Electron and High-Dose-Rate Brachytherapy Boost in the Conservative Treatment of Stage I–II Breast Cancer

First Results of the Randomized Budapest Boost Trial

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Background and Aims: To evaluate the effect of electron and high-dose-rate brachytherapy (HDR BT) boost on local tumor control (LTC), side effects and cosmesis after breast-conserving surgery (BCS) in a prospective randomized study.
Patients and Methods: 207 women with stage I–II breast cancer who underwent BCS were treated by 50 Gy irradiation to the whole breast and then randomly assigned to receive either a boost to the tumor bed (n = 104) or no further radiotherapy (n = 103). Boost treatments consisted of either 16 Gy electron irradiation (n = 52) or 12–14.25 Gy HDR BT (n = 52). Breast cancer-related events, side effects, and cosmetic results were assessed.
Results: At a median follow-up of 5.3 years, the crude rate of local recurrence was 6.7% (7/104) with and 15.5% (16/103) without boost. The 5-year probability of LTC, relapse-free survival (RFS), and cancer-specific survival (CSS) was 92.7% vs 84.9% (p = 0.049), 76.6% vs 66.2% (p = 0.044), and 90.4% vs 82.1% (p = 0.053), respectively. There was no significant difference in LTC between patients treated with electron or HDR BT boost (94.2% vs 91.4%; p = 0.74). On multivariate analysis, patient age < 40 years (RR: 4.53), positive margin status (RR: 4.17), and high mitotic activity index (RR: 3.60) were found to be significant risk factors for local recurrence. The incidence of grade 2–3 side effects was higher in the boost arm (17.3% vs 7.8%; p = 0.03). However, the rate of excellent/good cosmetic results was similar for the two arms (85.6% vs 91.3%; p = 0.14). Cosmesis was rated as excellent/good in 88.5% of patients treated with HDR BT and 82.7% of patients with electron boost (p = 0.29).
Conclusions: Boost dose significantly improves LTC and RFS in patients treated with BCS and radiotherapy. In spite of the higher incidence of late side effects in the boost arm, boost dose is strongly recommended for patients at high risk for local recurrence. Positive or close margin status, high mitotic activity index, and young patient age should be viewed as absolute indications for tumor bed boost. LTC and cosmesis are excellent and similar to patients boosted with either HDR BT or electrons.

Key Words: Breast cancer · Breast-conserving therapy · Boost irradiation · Electron · Brachytherapy · Local recurrence

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Elektronen- und High-Dose-Rate-Brachytherapie-Boost bei brusterhaltender Therapie des Mammakarzinoms im Stadium I–II. Erste Ergebnisse der randomisierten Budapester Boost-Studie

Hintergrund und Ziel: In einer prospektiv randomisierten Studie werden die Effekte eines Elektronenboosts und eines High-Dose-Rate-Brachytherapie-(HDR-BT-)Boosts bezüglich lokaler Tumorkontrolle (LTC), Nebenwirkungen und kosmetischer Ergebnisse nach brusterhaltender Operation (BCS) evaluiert.
Patienten und Methodik: 207 Patientinnen mit Brustkarzinomen im Stadium I–II wurden einer BCS zugeführt. Postoperativ erfolgte eine perkutane Radiatio der gesamten Brust bis 50 Gy. Daran schloss sich willkürlich entweder eine Boostbestrahlung des Tumorbetts (n = 104) oder keine weitere Radiatio (n = 103) an. Die Boostbestrahlung erfolgte perkutan mit 16 Gy Elektronen (n = 52) oder in Form einer HDR-BT mit 12–14,25 Gy (n = 52). Untersucht wurden LTC, Nebenwirkungen und kosmetische Ergebnisse.
Ergebnisse: Die mediane Nachbeobachtungszeit betrug 5,3 Jahre. Die Lokalrezidivrate lag mit Boostbestrahlung bei 6,7% (7/104), ohne Boost bei 15,5% (16/103). Die 5-Jahres-Überlebensraten für LTC, für die rezidivfreie Überlebenszeit (RFS) und für die krebsspezifische Überlebenszeit (CSS) betrugen 92,7% vs. 84,9% (p = 0,049), 76,6% vs. 66,2% (p = 0,044) und 90,4% vs. 82,1% (p = 0,053). Bezüglich der LTC bestand kein signifikanter Unterschied zwischen Patienten, die mit einem Elektronen- oder HDR-BT-Boost behandelt wurden (94,2% vs. 91,4%; p = 0,74). Die multivariate Analyse zeigte, dass Faktoren wie Patientenalter

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< 40 Jahre (RR: 4,53), positive Resektionsränder (RR: 4,17) und ein hoher Mitoseaktivitätsindex (RR: 3.60) das Risiko eines lokalen Rezidivs signifikant erhöhten. Die Inzidenz von Nebenwirkungen Grad 2–3 war im Boost-Arm höher (17,3% vs. 7,8%; p = 0,03). Allerdings waren die sehr guten kosmetischen Ergebnisse in beiden Armen gleich (85,6% vs. 91,3%; p = 0,14). Sehr gute kosmetische Ergebnisse wurden bei 88,5% der Patientinnen mit HDR-BT-Boost und 82,7% der Patientinnen mit Elektronenboost erreicht (p = 0,29).

Schlussfolgerungen: Die Boost-Dosis verbessert signifikant LTC und RFS bei Patientinnen, die einer BCS und anschließender Radiatio zugeführt wurden. Obwohl eine höhere Inzidenz an Spätnebenwirkungen im Boost-Arm gefunden wurde, wird eine Boost-Dosis für Patientinnen mit hohem Risiko für die Entwicklung eines Lokalrezidivs empfohlen. Unserer Meinung nach ist bei Faktoren wie positive Schnitträndern, schmaler Sicherheitssaum, hoher Mitoseaktivitätsindex und niedriges Patientenalter die absolute Indikation zur Boost-Bestrahlung des Tumorbetts gegeben. LTC und die kosmetischen Ergebnisse sind sehr gut und unterscheiden sich nicht in Bezug auf Elektronenboost oder HDR-BT-Boost.

Schlüsselwörter: Mammakarzinom · Brusterhaltende Therapie · Boost-Bestrahlung · Elektronen · Brachytherapie · Lokalrezidiv

Introduction

Long-term results of prospective clinical studies have proven that breast-conserving surgery (BCS) with radiotherapy (RT) is as effective as mastectomy for the management of stage I–II breast cancer, both in terms of local tumor control (LTC) and cancer-specific survival (CSS) [2, 5, 15, 28, 49, 56, 58]. The standard technique of RT after BCS is to treat the conserved breast via tangential fields up to a total dose of 45–50 Gy. However, there is no consensus among radiation oncologists about the necessity of a further boost dose to the tumor bed [22]. To date, only two randomized studies have been published on this issue [3, 47]. Both studies prove that boost dose significantly reduces the incidence of ipsilateral breast tumor recurrence. The EORTC trial demonstrated that young age was the most important prognostic factor for local recurrence [3]. However, generally accepted guidelines for the indication of boost dose are not available in the literature. Further controversy exists regarding the optimal boost technique (electron vs brachytherapy), and their impact on LTC and cosmesis [8, 11, 21, 22, 27, 36, 38, 41, 48, 55, 59, 61, 62]. To date, only limited information has been reported in the literature about the feasibility, efficacy, and late side effects of boost treatments using high-dose-rate brachytherapy (HDR BT) [8, 22–24, 26, 27, 35].

To answer these questions, a prospective randomized study was initiated in 1995 at the National Institute of Oncology, Budapest, Hungary. This report presents the interim results of the Budapest breast boost trial.

Patients and Methods

Study Design

Between August 1995 and October 1998, 604 women with T1–2, N0–1 breast cancer who underwent BCS were treated by 50 Gy irradiation to the conserved breast and randomly assigned to receive either a boost to the tumor bed or no further RT. Exclusion criteria included: bilateral breast carcinoma; prior uni- or contralateral breast cancer; concomitant or previous other malignancies (except basal cell carcinoma of the skin). We hypothesized that boost would improve the 5-year LTC from 90% to 96%. The required sample size (n = 285 per arm) was calculated to detect a 6% difference in LTC between the two patient groups with a statistical power of 80% (β = 20%) and at a significance level of 5% (α = 5%). Patients were randomly allocated to treatment options by a sealed-envelope system in blocks of 20. Randomization was done by the study coordinator (C.P.) 2–3 weeks after surgery. The trial protocol was accepted by the ethics committee of the National Institute of Oncology, Budapest, Hungary, and verbal informed consent was also required.

The first interim analysis was prospectively planned to the time when one third of patients would reach at least a 3-year follow-up period. So, current analysis is limited to the first 209 patients with a median follow-up of 64 months (range: 43–77 months). Two women were excluded because of ineligibility (early distant metastases); thus, the present analysis included 207 patients. One patient refused boost irradiation, but was analyzed according to the assigned treatment group. Distribution of patients between treatment arms is summarized in Figure 1. Boost treatments consisted of either 16 Gy electron irradiation (n = 52) or 12–14.25 Gy fractionated HDR BT (n = 52). The boost technique (electron vs. HDR BT) was based on the treating radiation oncologist's preference. HDR BT was preferred for patients with deeply seated tumor bed.

Primary endpoints were the occurrence of ipsilateral breast tumor recurrence for LTC, and the occurrence of local, regional or distant relapse – whichever came first – for relapse-free survival (RFS). Secondary endpoints were death from breast cancer for CSS, late side effects of skin and subcutaneous tissues scored by the RTOG/EORTC late radiation morbidity scheme [10], and cosmetic results scored by a 4-grade scale (excellent/good/fair/poor), as suggested by Perez et al [41].

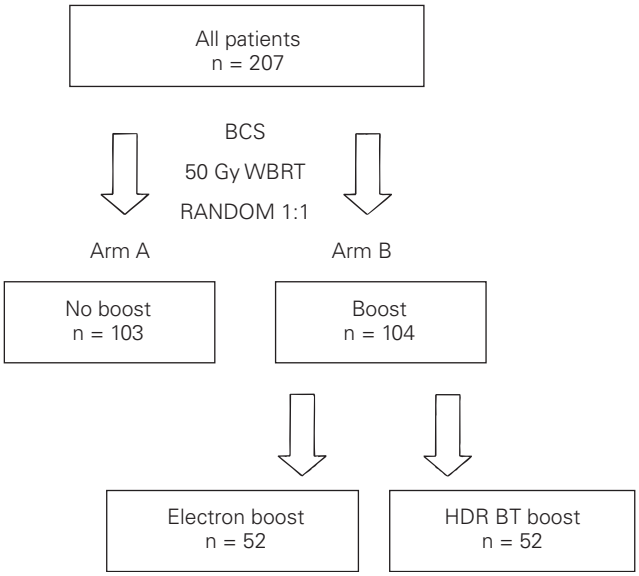

Figure 1. Distribution of patients between treatment arms. BCS: breast-conserving surgery; HDR BT: high-dose-rate brachytherapy; WBRT: whole breast radiotherapy.

Abbildung 1. Verteilung der Patientinnen in den Behandlungsarmen. BCS: brusterhaltende Operation; HDR BT: High-Dose-Rate-Brachytherapie; WBRT: Bestrahlung der gesamten Brust.

Surgery

All patients underwent wide excision, defined as a resection of the primary tumor with at least 1 cm of macroscopically free margin. During surgery, the walls of the excision cavity were marked with four to six titanium clips. In all patients, at least level I–II axillary dissection was performed.

Pathology

Breast carcinoma was classified according to World Health Organization criteria [63]. Histological grade was evaluated using the criteria of Elston-Ellis modification of Scarff-Bloom-Richardson grading system [14]. The microscopic pathology margins were assessed by multiple sections. Inking of the specimen surfaces was not routinely performed. Margins were considered positive if invasive or in situ tumor existed at the resection margin; margins were deemed close if the tumor existed within 2 mm of the margin; and margins were considered clear if the tumor was at least 2 mm from the edge. Extensive intraductal component (EIC) was said to be present when 25% or more of an invasive ductal cancer consisted of intraductal carcinoma, and ductal carcinoma in situ was also present in adjacent breast tissue. Vascular invasion was reported when tumor cells were seen within spaces lined by recognizable endothelial cells. Mitotic activity index (MAI) was counted as the number of mitotic figures found in ten consecutive high-power fields in the most mitotically active part of the tumor. Patient and tumor characteristics are listed in Table 1.

Table 1. Patient and tumor characteristics. EIC: extensive intraductal component; ER: estrogen receptor; MAI: mitotic activity index; NA: not applicable (for lobular and medullary carcinomas).

Tabelle 1. Patienten und Tumoreigenschaften.

Characteristic	No boost (n = 103) n (%)	Boost (n = 104) n (%)	p-value
Mean age[a] (range)	54 (36–79)	54 (34–75)	0.57
Pathologic T			
• pT1a	6 (5.8)	4 (3.8)	0.47
• pT1b	11 (10.7)	6 (5.8)	
• pT1c	51 (49.5)	48 (46.2)	
• pT2	35 (34.0)	46 (44.2)	
Pathologic N			0.72
• pN0	77 (74.8)	80 (76.9)	
• pN1	26 (25.2)	24 (23.1)	
Surgical margins			0.74
• Positive	10 (9.7)	7 (6.7)	
• Close	5 (4.9)	5 (4.8)	
• Clear	88 (85.4)	92 (88.5)	
Histology			0.48
• Ductal	87 (84.5)	84 (80.8)	
• All others	16 (15.5)	20 (19.2)	
Histological grade			0.55
• 1	16 (15.5)	17 (16.3)	
• 2	55 (53.4)	58 (55.8)	
• 3	32 (31.1)	29 (27.9)	
MAI			
• ≤ 10	30 (29.1)	35 (33.7)	0.65
• > 10	73 (70.9)	69 (66.3)	
EIC			0.34
• Positive	30 (29.1)	27 (26.0)	
• Negative	67 (65.1)	65 (62.5)	
• NA	6 (5.8)	12 (11.5)	
Vascular invasion			0.28
• Positive	40 (38.8)	33 (31.7)	
• Negative	63 (61.2)	71 (68.3)	
ER status			0.96
• Positive	55 (53.4)	57 (54.8)	
• Negative	39 (37.9)	39 (37.5)	
• Unknown	9 (8.7)	8 (7.7)	

[a]in years

Radiation Therapy

All patients (n = 207) received external-beam RT to the entire breast using wedged tangential cobalt, or 6- to 9-MV photon fields. The median dose was 50 Gy (range: 46–50 Gy) with conventional fractionation (2 Gy/day, five fractions/week).

In the boost arm, 52 out of 104 (50%) women received electron-beam boost to the tumor bed. Adequate field size and beam energy (6–16 MeV) were defined by CT-based treatment planning to encompass the clipped excision cavity with 1–1.5 cm margin. The median dose of electron boost was 16 Gy (mean: 15.2 Gy; range: 8–16 Gy).

The other 52 patients were boosted by BT with a microSelectron HDR remote afterloader (Nucletron B.V., Veenendaal, The Netherlands) using an iridium-192 isotope with 370

GBq (10 Ci) initial activity. Implantations were performed 3 weeks after whole breast radiotherapy (WBRT). The rules of the Paris System were used for the planning of implant geometry [43]. Our implant technique and the process of BT treatment planning have been described elsewhere in detail [44, 45]. Briefly, three to nine guide needles were inserted into the tumor bed in a triangular setting with template guidance. The target volume was defined as the clipped excision cavity with a margin of 1–1.5 cm. The spacing between the needles was 15 mm. Single-, double- and triple-plane implants were performed in three (5.8%), 47 (90.4%), and two (3.8%) cases, respectively. Having implanted all the guide needles, these were replaced with flexible afterloading catheters, and the ends were fixed with plastic buttons. Once the implantation was completed, two isocentric X-ray films were taken of the implanted breast. The "conformal semi-3-D" BT treatment planning was based on the 3-D reconstruction of the catheters, tumor bed clips and skin points with the help of the X-ray films. The active source positions, dwell times and reference dose points were defined individually in each catheter, and then dose optimization on dose points and geometry was performed. The distances of reference dose points from the catheters were 5–12 mm, and might vary from catheter to catheter.

The HDR fractionation schedules were calculated using the linear-quadratic model [29] with an α/β ratio of 4 Gy for late and 10 Gy for early effects. For the first 19 patients, the total boost dose was calculated to be equivalent to late effects of 20 Gy low-dose-rate (LDR) radiation. Since serious side effects were not observed, the total boost dose was increased for the next 33 patients to be equivalent to the early effects of 20 Gy LDR treatment. So, the prescribed HDR doses (calculated to the 100% isodose surface) consisted of three fractions of 4.0 Gy (n = 19) and 4.75 Gy (n = 33) over 3 days for a total boost dose of 12.0 Gy and 14.25 Gy, respectively.

For patients with negative axillary lymph nodes (pN0) or with metastasis ≤ 2 mm (pN1a), regional nodal irradiation (RNI) was omitted. All others received RNI by an anterior supraclavicular/axillary field. The median RNI dose was 50 Gy (range: 44–50 Gy) with conventional fractionation for 26 out of 103 (25.2%) and 24 out of 104 (23.1%) patients in the two treatment arms, respectively. Treatment of internal mammary chain was not intended.

Adjuvant Systemic Therapy

Adjuvant systemic therapy for node-negative patients was optional rather than mandatory before the 1998 St. Gallen's Consensus Conference [64]. 46 out of 103 (44.7%) and 40 out of 104 (38.5%) women received chemo- and/or hormonal therapy in the two treatment arms, respectively (p = 0.2225). Details of adjuvant systemic treatments are listed in Table 2. Chemotherapy for premenopausal women with positive axillary lymph nodes consisted of six cycles of CMF (cyclophosphamide, methotrexate, 5-fluorouracil) or CAF (cyclophosphamide, adriamycin, 5-fluorouracil). Postmenopausal patients with positive estrogen receptor status were offered a daily 20 mg of tamoxifen for 5 years.

Table 2. Adjuvant systemic treatment.

Tabelle 2. Adjuvant systemische Behandlung.

Treatment	No boost (n = 103) n (%)	Boost (n = 104) n (%)	p-value
Hormonal therapy	19 (18.5)	18 (17.3)	0.78
Chemotherapy	21 (20.4)	16 (15.4)	
Chemo- + hormonal therapy	6 (5.8)	6 (5.8)	
None	57 (55.3)	64 (61.5)	

Follow-up

Patients were seen every 3 months in the first 2 years after RT, and every 6 months thereafter. Mammography, chest X-ray, breast and abdominal ultrasound examinations, bone scan, and blood tests were performed at least annually. Local recurrence was defined as any detection of cancer in the treated breast, proven by histological examination in each case. Survival times were calculated from the day of surgery to the occurrence of the event or the end of follow-up period. No patient was lost to follow-up. The median follow-up time for surviving patients was 64 months (range: 43–77 months).

Statistical Methods

The Solo software (Department of Biometrics, University of California, Los Angeles, USA) was used for statistical analyses. Groups were compared using the χ^2 test for qualitative variables. The actuarial rate of LTC, RFS, and CSS was estimated by the Kaplan-Meier method [31]. The log-rank test was used to compare time distributions. Uni- and multivariate Cox proportional hazards analyses were used to evaluate prognostic factors with respect to LTC [9]. The relative risk (RR) and the 95% confidence interval (95% CI) were calculated from the regression coefficient. Differences in the incidence of side effects between study groups were compared using Fisher's exact test. A p-value ≤ 0.05 was considered to represent statistical significance. A trend to significance was established at p-values > 0.05 and ≤ 0.10.

Results

Treatment Results

At a median follow-up of 64 months, 23 (11.1%) patients developed ipsilateral breast tumor recurrence. The crude rates of breast cancer-related events according to treatment arms are summarized in Table 3. There have been seven (6.7%) local relapses in the boost arm and 16 (15.5%) in the control arm. Four out of seven (57.1%) and twelve out of 16 (75.0%)

Table 3. Incidence of breast cancer-related events according to boost treatment.

Tabelle 3. Inzidenz von Nebenwirkungen bezüglich der Boost-Behandlung.

Boost treatment	Tumor bed relapse % (n)[b]	Local relapse % (n)[b]	Any first relapse[a] % (n)[b]	Breast cancer death % (n)[b]
No boost	11.7 (12/103)	15.5 (16/103)	35.0 (36/103)	19.4 (20/103)
Boost	3.8 (4/104)	6.7 (7/104)	22.1 (23/104)	9.6 (10/104)

[a]local, regional or distant relapse (whichever came first); [b]n = number of events/patients

local relapses were true tumor bed recurrences, respectively. Elsewhere breast failures occurred in three (2.9%) and four (3.9%) women in the two treatment arms (p = 0.49). The 5-year probability of LTC (Figure 2), RFS (Figure 3), and CSS was 92.7% vs 84.9% (p = 0.049; RR: 0.42; 95% CI: 0.17–1.02), 76.6% vs 66.2% (p = 0.044; RR: 0.60; 95% CI: 0.36–1.01), and 90.4% vs 82.1% (p = 0.053; RR: 0.48; 95% CI: 0.22–1.03) in favor of the boost group. Three (5.8%) local recurrences were seen in patients treated with electron boost and four (7.7%) in the HDR BT group. There was no significant difference in the 5-year LTC according to boost technique (94.2% vs 91.4%; p = 0.74).

Local recurrence occurred as a first event in 5.8% (six of 104) in the boosted group, and in 11.7% (twelve of 103) in the control arm (p = 0.10). Mean time to isolated local relapse was 31 months (range: 10–70 months). Isolated local recurrence was followed by subsequent distant metastases in ten of the 18 patients (55.6%). Mean time between isolated local relapse and distant relapse was 14 months (range: 1–42 months).

Adjuvant systemic treatments (chemo- and/or hormonal therapy) had no significant impact on LTC. The 5-year actuarial rate of intra-breast relapse was 11.7% (eight of 86) with and 11.1% (15 of 121) without systemic therapy (p = NS).

Uni- and Multivariate Analysis of Prognostic Factors for Local Recurrence

Results of univariate Cox regression analysis of possible prognostic factors for local recurrence are summarized in Table 4. Only young age, positive margin status, and high MAI had a significant negative effect on LTC. Variables that reached the 0.05 level of significance were entered in the multivariate model. This analysis demonstrated that all three factors remained significant: younger age (p = 0.002; RR: 4.53; CI 95%: 1.74–11.79), positive margin status (p = 0.006; RR: 4.17; CI 95%: 1.50–11.57), and higher MAI (p = 0.04; RR: 3.60; CI 95%: 1.06–12.28).

The actuarial 5-year local recurrence rate for younger patients was 27.1 (two of eight) with and 34.4% (four of ten) without boost (p = NS). The same rates for patients older than 40 years were 5.8% (five of 96) and 13.2% (twelve of 93; p = 0.067).

Separate analysis of patients with negative surgical margins revealed a 5-year local recurrence rate of 6.8% (six of 97) with and 11.6% (twelve of 93) without boost (Figure 4). However, in case of positive or close surgical margins, boost dose decreased the 5-year actuarial breast relapse rate from 50.8% (seven of 15) to 8.3% (one of twelve).

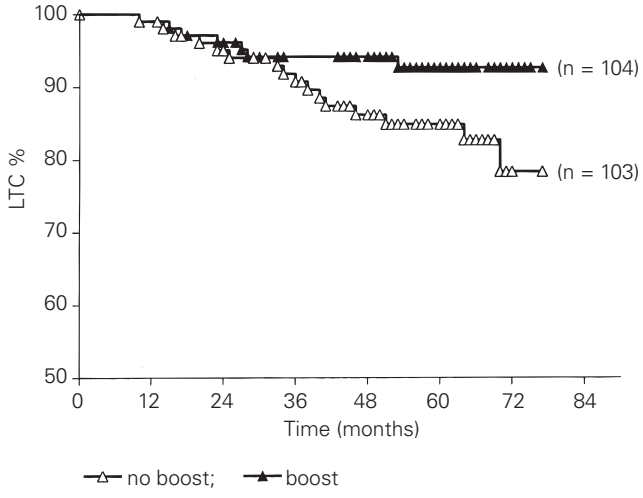

Figure 2. Time to local recurrence by Kaplan-Meier estimates. 5-year local tumor control (LTC): 92.7% (boost) vs 84.9% (no boost); p = 0.049.

Abbildung 2. Auftreten von Lokalrezidiven gemäß Kaplan-Meier-Berechnung. Lokale Tumorkontrolle, 5-Jahres-Überlebensraten (LTC): 92,7% (Boost) vs. 84,9% (ohne Boost); p = 0,049.

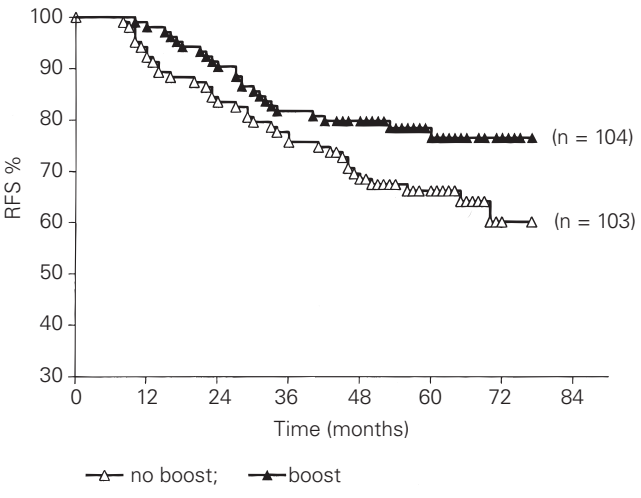

Figure 3. Time to first relapse by Kaplan-Meier estimates. 5-year relapse-ree survival (RFS): 76.6% (boost) vs 66.2% (no boost); p = 0.044.

Abbildung 3. Zeitspanne bis zum Auftreten des ersten Rezidivs gemäß Kaplan-Meier-Berechnung. Rezidivfreies Überleben, 5-Jahres-Überlebensraten (RFS): 76,6% (Boost) vs. 66,2% (ohne Boost); p = 0,044.

Table 4. 5-year actuarial local recurrence rate according to prognostic factors (univariate analysis). CI 95%: 95% confidence interval; EIC: extensive intraductal component; ER: estrogen receptor; MAI: mitotic activity index; NS: not significant; RR: relative risk.

Tabelle 4. Lokale 5-Jahres-Tumorkontrolle gemäß prognostischen Faktoren.

Characteristic	% (n)[a]	p-value	RR (CI 95%)
ER status[b]		NS	–
• Positive	7.9 (10/112)		
• Negative	13.4 (10/78)		
Histology			
• Ductal	12.3 (21/171)	NS	–
•All others	5.6 (2/36)		
Pathologic T			
• pT1	10.0 (13/126)	NS	–
• pT2	12.9 (10/81)		
Pathologic N			
• pN0	9.6 (16/157)	NS	–
• pN1	16.5 (7/50)		
Margin status			
• Negative	9.1 (18/190)	0.02	1
• Positive	32.4 (5/17)		3.23 (1.20–8.71)
EIC			
• Negative	9.7 (15/150)	NS	–
• Positive	14.6 (8/57)		
Histological grade			
• 1–2	9.5 (13/136)	NS	–
• 3	14.2 (10/71)		
MAI			
• ≤ 10	3.1 (3/65)	0.03	1
• > 10	15.1 (20/142)		3.77 (1.12–12.71)
Vascular invasion			
• Negative	10.2 (15/134)	NS	–
• Positive	12.5 (8/73)		
Age (years)			
• ≥ 40	9.3 (17/189)	0.001	1
• < 40	30.7 (6/18)		4.71 (1.85–12.01)

[a]n = number of events/patients; [b]local recurrence rate with unknown ER status: 20.5% (3/17)

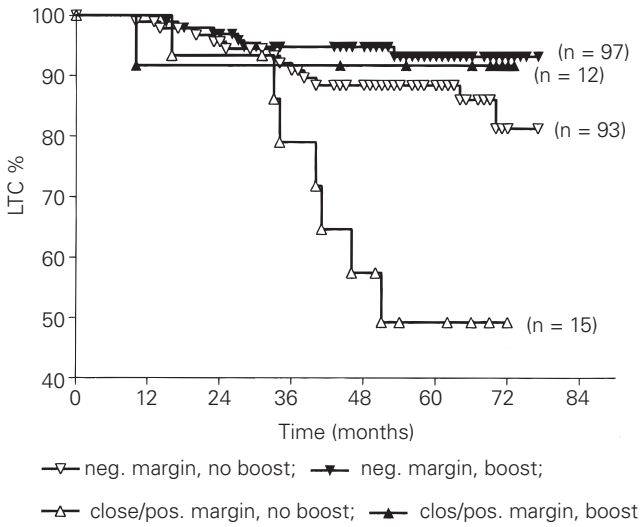

Figure 4. Time to local recurrence according to margin status and boost treatment by Kaplan-Meier estimates. 5-year local tumor control (LTC) for patients with negative surgical margins: 93.2% (boost) vs. 88.4% (no boost); p = 0.13. 5-year LTC for patients with close (≤ 2 mm) or positive margins: 91.7% (boost) vs 49.2% (no boost); p = 0.04.

Abbildung 4. Zeitspanne bis zum Auftreten eines Lokalrezidivs bezüglich des Status des Schnittrandes und der Boost-Behandlung gemäß Kaplan-Meier-Berechnung. Lokale Tumorkontrolle, 5-Jahres-Überlebensraten (LTC) bei Patientinnen mit negativen Schnitträndern: 93,2% (Boost) vs. 88,4% (ohne Boost); p = 0,13. Lokale Tumorkontrolle, 5-Jahres-Überlebensraten (LTC) bei Patientinnen mit schmalem (≤ 2 mm) oder positiven Schnitträndern: 91,7% (Boost) vs. 49,2% (ohne Boost); p = 0,04.

Late Side Effects and Cosmetic Results

Distribution of late radiation side effects according to treatment arms is summarized in Table 5. The incidence of skin side effects, fibrosis, and fat necrosis was higher in the boost arm, but the differences were not significant. However, when all grade 2–3 side effects were evaluated together, there was a significant difference between the two treatment arms (17.3% [18 of 104] with and 7.8% [eight of 103] without boost; p = 0.03). The respective rate of excellent/good cosmesis was 85.6% (89 of 104) and 91.3% (94 of 103; p = 0.14).

The impact of boost technique (HDR BT vs. electron) on late side effects and cosmesis was also evaluated. Grade 2–3 telangiectasia occurred in four out of 52 patients (7.7%) in both groups. The incidence of moderate/severe fibrosis was significantly higher after HDR BT boost (17.3% [nine of 52] vs 1.9% [one of 52]; p = 0.008). However, no statistically significant difference in the percentage of patients obtaining excellent/good cosmetic results was seen between HDR BT (88.5%; 46 of 52) and electrons (82.7%; 43 of 52; p = 0.29).

Discussion

The standard radiotherapy technique after breast conservation is WBRT up to 45–50 Gy with or without a boost [39]. Boost irradiation has been used in the majority of earlier trials yielding appropriate local control rate and acceptable cosmetic results [2, 5, 7, 28, 56, 58]. The rationale for boosting the primary tumor bed up to 60–70 Gy is based on the evidence that the majority (50–100%) of local recurrences occur in or close to the same quadrant as the index cancer [3, 19, 26, 34, 41, 59, 62]. A clear dose-local control relationship for doses > 45 Gy was found by several authors [25, 46, 57]. However, the precise indications for boost irradiation are not well defined. On the other hand, in the National Surgical Adjuvant Breast and Bowel Project (NSABP) B-06, the Uppsala-Örebro trials and other retrospective series, 50–56 Gy WBRT without local boost appeared highly effective for LTC – at least when tumor resection margins were pathologically free of cancer [4, 15, 18, 34, 42].

Table 5. Distribution of late radiation side effects according to treatment arms.

Tabelle 5. Verteilung der Spätnebenwirkungen in den Behandlungsarmen.

Side effect	No boost (n = 103) n (%)	Boost (n = 104) n (%)	p-value
Skin[a]			0.40
• Grade 0	91 (88.4)	86 (82.7)	
• Grade 1	9 (8.7)	10 (9.6)	
• Grade 2	2 (1.9)	7 (6.7)	
• Grade 3	1 (1.0)	1 (1.0)	
Fibrosis[a]			0.43
• Grade 0	80 (77.6)	72 (69.2)	
• Grade 1	18 (17.5)	22 (21.2)	
• Grade 2	4 (3.9)	9 (8.7)	
• Grade 3	1 (1.0)	1 (1.0)	
Fat necrosis			0.31
• Asymptomatic	6 (5.8)	10 (9.6)	
• Symptomatic	0 (0)	0 (0)	

[a]RTOG/EORTC late radiation morbidity scoring scheme [10]

To date, only two prospective studies have evaluated the impact of boost dose on local control [3, 47]. The interim results of a randomized clinical trial in Lyon show that a 10-Gy electron boost to the tumor bed significantly reduces the risk of ipsilateral breast tumor recurrence [47]. The difference in the 5-year LTC between the two treatment arms was only 0.9%. However, it is to be noted that only patients with tumors up to 3 cm and free "inked" surgical margins were entered into this trial. The disease-free survival rate was also significantly better in the boost arm, but the effect of boost on overall survival was modest.

The 5-year results of the EORTC "boost vs. no boost" study were reported very recently [3]. A boost dose of 16 Gy decreased the 5-year actuarial local recurrence rate by 3% in the 5,318 patients with complete excision ($p < 0.001$), but survival free of distant metastases and overall survival were similar in the two treatment groups.

Our results have also shown that 16 Gy electron or 12–14.25 Gy HDR BT boost significantly decreases the 5-year rate of local relapse from 15.1% to 7.3%. The 5-year RFS was significantly better in the boosted group (76.6%) than in the control arm (66.2%). However, the trial showed only a non-significant trend toward better CSS in the boost group. It is difficult to know whether the better survival result obtained in the boost arm is in part due to the small sample size, relatively short follow-up, or mere chance. The results of prospective and retrospective trials suggested that the addition of RT to lumpectomy offered a small but significant survival advantage [30, 33]. It is clear that an even smaller (if any) survival benefit would be expected with boost. To detect this modest effect on survival with appropriate statistical power, a large trial with thousands of patients and longer follow-up (10–15 years) is required.

The apparently higher local recurrence rate in our series compared to the Lyon and EORTC trials is explained by the worse prognostic characteristics of our patient population [3, 47]. In both studies, only patients with pathologically free surgical margins were analyzed. We also enrolled patients with involved resection margins (17 patients; 8.2%). Excluding cases with positive surgical margins, LTC was similar in our study to that reported by Romestaing et al [47] and Bartelink et al [3]. On the other hand, the greater number of high-risk patients in our study reflects the fact that our institution was enrolling low-risk patients in another clinical trial evaluating the effectiveness of sole BT after BCS, during the same period [45].

We found that age less than 40 years, positive margin status, and high MAI were significant prognostic factors associated with higher local recurrence rate. Young age, as a risk factor for local breast recurrence, has been widely disputed in the literature [3, 12, 13, 20]. Most series reported an increased breast failure rate using different age cutoffs. The EORTC boost trial demonstrated that young age was the most important prognostic factor for local recurrence, and the largest clinical benefit from boost was seen in patients younger than 40 years [3]. In our series, the 5-year local failure rate was also significantly higher for younger women (30.7% vs 9.3%). However, the benefit from boost in younger patients was smaller than in the EORTC trial. These results suggest that there is a distinct biological difference in breast carcinoma presenting in young women that predisposes them to local recurrence. On the other hand, boost dose decreased the incidence of breast relapses by a factor of 2 in elderly patients, as well.

Positive margin status has been generally accepted as a major risk factor for local breast recurrence [1, 51, 53, 54]. In our series, positive surgical margin also significantly increased the risk of local recurrence. However, in case of positive or close margins the boost dose significantly decreased the incidence of breast relapse. On the contrary, in the EORTC boost trial margin status had only a marginal impact on LTC [3].

Only a few authors examined the relationship between MAI and LTC. In the study by Schnitt et al [52], high mitotic activity was associated with significantly higher local recurrence rate. We also found that MAI > 10 was an independent risk factor for breast failure.

Boost dose significantly increased the incidence of late radiation side effects. However, the proportion of patients with excellent/good cosmesis was similar in the two arms. Romestaing et al [47] also found a significant effect of the boost on the frequency of telangiectasia, but it did not affect the overall cosmetic assessment. Vrieling et al [60] analyzed the influence of patient, tumor and treatment factors on the cosmetic results in the EORTC trial. The rate of excellent/good cosmesis at 3 years was 71% with and 86% without boost ($p < 0.001$). Several other studies also found that boost dose had a negative effect on cosmesis [37, 48, 61].

Only a few reports have compared outcome in patients treated with BT or electron boost [11, 21, 27, 36, 41, 55, 59].

Most of these authors used LDR Ir-192 implants [36, 41, 55, 59]. Mansfield et al [36] found that 20 Gy perioperative LDR BT boost yielded a significantly better LTC for stage II patients. Others reported similar local control and cosmesis for women boosted with either LDR BT or electrons [11, 21, 41, 55, 59].

The largest HDR series have been reported by Hammer et al [23, 24]. The 5-year local relapse rate of 3.5% with encouraging cosmetic results proved the safety of the use of HDR BT as a boost of 10 Gy in one fraction [24]. Jacobs [27] found that a 12- to 15-Gy boost with HDR BT given in a single treatment session resulted in better LTC than with electrons. To date, only two groups reported early experience with fractionated HDR BT boost [26, 35]. In the study by Hennequin et al [26], 106 patients were treated with a boost of 10 Gy in two fractions. The authors found a 5.1% local recurrence rate at 5 years and excellent/good cosmetic outcomes in 63.2%. In another series from Virginia, a total HDR boost dose of 15 Gy was delivered in six fractions of 2.5 Gy over 3 days to 18 women with close or focally positive surgical margins [35]. Inbreast failures have not been observed at a median follow-up of 50 months. 67% of patients were considered to have experienced excellent/good cosmesis.

Our results showed that local control and cosmetic outcome were excellent and similar to women boosted with either 12–14.25 Gy HDR BT in three daily fractions or 16 Gy electrons. Moderate/severe fibrosis occurred more frequently after BT, but fibrotic mass was always confined to the tumor bed and did not affect cosmetic appearance.

The impact of adjuvant systemic treatments on local control after breast conservation is controversial [6, 16, 17, 32, 36, 40, 50]. The NSABP B-13 and B-14 trials showed that both adjuvant chemotherapy and tamoxifen significantly reduced the local recurrence rate for patients treated with conservative surgery and RT [16, 17]. On the contrary, according to the results of several retrospective series chemotherapy had no influence on LTC [6, 36, 50]. Our trial was not designed to evaluate the effect of adjuvant systemic treatments on LTC. Neither did we find any significant difference in LTC for patients treated with or without adjuvant systemic therapy.

Conclusions

The interim results of our randomized study showed that 12–14.25 Gy HDR BT or 16 Gy electron boost significantly improved LTC and RFS for patients treated with BCS and RT. However, the influence of boost on survival is controversial and should be tested in further studies. In spite of the higher incidence of late side effects in the boost arm, boost dose is strongly recommended for patients at high risk for local recurrence. Young patient age, positive/close margin status, and high MAI should be viewed as absolute indications for tumor bed boost. LTC and cosmesis are excellent and similar in patients boosted with either HDR BT or electrons.

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