Accelerated Partial Breast Irradiation with Multicatheter Brachytherapy: 15-year Results of a Phase II Clinical Trial

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Background and purpose: To report the 15-year updated results of accelerated partial breast irradiation (APBI) using multicatheter interstitial high-dose-rate (HDR) brachytherapy (BT).

Patients and methods: Forty-five prospectively selected patients with T1N0-N1mi, nonlobular breast cancer without the presence of an extensive intraductal component and with negative surgical margins were treated with APBI after breast-conserving surgery (BCS) using interstitial HDR BT. A total dose of 30.3 Gy (n=8) and 36.4 Gy (n=37) in seven fractions within 4 days was delivered to the tumour bed plus a 1–2 cm margin. The median follow-up time was 166 months for surviving patients. Local control, disease-free (DFS), cancer-specific (CSS), and overall survival (OS), as well as late side effects, and cosmetic results were assessed.

Results: Five (11.1%) ipsilateral breast tumour recurrences were observed, for a 5-year, 10-year, and 15-year actuarial rate of 4.4%, 9.4%, and 11.9%, respectively. The 15-year DFS, CSS, and OS was 75.4%, 86.2%, and 82.0%, respectively. Grade 3 fibrosis was observed in 1 patient (2.2%). No patient developed grade 3 teleangiectasia. Fat necrosis requiring surgical intervention occurred in 1 woman (2.2%). Cosmetic results were rated excellent or good in 36 patients (80%).

Conclusions: Fifteen-year results with APBI using HDR multicatheter interstitial implants continue to demonstrate excellent long-term local tumour control, survival, and cosmetic results with a low-rate of late side effects.

Keywords: breast-conserving therapy, accelerated partial breast irradiation, high-dose-rate brachytherapy

Introduction

Over the last decades, breast-conserving surgery (BCS) followed by whole breast irradiation (WBI) became the standard of care for the treatment of early-stage breast carcinoma [1,2]. However, the necessity of giving WBI for all patients after BCS has been questioned, and several centers have evaluated the feasibility and efficacy of accelerated partial breast irradiation (APBI) [3–13]. The 7- and 12-year results of our institution's first prospective APBI study were reported elsewhere [9,10]. To determine the long-term stability of our findings we have updated the results of this original study with an extended follow-up.

Patients and methods

The study population consisted of 45 consecutive patients with invasive, early-stage breast cancer who were prospectively treated at the Hungarian National Institute of Oncology (HNIO) between 1996 and 1998 with APBI using multicatheter interstitial high-dose-rate (HDR) brachytherapy (BT) after BCS. During surgery, the boundaries of the excision cavity were marked with titanium clips. At least level I–II axillary dissection was performed for 35 patients (77.8%) and 2 women (4.4%) underwent sentinel lymph node biopsy. For the remaining 8 cases (17.8%) surgical axillary staging was omitted by the surgeons preference. Patients were eligible for APBI if they met all the following conditions and provided informed consent: unifocal tumour; primary tumour size by final pathology ≤20 mm (pT1); microscopically negative surgical margins; histologic grade 1–2; cN0 or pN0–pN1mi axillary status; and technical suitability for breast implantation (e.g. relatively deep-seated tumour bed to avoid radiation damage of skin vessels). Patients with pure ductal or lobular carcinoma in situ (pTis); invasive lobular carcinoma; or the presence of an extensive intraductal component (EIC) were excluded. Patient and tumour characteristics are listed in Table I.

Patients were treated with an HDR remote afterloading equipment (microSelectron, Nucletron B.V., Veenendaal, The Netherlands) using a 192Ir stepping source with 370 GBq initial activity. Our implant technique has been described in detail elsewhere [9,10]. Briefly, the implantations were performed 4 to 6 weeks after BCS under local anasthesia. The planning target volume (PTV) was defined as the excision cavity with a margin of 1 to 2 cm. Following preimplant simulation a median of 7 guide needles (range, 3–10) were inserted into the previously targeted area in a triangular setting using template guidance with 15 mm spacing between the needles. Single-, double-, and triple-plane implants were performed on 3 (6.7%), 34 (75.5%), and 8 (17.8%) patients, respectively. The guide needles were replaced with plastic catheters and secured with fixation buttons. The distance of the dose points from the catheters was 5 to 14 mm varying from catheter to catheter to achieve 100% isodose surface cover for all surgical clips with a margin of 1 to 2 cm. The prescribed dose, calculated to the 100% isodose surface, consisted of 7 fractions of 4.33 Gy (n=8; 17.8%) or 5.2 Gy (n=37; 82.2%), each

Table I. Patient and tumour characteristics

Characteristic	Study population (n=45)
Mean age (years)	56
Range	38–78
Histologic type	
Ductal	33 (74%)
All others	12 (26%)
Tumour size (mm)	
Median	12
Range	1–20
Surgical margins	
Positive	0 (0%)
Close (≤2 mm)	14 (31%)
Clear (>2 mm)	31 (69%)
Nodal status	
pN0 (ALND or SLNB)	36 (80%)
pN1mi (ALND)	1 (2%)
pNx (cN0)*	8 (18%)
Histologic grade	
1	24 (53%)
2	20 (45%)
NA	1 (2%)
ER status	
Positive	37 (82%)
Negative	8 (18%)
PR status	
Positive	36 (80%)
Negative	9 (20%)

ALND = axillary lymph node dissection; SLNB = sentinel lymph node biopsy; NG = nuclear grade; NA = not applicable (for medullary carcinoma); ER = estrogen receptor; PR = progesterone receptor. *Clinically N0, without surgical axillary staging. Data presented as number of patients, with percentage in parentheses, unless otherwise noted

given at least 6 hours apart within 4 days to a total dose of 30.3 Gy and 36.4 Gy, respectively.

Of the 45 women, 38 (84%) did not receive any adjuvant systemic therapy, and 7 (16%) underwent tamoxifen therapy for 5 years. No patient received chemotherapy.

The median follow-up for all patients was 159 months (range, 52 to 180 months) and 166 months (range, 149 to 180 months) for surviving patients. Patients were seen every 3 months in the first 2 years after treatment and every 6 months thereafter. Mammography, breast and abdominal ultrasound examinations, chest X-ray, and blood tests were performed annually. The cosmetic results and late side effects were prospectively followed and documented for all patients. The cosmetic results were assessed using the Harvard criteria [14]. Skin side effects and fibrosis were scored by the Radiation Therapy Oncology Group/European Organization for Research and Treatment of Cancer (RTOG/EORTC) late radiation morbidity scoring scheme [15]. All available mammography films were carefully reviewed for asymptomatic fat necrosis (i.e. oil-cysts and/or coarse calcifications). Our previously described institutional scoring scheme was used to grade fat necrosis [16].

All time intervals were calculated from the date of surgery. The actuarial rates of specific events and survivals were calculated using the Kaplan-Meier method [17]. The SOLO software (Department of Biometrics, University of California, Los Angeles, CA, USA) was used for statistical analyses.

Table II. Incidence of first events

Event	Study population (n=45)
Local recurrence	5 (11.1%)
Regional recurrence	2 (4.4%)
Axillary recurrence	2 (4.4%)
Others	0 (0%)
Distant metastasis	5 (11.1%)
Any first relapse*	11 (24.4%)
Contralateral breast cancer	0 (0%)
Second primary malignancy	5 (11.1%)
Non-breast cancer death	1 (2.2%)

* Any first relapse = local, regional, or distant failure, whichever came first.

Results

Treatment outcome

Overall, 5 patients (11.1%) developed ipsilateral breast failure and all LR occurred as a first event. All but one LRs were classified as elsewhere breast failures. The crude rates of first events are summarized in Table II. The 5-, 10-, and 15-year actuarial rate of LR was 4.4%, 9.4%, and 11.9%, respectively (Fig. 1). A total of 3 regional nodal failures (including 1 supraclavicular and 2 axillary recurences were observed for a 15-year actuarial rate of 7.0%. No contralateral breast cancer occurred during the follow-up period. Disease-free survival (DFS), distant metastasis-free survival (DMFS), cancer-specific survival (CSS), and overall survival (OS) at 15 years were 75.4%, 81.4%, 86.2%, and 82.0%, respectively.

Cosmetic results and side effects

The cosmetic results and late radiation side effects are listed in Table III. The rate of excellent/good cosmetic outcomes was 80.0%. Severe (≥ grade 3) side effects occurred only in two patients (4.4%); including one case with a grade 3

Table III. Cosmetic results and late radiation side effects

Variable	Study population (n=45)
Cosmetic results	
Excellent	12 (26.7%)
Good	24 (53.3%)
Fair	5 (11.1%)
Poor	4 (8.9%)
Skin side effects	
Grade 0	39 (86.7%)
Grade 1	4 (8.9%)
Grade 2	2 (4.4%)
Grade 3	0 (0%)
Fibrosis	
Grade 0	29 (64.4%)
Grade 1	12 (26.7%)
Grade 2	3 (6.7%)
Grade 3	1 (2.2%)
Fat necrosis	
Grade 0	29 (57.8%)
Grade 1	9 (20%)
Grade 2	9 (20%)
Grade 3	0 (0%)
Grade 4	1 (2.2%)

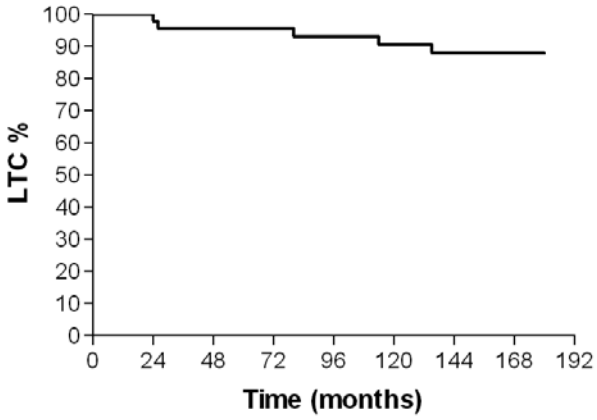

Fig. 1. Time to local recurrence by Kaplan-Meier estimates. LTC = local tumour control. 15-year LTC = 88.1%.

fibrosis and one with a grade 4 fat necrosis requiring surgical intervention (reexcision of the painful, inflammatory mass).

Discussion

Following the general acceptance of breast-conserving therapy including elective WBI, several centers have pioneered APBI, limiting radiotherapy to the immediate vicinity of the primary tumour site [3–13]. The majority of these trials using strict patient selection criteria and appropriate treatment technique were successful in yielding 5-year LR rates in the range of 0 to 4.7% (Table IV). However, to date only the William Beaumont Hospital's group reported their 10-year results with multicatheter APBI [3]. In their trial, 199 patients were treated prospectively with breast-conserving therapy and APBI using interstitial low-dose-rate or HDR BT. Patients in the APBI group were matched with 199 women treated with WBI to compare potential differences in LR rates. With a median follow-up of 9.6 years, APBI produced 10-year LR rates comparable to those from WBI (5% vs. 4%; p=0.48).

To our knowledge, this is the first report with a follow-up period beyond 12 years demonstrating that APBI using multicatheter HDR implants for appropriately selected patients produced 15-year actuarial LR rate similar to those reported with conventional WBI. Parallel with the growing evidence obtained from phase I–II studies supporting the use of APBI for selected early-stage breast cancer patients, at least seven phase III trials comparing different techniques of APBI to conventional WBI have been initiated in the last decade in Europe, Canada and the USA [7]. Among these, the 5-year results of the Hungarian single-institution randomized APBI study were reported in 2007 [8]. In this trial, 258 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 in 7 fractions of 5.2 Gy each) HDR multicatheter BT (n=88) or limited-field electron beam (EB) irradiation (n=40) giving a dose of 50 Gy in 25 fractions. In the most recent analysis, with a median follow-up of 6.8 years, no significant differences were seen in the 7-year rates of LR (5.1% vs. 3.3%), DFS (86.3% vs. 89.0%) or CSS (96.2% vs. 93.9%) in the PBI and WBI arms [7]. The 5-year results of other ongoing randomized trials are highly awaited, but will be available only in the next 5 to 10 years for the radiation oncology community. Thus, in the mean time it is of high importance to report periodically updated results of non-randomized APBI studies.

Conclusions

Fifteen-year results with APBI using HDR multicatheter interstitial implants continue to demonstrate excellent long-term local tumour control, survival, and cosmetic results with a low-rate of late side effects comparable to those achieved with conventional WBI in selected low-risk patients. However, long-term data from ongoing prospective randomized trials are needed to establish the equivalence of this treatment approach compared with standard WBI.

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Table IV. Long-term (≥5 years) results of contemporary APBI studies using multicatheter brachytherapy

Institution/study	Patient No. (n)	Dose Rate	Median FUP (years)	5-y LR %	10-y LR %	15-y LR %	Annual LR %
WBH [3,13]	199	LDR/HDR	9.6	2.2	5.0	NR	0.50
Örebro Med. Centre [5]	51	PDR	7.2	4.0	4.0*	NR	0.57
RTOG 95-17 [4]	99	LDR/HDR	7	4.0	NR	NR	0.80
HNIO, Phase III [7-8]	128	HDR/EBI	6.8	4.7	5.1*	NR	0.73
Ochsner Clinic [6]	51	LDR/HDR	6.25	3.9†	NR	NR	0.62
Ninewells Hospital [11]	11	LDR	5.6	0	NR	NR	0
Germany/Austria [12]	274	PDR/HDR	5.25	2.3	5.0‡	NR	0.63
Present study	45	HDR	13.8	4.4	9.4	11.9	0.79
All patients	858		5.25–13.8	0–4.7	4.0–9.4	11.9	0–0.80

APBI = accelerated partial breast irradiation; FUP = follow-up period; LR = local recurrence (actuarial rate unless otherwise specified); HDR = high-dose-rate; LDR = low-dose-rate; PDR = pulsed-dose-rate; EBI = external beam irradiation; WBH = William Beaumont Hospital; RTOG = Radiation Therapy Oncology Group; HNIO = Hungarian National Institute of Oncology; NR = not reported; *7-year actuarial rate; †crude rate; ‡8-year actuarial rate.

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