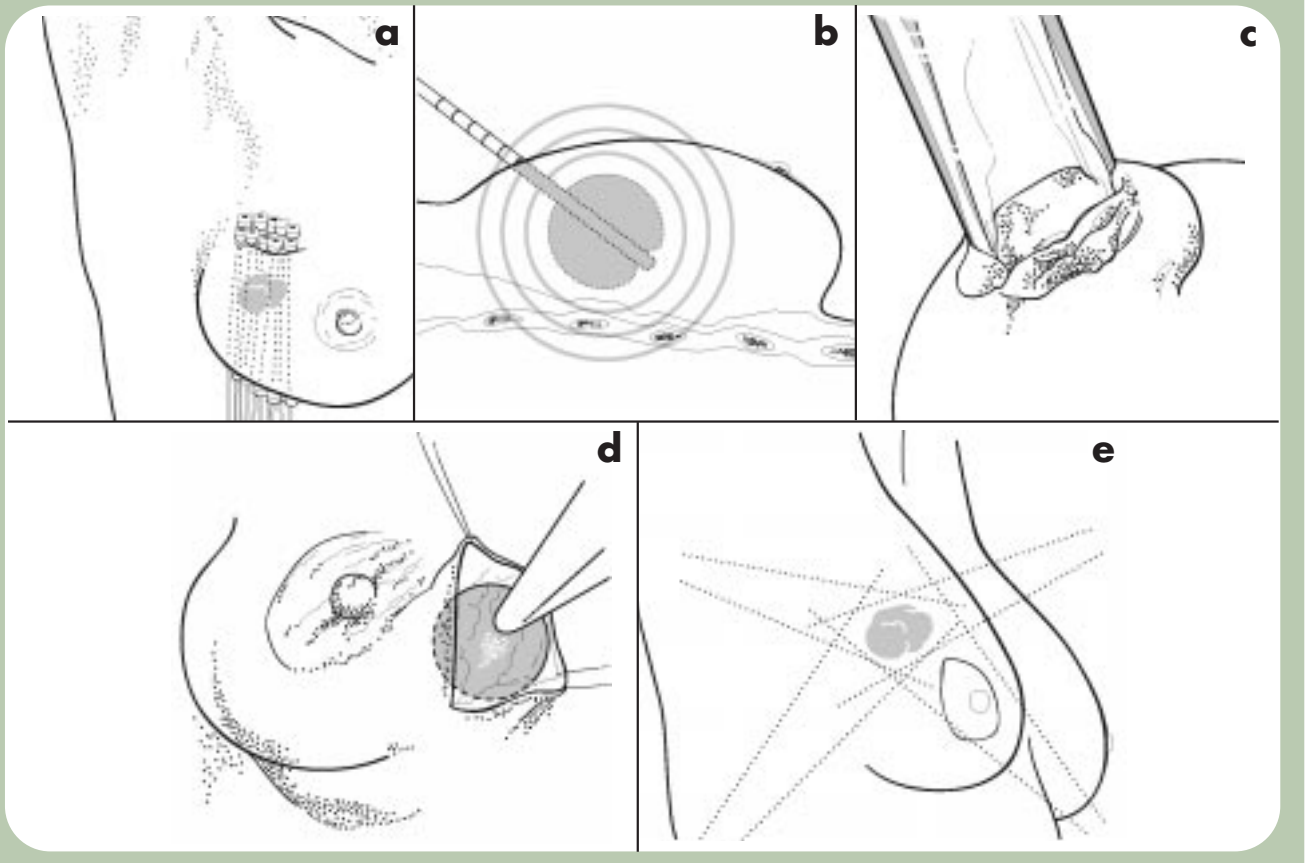
Multicatheter brachytherapy is a complex procedure that requires skilled radiation oncologists with special training.

TABLE 2. Initial experience using PBI

Author	No. of patients	Median followup (years)	Technique	Crude local recurrence
Clarke[27]	45	1.5	HDR* brachytherapy	15.6%
Fentiman[28]	27	6	LDR† brachytherapy	37%
Magee[29]	353	8	EBRT‡	19.5%

* HDR: high-dose rate
† LDR: low-dose rate
‡ external beam radiation therapy

FIGURE 1: Techniques for partial breast irradiation



a: Brachytherapy b: MammoSite c: Intraoperative RT with linear accelerator
d: Intraoperative RT with low energy X-rays e: 3D conformal RT

In 2002, the FDA approved a new brachytherapy device with a single balloon catheter, the MammoSite Radiation Therapy System, developed to provide a simpler technique for PBI. This dedicated applicator has an inflatable balloon catheter with a central lumen, which is placed in the lumpectomy cavity intraoperatively or postsurgically. The cavity is treated with a 1-cm margin using a central high-dose rate source, over a period of 5 days. In an initial clinical experience with 43 treated patients Keisch et al reported that MammoSite can be used safely with acceptable acute toxicity and good treatment delivery performance.[41,42] This device has limitations, however. Conforming the surface of the balloon to large or irregular surgical cavities can be difficult, leading to non-homogeneous doses in the treatment volume. Also, the risk of skin toxicity is substantial if the balloon is placed too close to the skin.

Intraoperative radiotherapy

Phase I/II studies conducted in Europe have tested new techniques of intraoperative radiotherapy (IORT) of the surgical bed, delivered in a single large fraction after quadrantectomy.[43,44] The European Institute of Oncology in Milan uses a dedicated portable linear accelerator that produces different electron energies and treats the surgical bed under direct visualization.[43] In England, University College Hospital reported a pilot study using a mobile spherical applicator placed inside the surgical cavity, able to deliver low-energy X-rays.[44] Although these IORT techniques are very convenient for patients, concerns have been raised, including the unavailability of complete pathologic assessment prior to delivery of treatment and the potential higher risk of toxicity on tissues radiated with a large single dose. Nevertheless, acceptable toxicity and encouraging early results reported by both groups have prompted Phase III trials.[45]

TABLE 3. Patient selection criteria for PBI recommended by the American Brachytherapy Society

All patients should:
- be appropriate candidates for standard BCT
- be ≥ 45 years old
- have invasive ductal carcinoma, unifocal
- have tumour size ≤ 3 cm
- have negative microscopic surgical margins
- be axillary node-negative by axillary dissection (Level I–II) or sentinel lymph node evaluation

Accelerated 3D conformal external beam RT

Another novel noninvasive method to treat the lumpectomy cavity is 3-dimensional conformal radiotherapy (3D-CRT) with an external photon beam. As with other PBI techniques, treatment is delivered over a short course of 5 days. The advantages over brachytherapy include no additional surgical procedure, potentially improved dose homogeneity, potentially reduced risk of complications, and widespread availability. The main disadvantage relates to the fact that the target may move with breathing and with differences in the patient's position for each treatment. To avoid missing the planned target a larger treatment volume is used.[46] Two Phase I/II studies have been reported[47,48] and an ongoing RTOG Phase I/II study is evaluating 3D-CRT confined to the tumour bed in selected Stage 1 and 2 breast cancer patients.

THE ROLE OF PARTIAL BREAST IRRADIATION IS UNFOLDING

In summary, interesting results are emerging from small Phase I/II studies and single institutions' experience using PBI in highly selected patients. Several new techniques have been developed to deliver radiation to the tumour bed, each with advantages and limitations. PBI is an innovative and exciting treatment approach for adjuvant RT of breast cancer with the potential to substantially reduce the duration of treatment. Long-term efficacy and toxicity, as well as the most appropriate techniques and parameters for selection of patients, remain to be fully clarified by carefully designed clinical trials. CE

TABLE 4. Recent experience of PBI using brachytherapy

Author	No. of patients	Median followup (months)	RT dose (Gy)	Local recurrence (%)
Low-dose rate brachytherapy				
King[32]	25	75	45	2
Krishnan[33]	24	47	20–25	0
Chen[34]	120	58	50	1.5*
Arthur[35]	18	31	45	0
Lawenda[36]	48	23.1	50–60	0
High-dose rate brachytherapy				
Chen[34]	76	24	32–34	1.5*
Wazer[37]	32	33	34	3
Polgar[38]	45	57	33–36.4	4.4
Arthur[35]	26	31	34	0

*local recurrence not reported separately for low-dose and high-dose rate groups

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DISCOURSE

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