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REVIEW ARTICLE

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Current status and perspectives of brachytherapy for breast cancer

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Abstract Before the era of breast-conserving therapy, brachytherapy implants were used to treat large inoperable breast tumors. In later years, interstitial brachytherapy with rigid needles or multiple flexible catheters has been used to deliver an additional (boost) dose to the tumor bed after breast-conserving surgery and whole-breast irradiation. Reexcision followed by reirradiation using interstitial breast implants has also been implemented as an alternative to mastectomy to treat ipsilateral breast local recurrence after previous breast-conserving therapy. In the past two decades, the new concept of accelerated partial breast irradiation opened a new perspective for breast brachytherapy. The first technique utilized in early accelerated partial breast irradiation studies was multicatheter interstitial brachytherapy. Beyond classical interstitial brachytherapy, recently, new intracavitary applicators have been developed in the United States to decrease the existing barriers against the widespread use of multicatheter brachytherapy. Furthermore, interstitial low-dose-rate seed implants have also been implemented as an alternative for stepping-source multicatheter brachytherapy. In this article, we give an overview of the past achievements, current status, and future perspectives of breast brachytherapy.

Key words Breast cancer · Brachytherapy · Local recurrence · Tumor bed boost · Accelerated partial breast irradiation

Introduction

The first report on the use of interstitial brachytherapy (BT) for the management of breast carcinoma was published in 1929.[1] The English surgeon Sir Geoffrey Keynes utilized interstitial radium needles to treat primary breast tumors. Before the era of breast-conserving therapy, BT implants (with or without external beam irradiation) were used to treat large inoperable tumors.[1,2] Later, interstitial BT with rigid needles (Fig. 1) or multiple flexible catheters (Fig. 2) was used to deliver an additional (boost) dose to the tumor bed after breast-conserving surgery (BCS) and whole-breast irradiation (WBI).[3,4]

Reexcision followed by interstitial breast implants has been also implemented as an alternative to mastectomy to treat ipsilateral breast local recurrence (LR) after previous breast-conserving therapy (including WBI).[5]

In the past two decades, the new concept of accelerated partial breast irradiation (APBI) opened a new perspective for breast BT.[6,7] The first technique utilized in early APBI studies was multicatheter interstitial BT.[8–15] The implementation of all other techniques (including three-dimensional [3D] conformal external beam irradiation and intraoperative radiotherapy) to deliver APBI was based on the success of these phase I-II clinical studies using low-dose-rate (LDR), high-dose-rate (HDR), and pulsed-dose-rate (PDR) multicatheter breast implants.[11,16–21] Beyond classical interstitial BT, recently new intracavitary applicators have been developed in the United States to decrease the existing barriers against the widespread use of multicatheter BT.[22–25] Furthermore, interstitial LDR seed BT has also been implemented as an alternative for stepping-source multicatheter BT.[26] In this article, we will give an overview of the past achievements, current status, and future perspectives of breast BT.

Brachytherapy as a boost after whole-breast irradiation (WBI)

The standard technique of radiotherapy (RT) after BCS is to treat the whole breast by teletherapy via tangential fields up to a total dose of 45 to 50 Gy.[27] The main rationale for giving an additional dose of 10 to 25 Gy to the tumor bed after WBI was based on the clinical observation that 67%–

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100% of ipsilateral breast recurrences originated from the vicinity of the original index lesion.[3] Based on the analysis of dose-response curves, Van Limbergen[4] reported that, above 50 Gy, an increase of 15 Gy would reduce the LR rate by a factor of 2. To date, three randomized trials have confirmed that a boost dose of 10 to 16 Gy after 50-Gy WBI significantly decreased the LR rate (Table 1).[3,28–31] Patient age less than 50 years, close, microscopically positive or unknown surgical margins, and the presence of an extensive intraductal component (EIC) are generally accepted as absolute indications for boost irradiation.[3,4] However, a controversy still exists regarding the optimal boost technique. Traditionally, LDR BT, electrons or photons have been used to deliver the boost dose to the tumor bed.[2,28,31–37] Later, HDR BT was also accepted as a safe alternative boost modality (Table 2).[38–48] Only a few reports have compared the outcome in patients treated with BT or external beam boost (Table 3).[2,29,30,32,34–37,42,43,47,49,50] In the majority of these studies, similar local control and cosmetic results have been reported for women boosted either with interstitial implants or with electrons/photons. Recently, Knauerhase et al.[47] reported that a median dose of 10 Gy HDR BT boost yielded a significantly lower 10-year actuarial LR rate compared to external beam boost (5.9% vs 12.5%; $P = 0.023$). In the European Organization for Research and Treatment of Cancer (EORTC) boost trial, the 10-year cumulative incidence of LR was 6.3% for the 1639 patients who received an electron boost, 5.3% in the 753 patients who received a photon boost, and only 3.7% in the 225 patients who had an interstitial LDR BT boost.[50] The difference was not significant ($P = 0.13$); however, the trial was not powered to detect the possible difference in local control between different boost modalities.

Based on these results, it seems that interstitial BT boost can be used in the conservative therapy of breast cancer with a low incidence of late side effects and with at least similar local tumor control to that achieved with percutaneous boost techniques. Furthermore, BT is preferable in some anatomical situations, especially in cases of deep-seated tumor bed in large-volume breasts. Obviously, BT offers the practical advantage of more conformal treatment of small volumes to higher doses and lower doses to the skin.[3–4] Van Limbergen[4] compared dose distributions of 4.5- to 15-MeV electron boosts to different settings of interstitial implants. He found that, for target depths reaching beyond 28 mm under the skin, interstitial implants had a ballistic advantage, delivering significantly lower skin doses than electron beams. Thus, in addition to external beam boost modalities, multicatheter BT remains a standard treatment option to deliver an additional dose to the tumor bed after BCS and WBI.

Brachytherapy in the treatment of breast recurrences

In spite of adequate BCS and RT, the rate of ipsilateral breast tumor recurrence is approximately 10%.[5,51,52] In

Table 1. Results of randomized "boost versus no boost" trials

Clinical trial	No. of patients	Technique	Boost dose (Gy)	Median FUP (years)	5-year LR Boost vs no boost (%)	10-year LR Boost vs no boost (%)	*P* value
EORTC[28]	5318	EBI/LDR BT	15–16	10.8	4.3 vs 7.3	6.2 vs 10.2	<0.0001
HNIO[3,29,30]	627	ELE/HDR BT	12–16	5	6.3 vs 13.3	NR	0.0017
Lyon[31]	1024	ELE	10	3.3	3.6 vs 4.5	NR	0.044

EORTC, European Organisation for Research and Treatment of Cancer; HNIO, Hungarian National Institute of Oncology; FUP, follow-up period; LR, local recurrence; EBI, external beam irradiation (photons or electrons); ELE, electrons; LDR, low-dose-rate; HDR, high-dose-rate; BT, brachytherapy; NR, not reported

Table 2. Results of HDR brachytherapy boost series

Institution	No. of patients	RT scheme (dose [Gy] × fraction no.)	Median FUP (years)	5-Year LR %	Annual LR %	Excellent/good cosmesis %
Barcelona[38]	294	2–2.5 × 8–11	5.8	9 (9-Year)	1.00	96
University Vienna[39]	274	7–12 × 1	8.7	3.9 (10-Year)	0.39	38
Brno[40]	215	8–12 × 1	5.8	1.5	0.30	73
Linz[41]	212	10 × 1	5.2	4.6	0.92	78
Saarbrücken[42]	202	12–15 × 1	>3	6.4[a]	NA	85
TMH, Mumbai[43]	153	10 × 1	3	8	1.6	83
Valencia[44]	125	4.4 × 3	7	4.2	0.84	77
Paris[45]	108	5 × 2	3.75	5.1	1.02	63
HNIO, Budapest[46]	98	4–4.75 × 3; 8–10.35 × 1	6.25	4.5	0.90	57
University Rostock[47]	75	8–12 × 1	7.8	5.9 (10-Year)	0.59	NR
Virgina C. University[48]	18	2.5 × 6	4.2	0	0	67
All patients	1774		3–8.7	0–9	0–1.6	38–96

RT: radiotherapy; FUP: follow-up period; LR: local recurrence; HNIO: Hungarian National Institute of Oncology; TMH: Tata Memorial Hospital; NR: not reported; NA: not applicable

[a] Crude rate

Table 3. Results of comparative studies with different boost techniques after whole-breast irradiation

Institution/Study	Technique	No. of patients	Boost dose (Gy)	Median FUP (years)	5-year LR % (*n*)	*P* value	Excellent/ good cosmesis %	*P* value
EORTC[49,50]	LDR	225	15	10.8	3.7 (10-Year)	0.13	NR	NA
	ELE	1639	16	10.8	6.3 (10-Year)		NR	
	Photons	753	16	10.8	5.3 (10-Year)		NR	
Thomas Jefferson[32]	LDR	654	15–20	3.3	7	0.21	91	NS
	ELE	416	20	3.3	8		95	
TMH, Mumbai[43]	HDR	153	10	3	8	0.43	83	<0.001 (HDR vs ELE)
	LDR	383	15–20	6	10		84	<0.00001 (LDR vs ELE)
	ELE	460	15	2.75	7		69	
Mallinckrodt Inst.[34]	LDR	119	10–20	5.6	6.7	NS	82	NS
	ELE	487	10–20	5.6	6.2		80	
WBH, Michigan[36]	LDR (I-125)	87	15	3.8	3 (8-Year)	0.46	94	0.59
	LDR (Ir-192)	190	15	6.3	9 (8-Year)		88	
	ELE	108	10–15	4.2	9 (8-Year)		90	
	Photons	15	10–15	4.5	0 (8-Year)		82	
Hopital Tenon, Paris[35]	LDR	169	15–25	6.7	8.1 (10-Year)	0.32	61	0.001
	ELE	161	5–20	6.9	13.5 (10-Year)		83	
HNIO, Budapest[29,30]	HDR	66	8–14.25	5	8.5	0.43	90	0.29
	ELE	237	16	5	5.6		86	
Saarbrücken[42]	HDR	202	12–15	>3	6.4[a]	NR	85	NA
	ELE	91	12–15	>3	8.8[a]		NR	
University Rostock[47]	HDR	75	8–12	7.8	5.9 (10-Year)	0.023	NR	NA
	ELE + photons	181	6–14	7.8	12.5 (10-Year)		NR	
Inst. Curie, Paris[b2]	LDR	126	20–25	8.1	24 (8-Year)	0.02	71	0.6
	Cobalt-60	129	11–36	8.1	39 (8-Year)		75	
Tufts University[37]	LDR	127	20	>6	3.9	0.62	90	0.001
	ELE	87	20	>6	3.2		78	

FUP: follow-up period; LR: local recurrence; LDR: low-dose-rate; HDR: high-dose-rate; ELE: electrons; EORTC: European Organisation for Research and Treatment of Cancer; HNIO: Hungarian National Institute of Oncology; TMH: Tata Memorial Hospital; WBH: William Beaumont Hospital; NS: not significant; NR: not reported; NA: not applicable

[a] Crude rate

[b] Patients treated with radiotherapy alone

Table 4. Results of multicatheter brachytherapy as reirradiation after repeat breast-conserving surgery

Institution	Technique	RT scheme (dose [Gy] × fraction no.)	Median FUP (years)	Second LR % (*n*)	Annual LR %	Cosmesis excellent/good %
Nice and Marseilles[53,54]	LDR	30 × 1; 45–50 × 1	4.2	15.9 (11 of 69)	3.8	NR
Beth Israel Med. Center[55]	LDR	30 × 1; 45 × 1	3	6.7 (1 of 15)	2.2	100[a]
University Paris[56]	LDR	30 × 1	3.3	26.7 (4 of 15)	8.1	16
University Vienna[57]	PDR	40–50/0.5–1[b]	5	0 (0 of 9)	0	29
HNIO, Budapest[58,59]	HDR	4.4 × 5	3	0 (0 of 11)	0	67
Barcelona[60]	HDR	2.5 × 12	NR (range, 1–12)	7.3 (3 of 41)	NR	90
All patients			3–5	11.9 (19 of 160)	0–8.1	16–100

HNIO, Hungarian National Institute of Oncology; RT, radiotherapy; FUP, follow-up period; LR, local recurrence; LDR, low-dose-rate; PDR, pulsed-dose-rate; HDR, high-dose-rate; NR, not reported

[a] Cosmetic results compared to baseline after second breast-conserving surgery

[b] Total dose/pulse dose

[c] Updated results by Polgár (see text; unpublished data)

such cases salvage mastectomy is the standard treatment; however, wide reexcision of the recurrent tumor is also a reasonable option for selected patients.[5] The incidence of a second LR after repeat conservative surgery has been reported to be in the range of 19% to 50%.[5] Theoretically, reirradiation after a second BCS may decrease the chance of a second LR. However, reirradiation of the whole breast with a significant dose is considered inappropriate because of the high risk of serious late side effects. Thus, several groups have suggested partial breast BT (i.e., multicatheter BT) as a possible treatment option to decrease the chance of a second LR after repeat BCS (Table 4).[5,53–60]

Maulard et al.[56] treated 15 patients by limited tumorectomy plus 30-Gy perioperative LDR BT for a 2.4-cm mean diameter isolated LR. With a median follow up of 40 months, 4 patients (26.7%) experienced a second LR.

In the combined series from Marseille and Nice, 69 patients with LR received a second lumpectomy followed by interstitial LDR BT.[53,54] The dose of salvage BT was

30 Gy ($n = 24$) in Nice and 45–50 Gy ($n = 45$) in Marseille. Eleven patients developed a second in-breast recurrence, yielding a 5-year actuarial LR rate of 22.6%. Grade 3 late complications occurred in 8.7% of patients. A significantly higher rate of grade 2–3 side effects was associated with a total dose (initial RT plus salvage BT) above 100 Gy (30% vs 4%; $P = 0.008$). The authors of the combined series recommended the delivery of an LDR BT dose of at least 46 Gy in two planes after initial WBI of 50 Gy.

Recently, authors from the Beth Israel Medical Center, New York, have reported the intial experience of a phase I-II study evaluating the feasibility of a second lumpectomy and breast BT for localized LR previously treated with BCS and RT.[55] The first six patients received an LDR BT dose of 30 Gy, while the BT dose was increased to 45 Gy for the other nine women. At a median follow-up of 36 months, only one patient (6.7%) developed a second LR. The 3-year rate of LR was 11%, without a negative impact of BT on the eventual cosmetic results.

At the Hungarian National Institute of Oncology (HNIO), 11 patients who developed LR after previous BCS and WBI were salvaged by a second BCS and fractionated (5 times 4.4 Gy), perioperative HDR BT.[58,59] According to the last update (unpublished results; C. Polgár), no second LR had occurred at a median follow up of 3 years, and two-thirds of the patients had good cosmetic results.

Another salvage HDR BT series was reported from Barcelona, Spain.[60] Overall, 41 patients with breast-only recurrences after conservative treatment were treated with a second lumpectomy followed by HDR BT of 30 Gy in 12 fractions over 5 days. The actuarial 12-year LR rate was only 14.8%, and cosmetic results were satisfactory in 90%.

To date, only one series has used PDR BT after repeat BCS to treat locally recurrent breast cancer.[57] Eight patients underwent a combination of PDR BT (12.5–28 Gy) and external beam RT (12–30 Gy), while nine patients were treated with PDR BT (40–50 Gy) alone. At a median follow up of 5 years, none of the nine patients treated with only PDR BT had a second LR.

Based on the promising results of single-institution studies, both European and American experts proposed multicentric phase II-III clinical trials to test the safety and efficacy of repeat BCS and APBI after an in-breast LR.[5,53,54,58,59] Optimal patient selection for such studies would include women with unicentric LRs measuring less than 2 cm without concurrent regional and distant recurrence diagnosed at least 3 years after the initial treatment of breast cancer.[5]

Accelerated partial breast brachytherapy (APBI)

APBI is an attractive treatment approach that shortens the 5- to 7-week course of conventional postoperative RT to 4–5 days. The acceleration of RT would eliminate some of the disadvantages of the extended treatment period, especially for elderly patients, working women, and those who live at a significant distance from the RT facility. The rationale for APBI is that the majority of LRs occur in close proximity to the tumor bed.[3,6,7] Fewer than 20% of LRs appear "elsewhere" in the breast, and the absolute number of such failures is very low (e.g., far less than 1% per year and similar to the rate of new contralateral tumors).[51,52] In addition, some elsewhere failures are likely to be new primary breast cancer that arose after the initial therapy and hence would not have been prevented by WBI. Thus, in the past two decades, APBI using LDR, HDR, or PDR interstitial implants has been intensively evaluated in phase I-II studies as a possible alternative to conventional WBI.[6,7]

Early APBI trials

Several European and American centers pioneered the use of different APBI regimens for unselected patients in the 1980s and early 1990s.[8–11,13,61,62] However, results in all but one of these early studies were poor, with high LR rates (Table 5). The high rates of local failure seen in these early APBI studies reflect inadequate patient selection critera and/or suboptimal treatment technique and lack of appropriate quality assurance (QA) procedures.[6,63–65]

Table 5. Results of early multicatheter brachytherapy APBI trials

Institution	Technique	RT scheme (dose [Gy]x fraction no.)	Median FUP (years)	Total LR % (*n*)	TR/MM % (*n*)	EF %	Annual LR %	Cosmesis excellent/ good %
Uzsoki Hosp.[61]	MDR	50 × 1	12	24 (17 of 70)	17 (12 of 70)	7 (5 of 70)	2	50
Guy's Hosp. I[9,10]	LDR	55 × 1	6	37 (10 of 27)	33 (9 of 27)	4 (1 of 27)	6.2	83
Guy's Hosp. II[11]	MDR	11 × 4	6.3	18 (9 of 49)	14 (7 of 49)	4 (2 of 49)	2.9	81
Florence Hosp.[8]	LDR	50–60	4.2	6 (7 of 115)	2 (2 of 115)	4 (5 of 115)	1.4	NR
Royal Devon/ Exeter[62]	HDR	20 × 2; 8 × 4; 6 × 6	1.5	16 (7 of 45)	9 (4 of 45)	7 (3 of 45)	10.7	95
London Reg. Ca. C[a13]	HDR	3.72 × 10	7.6	15 (6 of 39)	5 (2 of 39)	10 (4 of 39)	2	100
All patients			1.5–12	16 (56 of 345)	10 (36 of 345)	6 (20 of 345)	1.4–10.7	50–100

APBI: accelerated partial-breast irradiation; RT: radiotherapy; FUP: follow-up period; LR: local recurrence; TR/MM: true recurrence/marginal miss; EF: elsewhere failure; MDR: medium-dose rate; LDR: low-dose-rate; HDR: high-dose-rate; NR: not reported

[a] London Regional Cancer Center

Uzsoki Hospital's cobalt-needle APBI study

One of the first prospective APBI studies using interstitial implants was conducted in Hungary at the Uzsoki Hospital between 1987 and 1992.[61] Due to the limited availability of modern teletherapy equipments and the lack of iridium-192 wires in Hungary, special cobalt-60 sources were designed and manufactured to allow the manual afterloading of interstitial BT catheters. During this period, 70 patients were treated with these needles following conservative surgery, without the use of WBI. Any patient with a pathological T1 or T2 tumor that was clinically unifocal was eligible. A median of five (range, 2–8) catheters with 4-cm active length were implanted into the tumor bed (which was not delineated by surgical clips) in a single plane without template guidance. A dose of 50 Gy was prescribed at 5 mm from the surface of the sources, given in a single session of 10–22 h with 2.3–5.0 Gy per hour (medium-dose-rate; MDR). The volume included within the reference isodose surface was quite small (median, 36 cm^3). Updated 12-year results of this series showed that the crude LR rate was 24%, with 59% of patients having grade 3 or 4 complications.[61]

Unfortunately, in that era most patients did not have pre- or postoperative mammographic evaluation, and the vast majority of pathology reports did not contain such important information as pathological tumor size and the presence of multifocality. Other important pathological factors were also not assessed, such as pathological axillary node status (unknown for 80% of patients) and margin status (unknown for all patients). Hence, perhaps many or most of the patients treated in this study would not at all be considered eligible today for breast-conserving therapy. Therefore, it is likely that the high rate of LR in this study was due to the patients having persistent (not recurrent) tumors, due to inadequate patient selection criteria and radiological and pathological evaluation, as well as a very small, inadequate implant volume. The high rate of toxicity may have resulted from giving a high total dose (86 to 134 Gy LDR equivalent dose) delivered within a short overall treatment time without fractionation. American, Japanese, and European experts have declared that the defects in the Uzsoki Hospital's study cannot be used to disparage the concept of APBI, if properly performed.[6,63,64] Despite its obvious limitations, the pioneering experience of the Uzsoki Hospital subsequently served as a basis for the development of more successful APBI series at the HNIO, Budapest, carried out later.[6,14,19,20]

Guy's Hospital studies

Fentiman et al.[9–11] also explored the feasibility and limitations of partial breast BT, in two consecutive pilot trials performed at Guy's Hospital, London, United Kingdom. In the first study, conducted in 1987–1988, 27 patients were treated with LDR implants using rigid needles.[9,10] The target volume included a 2-cm margin around the tumor bed. The dose prescription was based on the Paris dosimetry system, with a dose of 55 Gy given over 5–6 days using manually afterloaded ^{192}Ir wires.[66] With a median follow up of 6 years, 10 of 27 patients (37%) experienced recurrence in the treated breast.[10] None of the patients developed breast fibrosis, and only 1 patient had telangiectasias. The cosmetic outcome was good or excellent in 83% of patients.

A second Guy's Hospital study enrolled 50 patients between 1990 and 1992.[11] Patient selection criteria and surgical and implant techniques were similar to those in the first Guy's Hospital series. An MDR remote-controlled afterloading system employing caesium-137 was used to give a total dose of 45 Gy in four fractions over 4 days. At a median follow up of 6.3 years, 9 of 49 patients (18%) developed a breast relapse. Only one LR (4%) occurred among patients with lesions smaller than 2 cm, while the rate was 35% for patients with tumors of 2 cm or larger. Cosmetic outcome was considered excellent or good in 81% of patients.

It is to be noted that the surgical techniques and patient selection criteria used in these studies were far from optimal. No attempt was made to achieve a wide excision either grossly or microscopically. As a consequence, the surgical margins were involved in 56% of patients in the first study and in 43% of patients in the second one. Furthermore, in the first study, 41% of patients had tumors containing EIC, and in both studies 44% had positive axillary lymph nodes.

Florence series

Between 1989 and 1993, Cionini et al.[8] in Florence, Italy, treated 115 patients with T1-2N0-1 tumors with quadrantectomy, axillary dissection, and LDR BT to the entire quadrant and the nipple, giving a dose of 50–60 Gy, using ^{192}Ir implants. Young patients, patients with positive or unknown margins, and patients with infiltrating lobular carcinoma were included in the study. Patients with positive axillary nodes (38%) received chemotherapy or tamoxifen. The 5-year actuarial LR rate was 6%. Cosmetic outcome and side effects were not reported.

Royal Devon/Exeter Hospital series

In a pilot study performed at the Royal Devon and Exeter Hospital in the United Kingdom, fractionated HDR interstitial BT was used to treat the quadrant after tumor excision in 45 patients.[62] Patients selected for BT alone had tumors smaller than 4 cm, grade 1 or 2 tumors, and clear or close margins. Three different fractionation schedules were used: 20 Gy given in two fractions; 28 Gy given in four fractions; and 32 Gy given in six fractions. The crude LR rate was 15.6% at a short follow up of 18 months. However, this study was also limited by the surgical techniques and pathological reports used, as axillary dissection was not performed routinely, and in many cases detailed histological findings were not available. Cosmetic outcome was excellent in 95% of patients.

London (Ontario) Regional Cancer Center's pilot study

One of the first APBI studies utilizing fractionated HDR BT was conducted in Canada.[13] Between 1992 and 1996, 39 patients with T1-2 breast cancers received 37.2 Gy in ten fractions over 1 week prescribed to a small volume (median, 30 cm^3) encompassing the surgical clips only. With a median follow up of 91 months, the 5-year actuarial LR rate was 16.2%. There were six breast recurrences, of which four occurred outside the implanted volume. However, this study has been criticized for inappropriately limiting the target volume to the boundaries of the excision cavity without adding any safety margin to sterilize possible residual tumor foci in the 1- to 2-cm vicinity of the tumor bed.[7,65]

Contemporary APBI trials

Based on the controversial results of earlier studies, several groups created APBI trial protocols incorporating stricter patient selection criteria and systematic QA procedures. As a result, the outcomes of these studies have been much improved (Table 6).[12,16–21,67–79]

Ochsner Clinic experience

The first group in the United States to evaluate the feasibility of APBI using multicatheter BT was King et al.,[12] at the Ochsner Clinic in New Orleans. Between 1992 and 1993, 50 patients (with 51 breast cancers) were treated with either 45-Gy LDR BT ($n = 25$) or 32-Gy HDR BT ($n = 26$) given in eight fractions of 4 Gy. All patients had tumors of less than 4 cm with negative margins. Patients with negative or up to three positive axillary nodes were eligible. Wide-volume implants were used to encompass the excision cavity, with 2-cm margins in each direction. At a median follow up of 75 months, only one breast recurrence (2%) and three regional nodal failures (6%) were observed. The authors compared the outcme of their patients with a matched control group of 94 patients who met the eligibility criteria for APBI but were treated with conventional WBI during the same time period. The two groups were similar for LR rates, cosmetic results, and grade 3 side effects.

William Beaumont Hospital (WBH) experience

One of the largest experiences using multicatheter BT to deliver APBI was published by the WBH group from Royal Oak, Michigan.[7,15,16,21] Between 1993 and 2001, 199 consecutive patients were treated with 50-Gy interstitial LDR ($n = 120$) or HDR ($n = 79$) BT. In the latter group, a total dose of 32 Gy in eight fractions ($n = 71$) or 34 Gy in ten fractions ($n = 8$) was delivered. Eligibility criteria included being older than 40 years, having infiltrating ductal carcinoma less than 3 cm in diameter, having negative surgical margins, and having negative or one to three positive axillary nodes. Patients with an EIC, pure infiltrating lobular histology, pure ductal carcinoma in situ, or clinically significant areas of lobular carcinoma in situ were excluded. All implants were designed to irradiate the lumpectomy cavity plus at least a surrounding 1- to 2-cm margin. According to the last updated report from Vicini et al.,[21] at a median follow up of 8.6 years, a total of six ipsilateral breast failures (3%) were observed, translating into 5-year and 10-year actuarial rates of 1.6% and 3.8%, respectively. Cosmetic results in 162 patients who had been followed for 5 or more years were considered to be good or excellent in 99%. Overall, 41 patients (20.6%) developed fat necroses, which were asymptomatic in 32 (78%).[16] The results of BT patients were compared with those in a matched cohort of 199 patients treated with conventional WBI at the same institution. There were no statistically significant differences in the 5-year actuarial rates of LR or regional recurrence.[7,15]

Hungarian National Institute of Oncology (HNIO) studies

Between 1996 and 1998, 45 selected patients with early-stage invasive breast cancer were treated with APBI using interstitial HDR implants at the HNIO, Budapest.[6,14,19,20,67] Patients were eligible for sole BT if they met all of the following conditions: unifocal tumor; tumor size 20 mm or less (pT1); microscopically clear surgical margins; pathologically negative axillary nodes or only axillary micrometastases (pN1mi); histological grade 1 or 2; and technical suitability for breast implantation. Exclusion criteria were: pure ductal or lobular carcinoma in situ (pTis); invasive lobular carcinoma; or the presence of EIC. During surgery, the boundaries of the excision cavity were marked with titanium clips. Implantation was performed 4–6 weeks after surgery under local anesthesia. The planning target volume (PTV) was defined as the excision cavity (delineated by the surgical clips) plus a margin of 1 to 2 cm. Single-, double-, and triple-plane implants were performed in 3, 34, and 8 patients (7%, 75%, and 18%), respectively. A total dose of 30.3 Gy ($n = 8$) or 36.4 Gy ($n = 37$) in seven fractions over 4 days was delivered to the PTV. The mean volume encompassed by the 100% isodose surface was 50 cm^3. Only 7 patients (16%) received adjuvant tamoxifen therapy.

A 12-year update of this study was reported, including comparison with the results of a control group treated during the same time period with conventional breast-conserving therapy.[20,67] The control group comprised 80 consecutive patients who met the eligibility criteria for APBI, but who were treated with 50-Gy WBI with ($n = 36$) or without ($n = 44$) a 10- to 16-Gy tumor bed boost. The 12-year actuarial rate of LR was not significantly different between patients treated with APBI (9.3%) and those treated with WBI (11.1%). There were no significant differences in either the 12-year probability of disease-free survival (75% and 74%, respectively), or cancer-specific survival (91% and 89%, respectively). The rate of excellent or good cosmetic results was 78% in the APBI group and 67% in the control group ($P = 0.045$). Similar incidences

Table 6. Results of contemporary multicatheter brachytherapy APBI trials

Institution/Study	Technique	RT scheme (dose [Gy]x fraction no.)	Median FUP (years)	Total LR % (*n*)	TR/MM % (*n*)	EF % (*n*)	Annual LR %	Excellent/good cosmesis %
HNIO, Budapest I[20,67]	HDR	4.33 × 7; 5.2 × 7	11.1	8.9 (4 of 45)	0 (0 of 45)	8.9 (4 of 45)	0.80	78
WBH, Michigan[16,21]	LDR/HDR	50 × 1; 4 × 8; 3.4 × 10	8.6	3.0 (6 of 199)	1.5 (3 of 199)	1.5 (3 of 199)	0.35	99
Örebro Med. Centre[17]	PDR	50/0.83[b]	7.2	6.0 (3 of 50)	2 (1 of 50)	4 (2 of 50)	0.83	56
Tufts Univ., Boston[68]	HDR	3.4 × 10	7	9.1 (3 of 33)	0 (0 of 33)	9.1 (3 of 33)	1.30	93
HNIO, Budapest II[19,67]	HDR	5.2 × 7	6.8	4.5 (4 of 88)	2.3 (2 of 88)	2.3 (2 of 88)	0.66	81
RTOG 95-17[69]	LDR/HDR	45 × 1; 3.4 × 10	6.7	6.1 (6 of 99)	5.1 (5 of 99)	2 (2 of 99)	0.91	NR
Ochsner Clinic[12]	LDR/HDR	45 × 1; 4 × 8	6.25	2 (1 of 51)	2 (1 of 51)	0 (0 of 51)	0.32	75
Ninewells Hosp.[70]	LDR	46–55 × 1	5.6	0 (0 of 11)	0 (0 of 11)	0 (0 of 11)	0	91
Univ. Navarra[71]	HDR	3.4 × 10	4.4	3.8 (1 of 26)	0 (0 of 26)	3.8 (1 of 26)	0.86	87
Osaka Medical Center[72]	HDR	6 × 6; 6 × 7	4.3	5.0 (1 of 20)	5.0 (1 of 20)	0 (0 of 20)	1.15	75
Germany/Austria[18]	PDR/HDR	50/0.6[b]; 4 × 8	4	2.2 (6 of 274)	1.1 (3 of 274)	1.1 (3 of 274)	0.55	92
Wisconsin Univ.[73]	HDR[c]	4 × 8; 3.4 × 10	4	2.9 (8 of 273)	NR	NR	0.72	NR
Univ. Kansas[74]	LDR	20–25 × 1	3.9	0 (0 of 25)	0 (0 of 25)	0 (0 of 25)	0	100
Masaryk Cancer Inst.[75]	HDR	3.4 × 10	3.7	5.2 (1 of 19)	0 (0 of 19)	5.2 (1 of 19)	1.41	100
Virginia C. Univ.[76]	LDR/HDR	45 × 1; 3.4 × 10	3.5	0 (0 of 44)	0 (0 of 44)	0 (0 of 44)	0	80
Osaka National Hosp.[77]	HDR	6 × 6; 6 × 7	2.6	4.4 (2 of 45)	4.4 (2 of 45)	0 (0 of 45)	1.69	NR
Univ. Perugia[78]	HDR	4 × 8	2.5	0 (0 of 80)	0 (0 of 80)	0 (0 of 80)	0	99
Massachusett Gen. Hosp.[79]	LDR	50–60 × 1	1.9	0 (0 of 48)	0 (0 of 48)	0 (0 of 48)	0	96
All patients			1.2–11.1	3.2 (46 of 1430)	1.6 (18 of 1157)	1.8 (21 of 1157)	0–1.69	56–100

APBI: accelerated partial breast irradiation; FUP: follow-up period; LR: local recurrence; TR/MM: true recurrence/marginal miss; EF: elsewhere failure; LDR: low-dose-rate; HDR: high-dose-rate; PDR, pulsed-dose-rate; HNIO: Hungarian National Institute of Oncology; RTOG: Radiation Therapy Oncology Group; WBH: William Beaumont Hospital; NR: not reported

[a] Updated results by Strnad (see text; unpublished data)

[b] Total dose/pulse dose

[c] Twenty-six patients (9.5%) were treated with the MammoSite (Cytyc Corporation, Marlborough, MA, USA) applicator

of fat necrosis were identified in both the APBI (38%) and control (31%) groups (P, not significant [NS]).

Based on the encouraging results of the first HNIO study, a randomized study was conducted between 1998 and 2004 at the same institution in Budapest.[6,14,19,67] Initial eligibility criteria were similar to those for the previous study, although following the publication of the EORTC boost trial in 2001, patients aged 40 years or younger were excluded. In addition, the trial allowed patients with breast technically unsuitable for performing interstitial implantation to enroll and be treated with an external-beam (EB) approach. By May 2004, 258 eligible patients had been randomized to receive either 50-Gy WBI ($n = 130$) or partial breast irradiation (PBI; $n = 128$). The latter consisted of either 36.4 Gy (given over 4 days using 7 fractions of 5.2 Gy each) with HDR multicatheter BT ($n = 88$) or limited-field electron irradiation ($n = 40$) giving a dose of 50 Gy in 25 fractions. One-, two-, three-, or four-plane implants were performed in 1 (1%), 47 (55%), 37 (43%), and 1 patients (1%), respectively. The mean volume encompassed by the reference isodose surface was 62 cm^3. The majority of patients in both arms (70%) received adjuvant hormone therapy.

The 5-year results of the Hungarian randomized study were published in 2007.[19] In the most recent analysis, at a median follow-up time of 6.8 years, there was no significant difference in local and regional tumor control, or in disease-free, cancer-specific, or distant metastasis-free survival between the two treatment arms (Table 7).[67] In univariate analysis patient age of 40 years or less was found to be the most important negative prognostic factor for LR (unpublished results; C. Polgár). The 5-year actuarial rate of LR for patients below the age of 41 was 22.2%, in contrast to older women, with a corresponding LR rate of 3% ($P = 0.016$; hazard ratio, 6.69). Therefore, we strongly suggest the exclusion of such young patients from APBI protocols.

The rate of an excellent-to-good cosmetic result was 77% in the PBI group (81% after HDR BT; 68% after EB) and 65% in the control group ($P_{WBI/PBI} = 0.024$). In a separate analysis, the 4-year actuarial rates of fat necrosis were 31.9%, 36.5%, and 17.7% after WBI, HDR BT, and EB, respectively.[80] However, the incidence of symptomatic fat necrosis was not significantly different after WBI (8.5%), HDR-BT (11.4%), and EB (7.5%). Among the evaluated patient-, tumor-, and treatment related variables, only larger bra cup size was significantly associated with the incidence of fat necrosis.

Örebro series

The first APBI study using PDR BT was begun in December 1993 at the Örebro Medical Centre in Sweden.[17] Inclusion criteria included being age 40 years or older with a unifocal breast cancer measuring 5 cm or less (without an EIC), which was excised with clear inked margins, and up to three positive axillary lymph nodes. Free-hand plastic tube implants were used to cover the PTV, defined as the excision cavity plus 3-cm margins. Fifty patients were treated, to a total dose of 50 Gy, using pulses of 0.83 Gy delivered over 5 days. At a median follow-up time of 86 months, the 7-year actuarial LR rate was 4%. Grade 2 and 3 fibrosis located in the treatment volume was reported in 18% and 8%, respectively. Grade 2 and 3 telangiectasia developed in 14% and 8% of patients, respectively. Fat necrosis was seen in 10 patients (20%). The oncology nurse scored the cosmetic outcome as good or excellent in 56% of the patients. However, the authors noted that surgical factors (volume reduction, deformation, scarring) were associated with cosmetic failure at least in 44% of the patients.

German-Austrian multicentric APBI trial

In the year 2000 two German (Erlangen and Leipzig) and two Austrian (Vienna and Linz) institutions decided to start the first European multi-institutional phase II trial to investigate the efficacy and safety of HDR/PDR multicatheter APBI.[6,18] The four participating centers recruited 274 patients between 2000 and 2005.

Patients were eligible for APBI if they had a tumor diameter of 3 cm or less, complete resection with clear margins of 2 mm or more, pathologically negative axillary lymph nodes, or singular nodal micrometastasis (pN1mi), hormone receptor-positive tumors, and patient age 35 years or more. Patients were excluded from the protocol if they showed a multicentric invasive growth pattern, poorly differentiated tumors, residual microcalcifications, EIC, or lymph vessel invasion.

Among the 274 patients, 175 (64%) received PDR and 99 (36%), HDR BT. The prescribed reference dose in the PDR BT group was 49.8 Gy in 83 pulses of 0.6 Gy each h. The prescribed reference dose for HDR BT was 32 Gy in eight fractions of 4 Gy, twice daily. Total treatment time for both groups was 5 days. The planning target volume (PTV)

Table 7. Seven-year actuarial results of the Budapest phase III APBI trial

Treatment arm	LR% (n)	RR% (n)	CSS%	DFS%	DMFS%
Partial breast irradiation	5.1 (6 of 128)	1.6 (2 of 128)	96.2	86.3	91.0
Whole-breast irradiation	3.3 (4 of 130)	1.7 (2 of 130)	93.9	89.0	92.3
P value	0.53	0.99	0.45	0.65	0.94

APBI: accelerated partial breast irradiation; LR: local recurrence; RR: regional recurrence; CSS: cancer-specific survival; DFS: disease-free survival; DMFS: distant metastasis-free survival

was confined to the tumor bed plus a safety margin of 2–3 cm in each direction. Two- or three-plane implants were used in 58% and 42%, respectively. The mean implant volume enclosed by the 85% reference dose was 75 cm^3.

According to the last update of this study (personal communication; V. Strnad and O.J. Ott, June 2008), six patients (2.2%) had developed ipsilateral breast recurrence after a median follow up of 48 months, yielding a 4-year actuarial LR rate of 0.6%. Physicians judged the cosmetic results as excellent or good in 92%, and as fair in 8% of the women. Patients subjectively judged the cosmetic outcome as excellent or good in 91.6%, fair in 6.9%, and poor in 1.5%. Immediately before the beginning of BT, physicians and patients had declared cosmetic outcome as good to excellent in 93.4% and 91.5%, respectively. This indicates that the use of multicatheter BT did not significantly impact cosmetic outcome after a median follow up of 4 years. At a median follow up of 32 months, the rate of histologically proven asymptomatic fat necrosis was 4.7% (n = 13), and no patient underwent surgical intervention because of fat necrosis-related pain.[18]

Radiation Therapy Oncology Group (RTOG) 95-17 phase II APBI trial

Based on the success of single-institution phase I-II APBI studies, the RTOG conducted a multi-institutional phase II trial investigating the use of multicatheter BT as the sole method of RT after BCS.[69] Eligibility criteria included unicentric infiltrating nonlobular breast carcinomas of 3 cm or less that had been resected with clear margins, with none to three positive axillary nodes without extracapsular extension. Ineligibility criteria included evidence of EIC or any lobular component.

Between 1997 and 2000, 99 eligible patients were enrolled from 11 institutions. Two-thirds of the patients (n = 66) received HDR BT with a prescribed dose of 34 Gy in ten fractions, and one-third (n = 33) were treated with 45-Gy LDR BT. The PTV was defined as a 2-cm margin peripheral to the cavity and 1 cm anteriorly and posteriorly.

At a median follow up of 6.7 years, the estimated 5-year LR rate for the entire cohort was 4% (3% in the HDR and 6% in the LDR groups). It is to be noted that patients of all ages were eligible for the study. Of the six LRs, four occurred in patients younger than 50 years. The crude rates of LR for patients below and above the age of 50 years were 19% and 2.6%, respectively.

University of Wisconsin experience

In the prospective APBI study of the Wisconsin University, eligibility criteria similar to those in the RTOG 95-17 trial were used.[73] Between 2000 and 2005, 273 patients were treated with a total dose of 32–34 Gy in eight to ten twice-daily fractions within 4–5 days, using HDR BT. The majority of patients (n = 247) were treated using multicatheter BT, while the others (n = 26) were treated with a MammoSite (Cytyc Corporation, Marlborough, MA, USA) applicator. For study purposes, the authors separated their patients into two groups: high-risk patients, who satisfied one or more of the so-called "high-risk" criteria, i.e., age less than 50 years, estrogen receptor-negative, and/or positive lymph nodes (n = 90), and low-risk patients, who comprised the remainder of the cohort (n = 183). At a median follow up of 4 years, the actuarial 5-year LR rates in the high- and low-risk groups were 6.4% and 2.2%, respectively. Although the difference was not significant (P = 0.29), the threefold higher LR rate in the high-risk group emphasizes the necessity of keeping the conservative eligibility criteria successfully used in other APBI series.

Japanese experience

To date, two Japanese APBI series using HDR BT have been reported in the literature.[72,77] In both studies broader patient selection criteria were used than in the European and American studies, including patients younger than 40 years, with tumors containing an EIC or excised with close/positive surgical margins. An aggressive fractionation schedule of 36 to 42 Gy total dose in 6-Gy fractions was used by the authors to compensate for the high-risk profile of the patient groups.

In the pilot study of Nose et al.,[72] only 1 of 20 patients (5%) had experienced an LR at a median follow up of 52 months. The rates of good-to-excellent cosmetic results in patients treated with 36- and 42-Gy total doses were 87% and 40%, respectively.

Based on the acceptable results of the study at the Osaka Medical Center, a second Japanese APBI trial was initiated in 2002, at the Osaka National Hospital, using similar eligibility criteria, total dose, and fractionation.[77] Recently, Yoshida et al.[77] published the preliminary results of this trial. At a median follow up of 31 months, 2 of the 45 patients (4.4%) had developed an LR. However, wound complications occurred in 7 patients (16%), and 2 patients (4.4%) had rib fracture near the implanted area. The authors found that the nonadministration of prophylactic antibiotics, the open cavity implant technique, and large V100 (volume covered by the 100% indose shell), V150, and V200 were associated with a significantly higher risk of developing wound complications.

Although the preliminary results of these Japanese studies are promising, the annual LR rates (1.15% in the former and 1.69% in the latter study) were significantly higher than the annual LR rates (ranging from 0.32% to 0.83%) reported from European and American studies using strict eligibility criteria. Furthermore, longer follow up is needed to prove the safety of the significantly higher total dose and dose per fraction used in these Japanese studies.

Other multicatheter APBI experiences

Additional experiences with multicatheter APBI have been published by other groups (with smaller sample sizes and/or

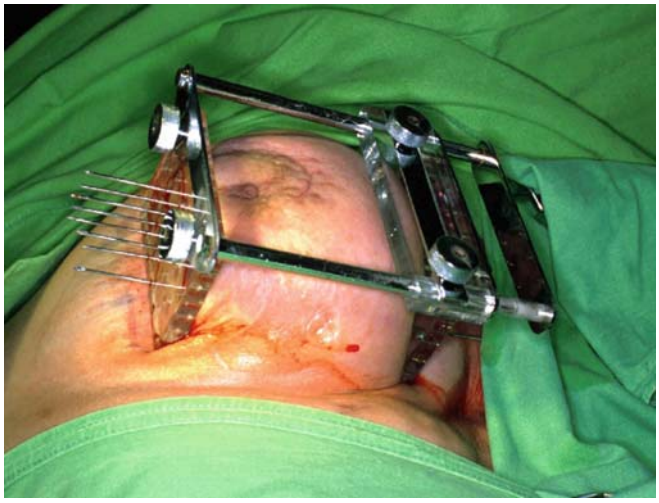

Fig. 1. Template-guided interstitial breast implanation with steel-needles

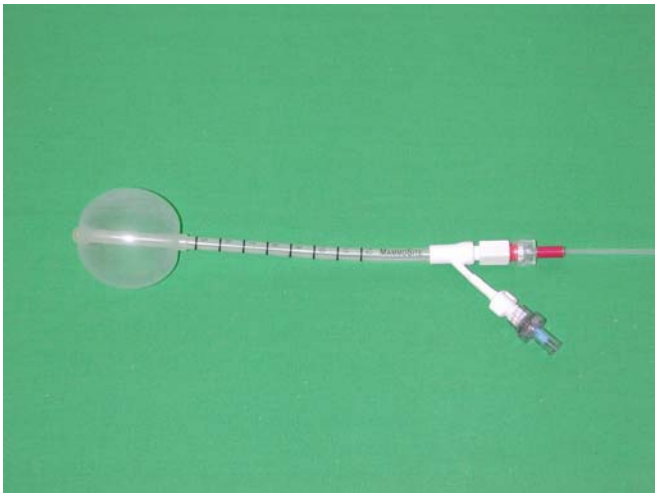

Fig. 3. The MammoSite (Cytyc Corporation, Marlborough, MA, USA) brachytherapy device for intracavitary breast brachytherapy

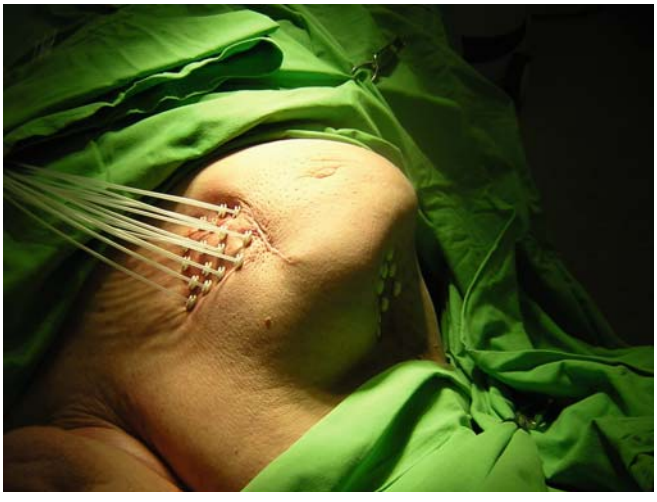

Fig. 2. Interstitial multicatheter breast implantation

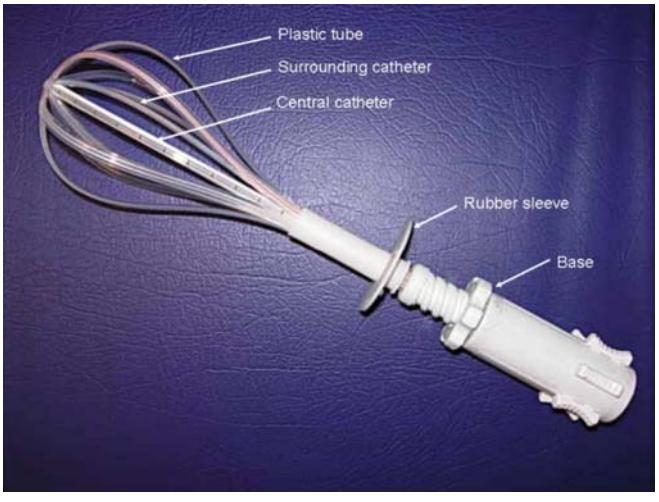

Fig. 4. The ClearPath (North American Scientific Inc., Chatsworth, CA, USA) hybrid brachytherapy device for intracavitary breast brachytherapy

less mature follow up) (see Table 6). In the majority of these trials, local tumor control rates were similar to those achieved in other breast-conserving series using conventional WBI.[68,70,71,74–76,78,79]

APBI using permanent LDR seed implants

Recently, a new technique of APBI using ^{103}Pd permanent seed implants was implemented by Pignol et al.[26] Investigators from the University of Toronto implanted 16 patients with a mean of 70 seeds per patient. A dose of 90 Gy was prescribed as the minimal peripheral dose that was set to cover the PTV, defined as the lumpectomy cavity plus a margin of 1 cm. Patients with a PTV volume greater than 70 cm^3 were excluded, to avoid the implantation of an excessive amount of radioactivity. During the study the coverage index was improved with operator experience, from a mean of 0.74 to 0.87, and no significant seed motion was noticed on the 2-month computed tomography (CT) scans. In spite of the feasibility of breast seed implantation, only 52% of eligible patients received the treatment. Thus, further studies are necessary to define the practicability and efficacy, and the risks associated with this new technique of APBI.

APBI trials using the MammoSite and hybrid brachytherapy applicators

APBI with interstitial BT using multicatheter systems requires high experience in all members of the staff. To decrease the existing barriers against the widespread use of multicatheter BT, a new and simple BT applicator was developed in the United States.[24] The MammoSite Radiation Therapy System (RTS) is a dual-lumen spherical balloon catheter (Fig. 3). One lumen allows inflating the balloon to a diameter of 4–5 cm; the other provides a

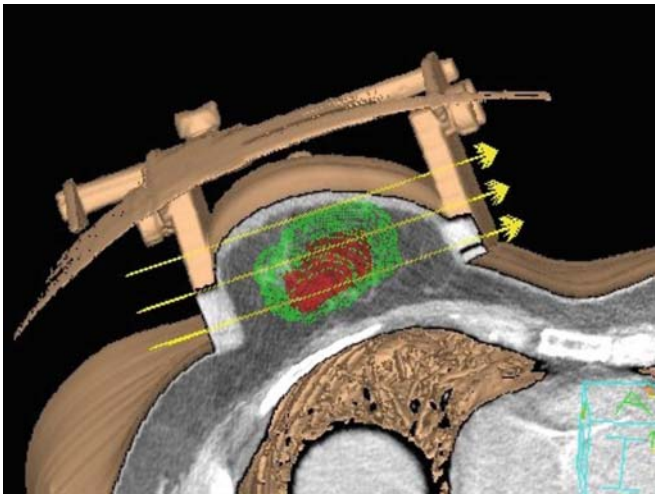

Fig. 5. Three-dimensional computed tomography (CT) image-based virtual brachytherapy – pre-implant planning of the catheter positions. *Red shell*, tumor bed; *green wire-frame*, planning target volume (PTV); *yellow arrows*, preplanned catheter positions

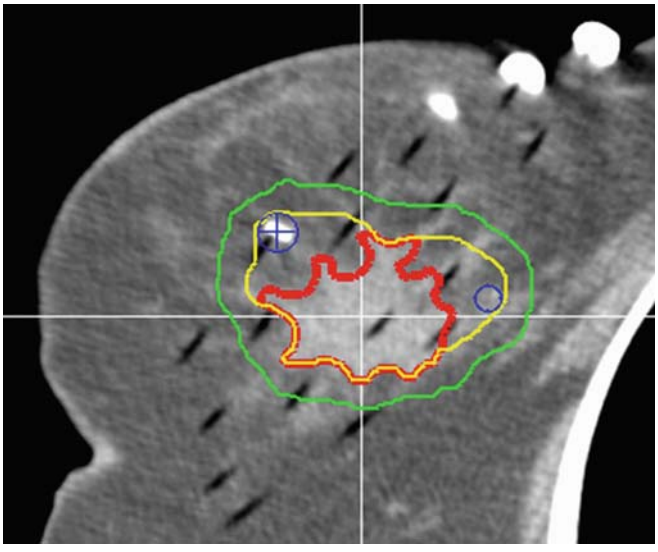

Fig. 6. PTV definition on a post-implant CT scan for a five-plane multicatheter brachytherapy implant. *Red line*, seroma; *yellow line*, tumor bed; *green line*, PTV

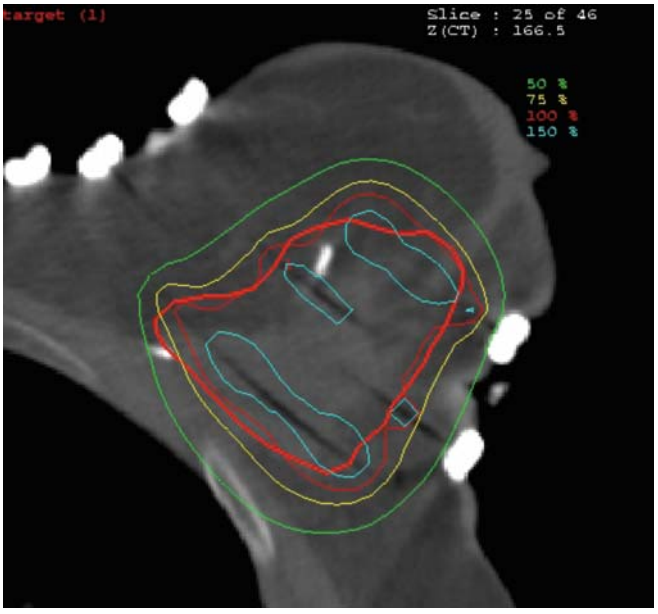

Fig. 7. Post-implant CT image with dose distribution using geometrical and graphical dose optimization. *Thick red line*, PTV; *thin red line*, isodose line of the prescribed (100%) dose; *blue line*, 150% isodose line; *yellow line*, 75% isodose line; *green line*, 50% isodose line

pathway for the ^{192}Ir source. The advantage of this system is that only one applicator is implanted to deliver fractionated HDR BT to the tumor bed, as compared to interstitial BT, which requires the implantation of 10–20 catheters. Since 2002, this system has been available for commercial use. In the United States, the MammoSite system has been implemented by a number of institutions.[81–87] In Europe, several feasibility studies have been initiated to investigate the practicability and safety of the system.[88–92] Most of these trials have been designed to test the device as the sole method for APBI and for the delivery of a boost dose in combination with WBI.

The preliminary results of these studies are summarized in Table 8.[81–92] To date, only two groups have reported their results with a mature follow-up period of beyond 5 years. In the initial FDA MammoSite APBI trial, 43 of 70 eligible patients (61%) were treated from May 2000 to October 2001.[81] Criteria for entry into the study were unifocal invasive ductal carcinoma, tumor size 2 cm or less, age 45 years or more, absence of EIC, cavity size 3 cm or more, negative axillary nodes, and clear final surgical margins. A minimum balloon-to-skin surface distance of 5 mm was required. A dose of 34 Gy was delivered in ten fractions over 5 days prescribed to 1 cm from the applicator surface, using HDR BT. At a median follow up of 5.5 years, no LRs or regional failures have occurred. Good-to-excellent cosmetic outcomes were achieved in 81%, but this proportion was only 67% for patients having less than 7-mm skin spacing. Furthermore, a very high rate of telangiectasia (39.5%) was identified, and this rate was exceptionally high (75%) in patients with less than 7-mm skin spacing.

Overall, 54 patients were enrolled in the early European studies.[90] Eligibility criteria for the sole modality were: age at least 60 years (age at least 40 years for boost); tumor size 2 cm or less (≤2.5 cm for boost); invasive ductal histology; grade 1–2 (grade 2–3 for boost); free surgical margins of 5 mm or more (negative margins for boost); applicator placement within 10 weeks of final lumpectomy procedure; excision cavity with one dimension of at least 3 cm. In contrast to the United States studies, a skin-to-balloon distance of at least 7 mm was demanded. Exclusion criteria were: presence of EIC, pure intraductal cancer, lobular histology, multifocal or multicentric lesions. For sole MammoSite therapy, a total dose of 34 Gy in ten fractions was delivered over 5–7 days. In the boost group, a total dose of 10–20 Gy was delivered with a fraction dose of 2.5 Gy over 2–4 days. Of 54 implanted patients, 10 (18.5%) had to be excluded

Table 8. Results of MammoSite HDR brachytherapy APBI trials

Institution/Study	RT scheme (dose [Gy]x fraction no.)	Median FUP (years)	Total LR % (*n*)	TR/MM % (*n*)	EF % (*n*)	Annual LR %	Excellent/ good cosmesis %	Teleangiectasia %
FDA Trial, USA[81]	3.4 × 10	5.2	0 (0 of 43)	0 (0 of 43)	0 (0 of 43)	0	81	39.5
Kiel-HNIO[91,92]	3.4 × 10	5	0 (0 of 11)	0 (0 of 11)	0 (0 of 11)	0	45	64
ASBS Registry Trial[87]	3.4 × 10	2.5	1.6 (23 of 1449)	0.4 (6 of 1449)	1.2 (17 of 1449)	0.64	93	NR
Rush University[83]	3.4 × 10	2.2	5.7 (4 of 70)	1.4 (1 of 70)	4.3 (3 of 70)	2.6	NR	NR
USA multicentric[84]	3.4 × 10	2	1.2 (6 of 483)	0.4 (2 of 483)	0.8 (4 of 483)	0.6	91	17
Univ. South Carolina[85]	3.4 × 10	2	2.2 (2 of 90)	0 (0 of 90)	2.2 (2 of 90)	1.1	90	NR
WBH, Michigan[82]	3.4 × 10	1.8	2.5 (2 of 80)	1.25 (1 of 80)	1.25 (1 of 80)	1.4	97	NR
Pittsburgh[86]	3.4 × 10	1.7	0 (0 of 92)	0 (0 of 92)	0 (0 of 92)	0	99	11
European multicenter[90]	3.4 × 10	1.2	0 (0 of 28)	0 (0 of 28)	0 (0 of 28)	0	76	18
Lille University[88]	3.4 × 10	1.1	0 (0 of 25)	0 (0 of 25)	0 (0 of 25)	0	84	8
All patients		1.1–5.2	1.6 (37 of 2371)	0.4 (10 of 2371)	1.1 (27 of 2371)	0–2.6	45–97	8–64

APBI: accelerated partial breast irradiation; HDR: high-dose-rate; RT: radiotherapy; FUP: follow-up period; LR: local recurrence; TR/MM: true recurrence/marginal miss; EF: elsewhere failure; ASBS: American Society of Breast Surgeons; HNIO: Hungarian National Institute of Oncology; WBH: William Beaumont Hospital; NR: not reported

[a]Updated results by Niehoff (see text; unpublished data)

from the clinical trial. At the final decision, 28 patients were eligible for BT alone and 16 patients were treated with a boost BT followed by WBI. No LR had occurred after a mean follow up of 14 months (range, 3–31 months).[90]

Late side effects in patients ($n = 24$) treated in Germany and Hungary are listed in Table 9. The balloon-to-skin distance is a critical point in terms of toxicity. According to our preliminary analysis, in the German-Hungarian Trial, 26% (37% in the primary and 16% in the boost group) of patients developed telangiectasia after a mean follow up of 20 months.[91,92] An update after a median of 5 years showed a telangiectasia rate of 54% (64% in the primary, and 46% in the boost group; unpublished results; P. Niehoff et al.). In other United States MammoSite studies also high rates of telangiectasia (range, 11% to 39.5%) were observed.[81,84,86] In a recent analysis from Pittsburgh, the telangiectasia incidences for maximum skin doses of more than 100% and more than 125% of the prescribed dose were 28% and 63%, compared with 0% and 4.2% for doses of 100% or less and 125% or less, respectively.[86] Therefore, in Europe we suggested that the use of the MammoSite system should be avoided for patients with less than 15-mm balloon-to-skin distance.[92] Due to the flexibility for dose shaping with multicatheter BT, we prefer interstitial implants for those patients with an inadequate (<15 mm) skin distance, instead of using the MammoSite applicator.

Recently, several new BT devices (Fig. 4) have been developed to combine the advantages of multicatheter and MammoSite balloon BT, blending the versatility and flexibility of interstitial BT for dose shaping with the simplicity and convenience of a single-entry device.[22,23,25] Each of the Strut-Adjusted Volume Implant (SAVI) (Cianna Medical, Aliso Viejo, CA, USA), the SenoRx Contura (SenoRx Inc., Aliso Viejo, CA, USA), and the ClearPath (North American Scientific Inc., Chatsworth, CA, USA) applicators represents a marriage of these two techniques and they all use multiple struts, which can be differentially loaded to maximize the tumor bed dose and minimize the normal tissue dose. According to the limited experience with these hybrid breast BT applicators, the skin dose can be reduced significantly without comprising PTV coverage.[22,25] Nevertheless, the use of hybrid breast BT devices has the potential to increase the applicability of APBI in patients with inadequate balloon-to-skin distance.

Based on the American and European experiences, the MammoSite and other recently developed hybrid breast BT devices have gained rapid acceptance and popularity by both the patients and their treating physicians. Obviously, these applicators offer an alternative method of APBI for a selected group of patients. Unfortunately, in most European countries the high costs of these applicators are not reimbursed by the health insurance systems.

Multicentric phase III APBI trials

In addition to the Hungarian randomized APBI study, to date seven prospective phase III clinical trials have been activated to compare the efficacy of APBI to that of con-

Table 9. Late side effects and cosmetic results of MammoSite brachytherapy[a]

Side effect	Primary (n = 11) n (%)	Boost (n = 13) n (%)	All patients (n = 24) n (%)
Teleangiectasia	7 (64%)	6 (46%)	13 (54%)
Hyperpigmentation	6 (55%)	2 (15%)	8 (33%)
Fibrosis (any grade)	4 (36%)	10 (77%)	14 (58%)
Fat necrosis	5 (45%)	8 (62%)	13 (54%)
Pain (any grade)	1 (9%)	4 (31%)	5 (21%)
Persistent seroma	0 (0%)	1 (8%)	1 (4%)
Excellent-good cosmetic result	5 (45%)	6 (46%)	11 (46%)

[a] Subgroup analysis of the German-Hungarian MammoSite study (updated results by Niehoff et al.; unpublished data)

ventional WBI. Among these, two protocols [the European GEC-ESTRO (Groupe Européen de Curiethérapie European Society for Therapeutic Radiology and Oncology) and the American NSABP (National Surgical Adjuvant Breast and Bowel Project)/RTOG trial] use BT for the delivery of APBI in the investigational arm.[6,7]

European (GEC-ESTRO) multicentric randomized APBI trial

Based on the success of the Hungarian and German-Austrian APBI studies, a multicentric phase III APBI protocol has been developed by the Breast Cancer Working Group of the GEC-ESTRO.[6] As long-term results beyond 5 years are available only with interstitial implants, proving that multicatheter BT can be used with adequate reproducibility, low toxicity, and appropriate local control, it has been decided that only interstitial HDR or PDR BT will be allowed for the APBI arm of this European multicentric phase III trial. The first patient was randomized in May 2004. To date, 16 centers from seven European countries have activated the protocol. Patients in the control group are treated with 50-Gy WBI plus 10-Gy electron boost. Patients in the APBI arm are treated with HDR or PDR multicatheter BT. The primary endpoint of the study is LR as a first event within 5 years. The scientific hypothesis to be assessed and statistically tested is the "nonrelevant noninferiority" of the experimental treatment. For adequate statistical power, 1170 patients will be enrolled, based on the desire to detect a difference of 3% in LR rates between the arms. Secondary endpoints will address overall, disease-free, and distant metastasis-free survival; contralateral breast cancer; early and late side effects; cosmesis; and quality of life. Eligibility criteria include unifocal ductal carcinoma in situ (DCIS) or invasive carcinoma of the breast, tumor size 3 cm or less, microscopic negative margins of at least 2 mm (5 mm for DCIS or invasive lobular carcinoma), no EIC, no lymphovascular invasion, no more than one micrometastasis in axillary lymph nodes (pN1mi), and patient age 40 years or more. Patients are stratified before randomization according to the treatment center, as having DCIS or invasive carcinoma, and regarding menopausal status. The QA program for partial breast BT includes preimplant PTV definition by surgical clips and/or preimplant CT image-based preplanning of the implant geometry. The PTV is defined as the excision cavity plus a 2-cm margin minus the minimum clear pathological margin. Postimplant CT scans are mandatory for the documentation of target coverage and dose homogeneity. Acceptable treatment parameters for CT image-based treatment planning include:

- Dose-volume histogram (DVH) analysis of target coverage confirming that the prescribed dose covers 90% or more of the PTV (coverage index ≥0.9)
- Dose nonuniformity ratio (DNR) 0.35 or less
- Maximum skin dose less than 70% of the prescribed dose.

The GEC-ESTRO APBI trial is financially supported by a grant from German Cancer Aid (Deutsche Krebshilfe) for a study period of 4 years between 2005 and 2009. To date (November 17, 2008), 1054 patients have been randomized. It is anticipated that the required accrual goal will be achieved in March 2009.

American (NSABP B-39/RTOG 0413) multicentric randomized APBI trial

The American multicentric phase III trial investigating APBI was initiated in March 2005 by the NSABP together with the RTOG.[7] Patients are randomized between standard WBI and APBI. The latter may be delivered with any of the three techniques of multicatheter HDR BT, MammoSite BT, or three-dimensional (3-D) EB RT. Eligibility criteria include unicentric DCIS or invasive carcinoma allowing microscopic multifocality confined to one quadrant of the breast, tumor size 3 cm or less, microscopic negative margins by the NSABP criteria (no tumor on inked margins), and no more than three positive axillary lymph nodes (pN0-1a) without extracapsular extension. In contrast to the GEC-ESTRO trial, patients below the age of 40 years with tumors excised with close (but clear) surgical margins or containing an EIC, as well as patients with one to three positive nodes, are eligible for the NSABP/RTOG trial. Due to the rapid enrollment of low-risk patients by multiple American centers, the original accrual goal (3000 patients) was increased to 4300. In December 2006, the trial closed enrollment to low-risk patients, thereby limiting further accrual to patients satisfying one or more of the high-risk criteria, including age less than 50 years, estrogen receptor negativity, or one to three positive nodes.[73] However, the principal investigators of the study suggested avoiding the overextension of APBI (in daily clinical practice outside clinical trials) beyond the conservative patient

selection criteria previously proposed by the American Brachytherapy Society.[7,93] Until August 2008, more than 3200 patients had been randomized (personal communication; F. A..Vicini). Unfortunately, only 29% of patients randomized to APBI have been treated with BT (23.3% with MammoSite BT, and only 5.7% with multicatheter BT).

The role of CT image-based conformal treatment planning of breast implants

A good implant in interstitial BT is characterized by an adequate dose coverage of the PTV, a high dose homogeneity inside, and a steep dose fall-off outside the target volume. Recently, the concepts of BT planning have changed a lot. Traditional classical dosimetry systems were based on the implant geometry which was reconstructed by X-ray beam projections. The use of a two-film localization technique allows the reconstruction of the catheters in three dimensions, but the definition of actual extensions of the PTV is impossible. The Paris dosimetry system (PDS) has been successfully used clinically for different treatment sites for decades.[66] Originally, the PDS was based on LDR wire sources, but later its application was extended to the HDR technique, where the linear source was simulated by a stepping source with uniform dwell times. However, the recent evolution of image-based BT has highlighted the limitations of the PDS.[94] In modern BT, both the treatment planning and plan evaluation have to be based on the real 3-D volume of the PTV.

CT-based treatment planning has been used in teletherapy for decades, but CT imaging was introduced for interstitial BT planning only in the 1990s. CT-based treatment planning in BT allows 3-D reconstruction of the catheters, exact demarcation of the lumpectomy cavity, and definition of the PTV, as well as outlining nearby organs at risk (OARs) (Figs. 5–6). Furthermore, with the utilization of DVHs related to outlined structures, quantitative parameters can be used for evaluating the treatment plans, in addition to the traditional visual inspection of dose distribution. Target volume coverage and dose homogeneity can be concurrently analyzed, and the correlation between these parameters and clinical outcome can be established (Fig. 7).

In the past decade, several groups have implemented 3-D CT image-based BT treatment planning for t he management of breast cancer.[95–104] Our group justified the superiority of conformal BT planning over 2-D treatment planning with better conformity parameters, but no anatomic DVHs were applied.[95] Vicini et al.[96] were the first group who used CT imaging at the implementation of 3-D virtual BT in the management of breast cancer. They used the preimplant images to define the positions of the needles and the postimplant images to compare the actual PTV coverage with the virtual implant. Later, the same group performed CT-based 3-D dose-volume analyses of HDR breast implants to evaluate the dose coverage of the PTV.[97,98] On average, a coverage index of 0.68 (ratio of the PTV covered by the prescribed dose) and a D90 (relative dose received by 90% of the PTV) of 0.69 were achieved. But, it has to be noted that postimplant CT images were only used for the retrospective evaluation of treatment plans. Weed et al.[99] reported a V100 of only 58% for their ten interstitial breast implants. In a previous study, we reported 70% target volume coverage by the reference dose for 17 patients treated with a fluoroscopy-based implantation technique.[100] Das et al.[101] reported their experience with CT-based interstitial breast implants, and they demonstrated the technical feasibility of this approach, along with improved PTV delineation and optimal coverage. On evaluating 50 patients, the PTV coverage by the prescribed dose ranged between 75% and 100%, with a mean value of 95%. Cuttino et al.[102] reported that the percentage of patients satisfying their dosimetric goals of target coverage and dose homogeneity increased from 42% to 93% when a CT-guided technique was used instead of a fluoroscopic-guided free-handed catheter insertion technique. In a recent article, we reported our dosimetric experience with image-guided APBI.[103] Our technique is based on two sets of CT images. The preimplant CT imaging is used for defining the number and positions of the catheters, while the postimplant CT images are used for catheter reconstruction, PTV, and OAR definition, and plan evaluation using DVHs. In our method the dose prescription is also DVH-based. A prescription isodose is selected in such a way that the target volume coverage by the reference dose is at least 90%. In order to obtain acceptable dose homogeneity, our aim was to keep the dose homogeneity index (DHI) at more than 0.65. Using DVHs we evaluated the dose to OARs, too. With this technique we achieved 91% target coverage by the prescription dose, compared to the 70% when the CT images were used only for plan evaluation, but the implantation was still fluoroscopy-based. The introduction of 3-D imaging in interstitial breast BT has significantly improved the quality of the implants. Table 10 summarizes the dosimetric data of clinical studies which reported target-oriented dose-volume parameters.[95–104] The studies are divided into two groups. In

Table 10. Clinical studies reporting dose-volume parameters of high-dose-rate interstitial breast brachytherapy

Author	*n*	V90	V100	D90	DHI
Standard techniques					
Vicini[97]	8	NR	68%	69%	0.86
Kestin[98]	11	NR	68%	NR	0.83
Weed[99]	10	68%	58%	NR	NR
Major[100]	17	76%	70%	72%	0.65
Cuttino[102]	15	89%[a]	96%[b]	NR	0.77
Image-guided techniques					
Das[1013]	50	NR	96%	NR	0.73
Cuttino[102]	14	95%[a]	98%[b]	NR	0.82
Major[103]	28	96%	91%	102%	0.64
Kolotas[104]	42	NR	90%	NR	NR

n, number of patients; NR, not reported; V90 and V100, percentage volume of PTV receiving 90% and 100% of reference dose, respectively; D90, relative dose received by 90% of PTV; DHI, dose homogeneity index

[a] For PTV defined as the excision cavity + 2 cm

[b] For PTV defined as the excision cavity + 1 cm

the first group, the catheters were inserted using standard fluoroscopy-guided techniques followed by conventional planning, and CT scanning was done after the implantation for plan evaluation purposes only. The second group contains studies in which the implantation was performed by image-guided techniques using real 3-D anatomical information of the PTV, and in addition the plan evaluation was target-oriented. It is evident (see Table 10.) that significantly better PTV coverage can be achieved with the 3-D CT image-based implant technique than with the conventional X-ray image-based method. The question of homogeneity, however, is still debatable. To date, there is no consensus about the clinical importance of dose homogeneity.

CT image-based breast BT provides 3-D tools for assessing treatment plans of interstitial implants. Reporting dose-volume parameters is recommended in order to establish their associations with treatment outcome and complications. It is anticipated that 3-D CT image-based treatment planning will further improve the quality of breast implants, translating into improved local tumor control (by better PTV coverage) and fewer side effects with better cosmetic results (by improved sparing of OARs).

Summary and future perspectives of breast brachytherapy

Before the era of breast-conserving therapy, BT implants were used to treat large inoperable breast tumors. Later, interstitial BT was used to deliver an additional dose to the tumor bed after BCS and WBI. Based on the obvious dosimetric advantages of interstitial breast implants (over EB techniques) supported by the encouraging results of modern boost series utilizing stepping-source afterloading technology, multicatheter HDR/PDR BT remains a standard treatment option for boosting the tumor bed after BCS and WBI.

Reexcision followed by reirradiation using interstitial breast implants has also been implemented as an alternative to mastectomy for the management of ipsilateral breast LR after previous breast-conserving therapy. Promising single-institution experiences warrant further prospective studies to explore the possible advantages of salvage breast BT.

APBI is an attractive treatment approach with considerable advantages over conventional WBI, opening new prospects for breast BT. Contemporary APBI trials using interstitial or intracavitary BT, with strict patient selection criteria and systematic QA procedures, have resulted in an annual LR rate of less than 1%. The long-term results from single-institution phase I/II APBI studies, and the 7-year results of the Hungarian randomized trial, certainly support the continuation of current multicentric phase III APBI trials. Issues of patient selection, PTV definition, total dose, and fractionation will be addressed and refined in such randomized trials. As data from the Hungarian trial and other trials mature, they will support the implementation of APBI into routine clinical practice.

The development of new standards for 3-D CT image-based BT treatment planning, together with the implementation of inverse dose planning, will further improve the conformity of dose distribution delivered by multicatheter implants, maximizing the ballistic advantage of breast BT.

Conflict of interest

No author has any conflict of interest.

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