



Breast conserving surgery in combination with intraoperative radiotherapy after previous external beam therapy: an option to avoid mastectomy

F. Thangarajah^{1,2} · J. Heilmann⁴ · W. Malter^{1,2} · S. Kunze³ · S. Marnitz³ · P. Mallmann¹ · F. Wenz⁴ · E. Sperk⁴

Received: 23 December 2017 / Accepted: 30 December 2017
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Abstract

Purpose Mastectomy is the standard procedure in patients with in-breast tumor recurrence (IBTR) or breast cancer after irradiation of the chest due to Hodgkin's disease. In certain cases a second breast conserving surgery (BCS) in combination with intraoperative radiotherapy (IORT) is possible. To date, data concerning BCS in combination with IORT in pre-irradiated patients are limited. This is the first pooled analysis of this special indication with a mature follow-up of 5 years.

Methods Patients with IBTR after external beam radiotherapy (EBRT; treated in two centers) for breast cancer were included. Patients with previous EBRT including the breast tissue due to other diseases were also included. IORT was performed with the IntrabeamTM-device using low kV X-rays. Clinical data including outcome for all patients and toxicity for a representative cohort (LENT-SOMA scales) were obtained. Statistical analyses were done including Kaplan–Meier estimates for local recurrence, distant metastasis and overall survival.

Results A total of 41 patients were identified (39 patients with IBTR, 2 with Hodgkin's disease in previous medical history). Median follow-up was 58 months (range 4–170). No grade 3/4 acute toxicity occurred within 9 weeks. Local recurrence-free survival rate was 89.9% and overall survival was 82.7% at 5 years. Seven patients developed metastasis within the whole follow-up.

Conclusions BCS in combination with IORT in IBTR in pre-irradiated patients is a feasible method to avoid mastectomy with a low risk of side effects and an excellent local control and good overall survival.

Keywords IORT · BCS · IBTR · Previous irradiation · Re-irradiation

Introduction

In patients with locally recurrent breast cancer mastectomy is still the standard surgical procedure [1]. Mastectomy in the setting of recurrent disease results in a second local

recurrence rate of 2–31% [2, 3]. In patients with an in-breast tumor recurrence (IBTR), 5-year overall survival rates after mastectomy range from 52 to 84% in different studies [3–8].

Individual options for treating locally recurrent breast cancer or patients with previous irradiation due to other diseases, e.g., Hodgkin's disease with a (second) breast conserving surgery (BCS) are limited. BCS is usually avoided because a second full-course external beam radiotherapy (EBRT) of the breast tissue is potentially associated with late toxicity like rib fractures, fibroses and unfavorable cosmesis. Current alternative options are BCS with re-irradiation of the breast using intraoperative radiotherapy (IORT) where only a small but relevant amount of normal tissue is exposed to a high single dose (accelerated partial breast irradiation = APBI) or BCS with external partial breast irradiation or without any radiation.

The results concerning local excision for locally recurrent breast cancer are inconsistent.

✉ F. Thangarajah
Fabinsky.Thangarajah@uk-koeln.de

¹ Department of Gynecology and Obstetrics, Faculty of Medicine, University Hospital of Cologne, University of Cologne, Kerpener Str. 34, 50931 Cologne, Germany

² Breast Center, University Hospital of Cologne, University of Cologne, Cologne, Germany

³ Department of Radiation Oncology, University Hospital of Cologne, University of Cologne, Cologne, Germany

⁴ Department of Radiation Oncology, Universitätsmedizin Mannheim, University of Heidelberg, Mannheim, Germany

Wide local excision without irradiation for isolated locally recurrent breast cancer is associated with a 5-year local control and cause-specific survival of 79% which is comparable to results reported after mastectomy shown by Kurtz et al. [3, 9].

In contrast, Salvadori et al. reported that the risk of a second local recurrence was significantly increased in patients with a local resection at 19% versus 4% for patients with total mastectomy [3, 4].

BCS with re-irradiation of the whole breast is associated with increased rates of toxicity and fibrosis and is, therefore, not widely used [10]. BCS in combination with IORT is one option to deliver high doses to a limited area at risk after resection of the tumor. IORT can be delivered with dedicated linear accelerators in the operation room or novel mobile devices using electrons or low-energy X-rays [11, 12].

IORT in combination with BCS prolongs slightly the surgical procedure depending on the technique used in different series [13].

Up to date, data reporting outcome or even toxicity after BCS in combination with IORT in locally recurrent breast cancer and patients with a history of irradiation to the breast due to other diseases are limited and often have a short median follow-up.

Hence, we aimed to analyze a pooled cohort with BCS in combination with IORT as a therapeutic option in selected patients with pre-irradiation to the breast with a mature follow-up of 5 years.

Methods

Patients with in-breast tumor recurrence after external beam therapy who were treated in the University Hospital of Cologne ($n = 10$) and the University Hospital of Mannheim ($n = 29$) between 2002 and 2015 were included in this analysis. Additionally, patients with external beam therapy in the past due to other diseases were also assessed and analyzed ($n = 2$).

IORT was performed with the Intrabeam™-device (Carl Zeiss Meditec, Oberkochen, Germany) using 50 kV X-rays. The dose at the applicator surface was 20.0 Gy in most patients ($n = 39$), in two patients a dose of 14.7 Gy was applied (due to technical reasons). Applicator diameter varied from 2.5 to 5.0 cm. In 31.7% of all cases an applicator diameter of 4 cm was selected. Details of the procedure has been reported elsewhere [14]. Mean radiation time was 26.0 (range 12–52) min.

Patients had regular yearly follow-up with clinical examination, mammograms and ultrasound and evaluation of cosmesis. For this analysis all available patient and tumor characteristics were obtained and development of local

recurrence, distant metastasis, secondary cancer and survival were noted.

Acute and late toxicities were documented systematically. Skin toxicities were documented according to the Late Effects in Normal Tissues—Subjective, Objective, Management and Analytic (LENT-SOMA) scoring system in subgroup of 15 representative patients [15].

Statistical analysis

Statistical analysis was performed with SPSS statistics 24 for descriptive statistic. Disease-free survival between primary diagnosis and recurrent breast cancer, disease-free survival between occurrence of recurrent breast cancer and time of analysis and overall survival were calculated using the Kaplan–Meier method. Acute and late toxicities were reported yearly.

Results

A total of 41 patients were included in this analysis. Patient characteristics regarding current breast cancer are illustrated in Table 1.

Mean age of the patients was 60 years (range 41–86 years). In this cohort 39 patients were included due to an in-breast tumor recurrence (IBTR) and two patients with Hodgkin's disease and previous external beam therapy for the mediastinum. Of these patients, three patients had a DCIS recurrence after breast cancer in history. Details including the histological subtype of all patients are presented in Table 2.

The median interval between first diagnosis and IBTR was 9.3 years (range 1.9–22.4 years).

Short- and long-term effects

No grade 3 or 4 acute toxicity occurred during a follow-up of 9 weeks. In 15 patients, long-term effects after 5 years of follow-up could be obtained: 4 patients developed grade 2 or higher grade of fibrosis, one patient experienced circumscribed telangiectasia of the skin, three patients developed moderate retractions and four patients had moderate pain within the irradiated volume. Complete results are presented in Fig. 1.

Follow-up data

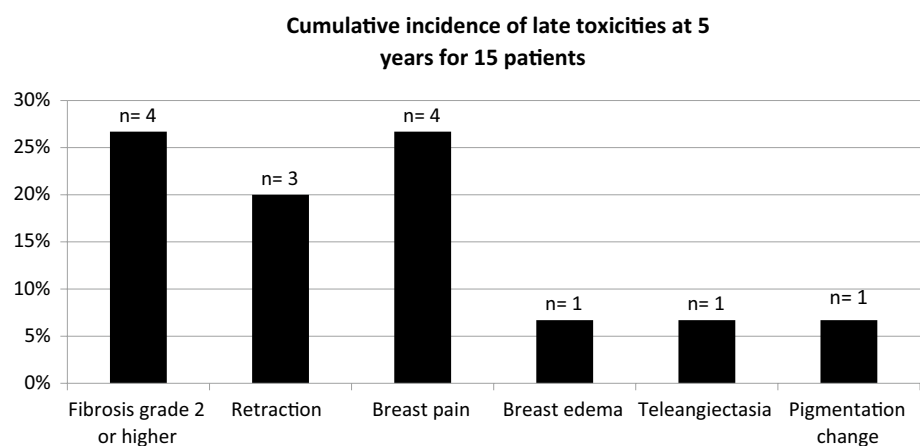
For 38 patients follow-up data could be obtained, three patients were lost to follow-up. Three patients with synchronous metastasis at the time of BCS and IORT were excluded for the calculation of the metastasis-free survival. Local recurrences occurred in three patients [7.9%, median

Table 1 Patients' characteristics

	Percentage	<i>n</i>
T stage		
Tis	7.3	3
T1a-c	85.4	35
T2	7.3	3
Receptor status		
Estrogen receptor positive	68.3	28
Progesterone receptor positive	61.0	25
HER2 enriched	17.1	7
N stage		
N0	43.9	18
N1	4.9	2
Nx	51.2	21
M stage		
M0	92.3	38
M1	7.3	3
Localisation of the tumor within breast		
3 O'Clock	2.5	1
6 O'Clock	5.0	2
9 O'Clock	2.5	1
12 O'Clock	2.5	1
Upper inner	15	6
Upper outer	40	16
Lower inner	15	6
Lower outer	7.5	3
Central	10	4

Table 2 Histologic subtype

Histologic subtype percentage <i>n</i>		
Invasive ductal	73.2	30
Invasive tubulolobular	14.6	6
Mucinous	2.4	1
Adenoid cystic	2.4	1
DCIS	7.3	3

Fig. 1 Cumulative incidence of late toxicities at 5 years for 15 patients according to LENT-SOMA

follow-up 52.5 months (range 4–170 months)], metastases in seven patients [20.0%, median follow-up 58.0 months (range 2–170 months)] and nine patients died (23.7%, median follow-up 58.0 months [range 4–170 months]). Local recurrence-free survival was 89.7% at 5 years (Fig. 2). Metastasis-free survival was 79.7% at 5 years (Fig. 3) and overall survival 82.7% at 5 years (Fig. 4).

Discussion

As mastectomy is the standard procedure in in-breast tumor recurrence it can lead to adverse psychological impact of patients compared to patients with BCS [16]. Patients often face disfigurement caused by the loss of their breast [17]. Besides, mastectomy is associated with surgical complications, e.g., higher blood loss and increased hospital stay [18].

As an alternative to mastectomy we aimed to analyze BCS in combination with IORT in in-breast tumor recurrence and patients with Hodgkin's disease with previous external beam therapy. Retrospectively we analyzed 41 patients who received a BCS with IORT with 50 kV X-rays. They experienced no acute grade 3 or 4 toxicity, an acceptable rate of late toxicity with 26.7% higher grade fibrosis and low chronic skin toxicity rates of < 7% telangiectasia and pigmentation change each. No rib fracture occurred. Local recurrence rate was low with 7.9% during the whole follow-up and a good overall all survival with 83% at 5 years could be demonstrated.

Re-irradiation

Although some authors confirm that re-irradiation after BCS results in good local control rate of 93% and less side effects [19], most authors fear increased rates of toxicity and fibrosis and fractures caused by re-irradiation of the whole breast tissue [10]. Within our cohort no patient experienced acute toxicities during surgery or after surgery with IORT. Among

Fig. 2 Local recurrence-free survival of overall cohort

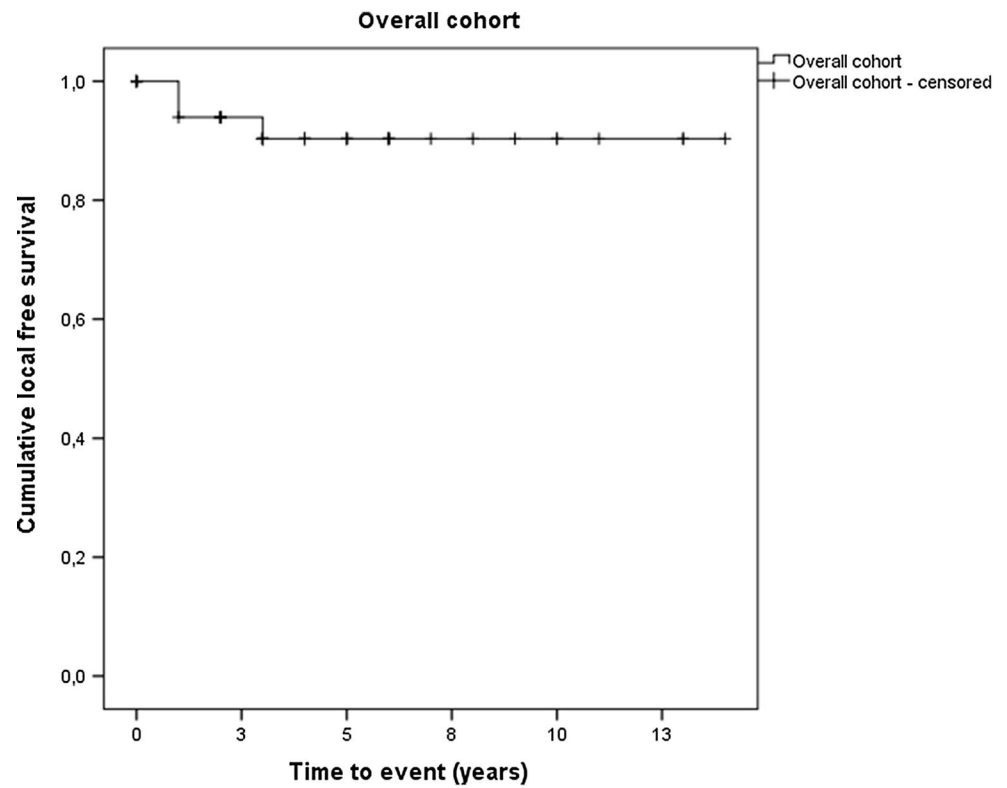
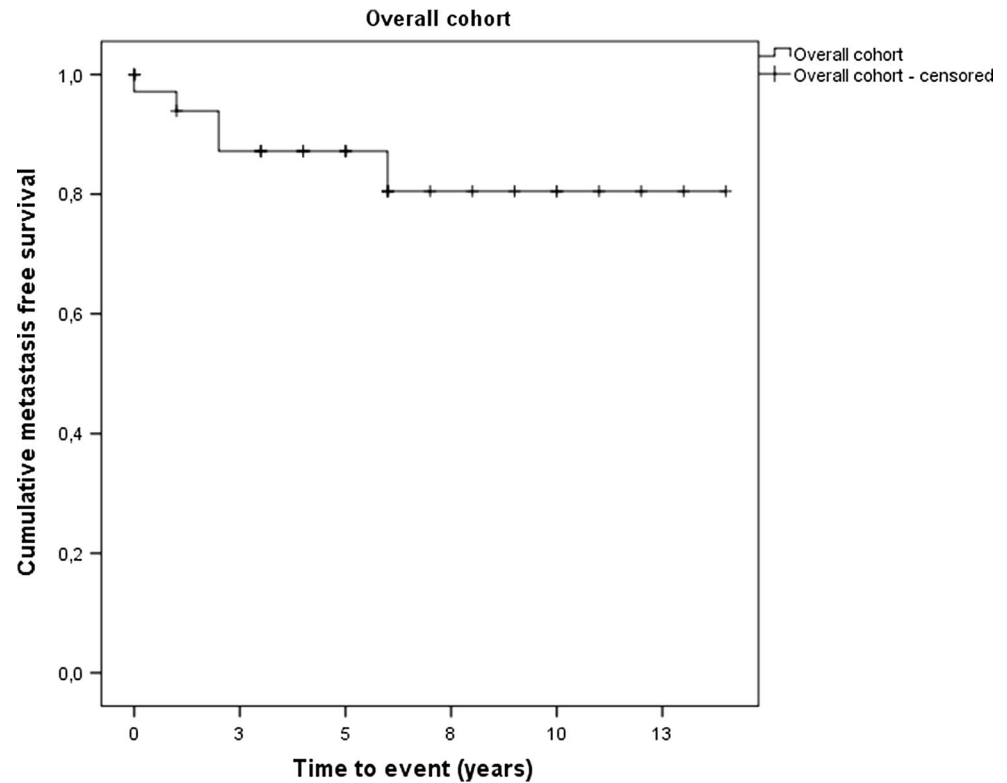


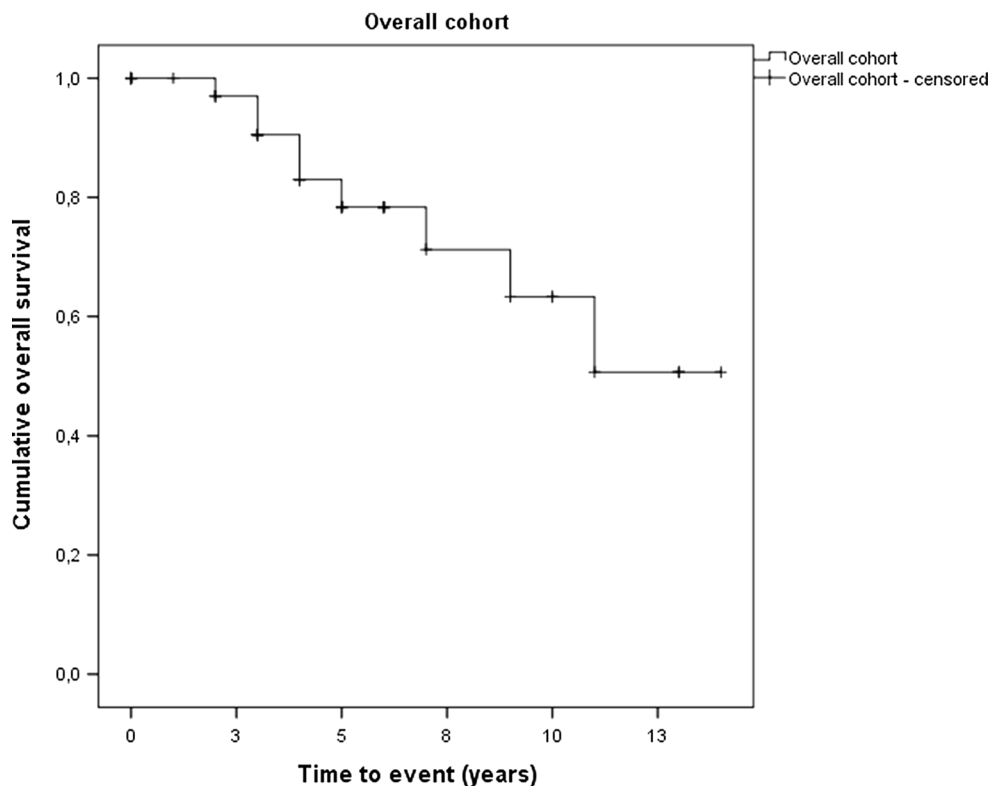
Fig. 3 Cumulative metastatic-free survival



the 15 patients who have been systematically evaluated with the LENT-SOMA score, 4 patients experienced grade 2 or higher grade of fibrosis (26.7%). This is in range with results

after breast irradiation for the first time and represents a normal range in this special group of pre-irradiated patients. But the sample size appears limited to draw final conclusions.

Fig. 4 Overall survival of the cohort



BCS and IORT

The combined therapy of BCS and IORT with 50 kV X-rays in case of in-breast tumor recurrence after previous whole breast irradiation has been described by Kraus-Tiefenbacher et al. They retrospectively analyzed 21 patients who received BCS with IORT [12]. After a median follow-up of 26 months no local recurrence occurred. The present results

are similar with three local recurrences in a median follow-up time of 52 months, respectively. These results confirm a good local control.

Kraus-Tiefenbacher et al. report that 14 out of 17 patients were alive and free of progression. Two patients were alive with distant metastases. One patient died 26 months after BCS with IORT [12]. Our results show rates after a mature

Table 3 Efficacy of BCS with partial breast irradiation after previous irradiation of the breast in comparison to the literature

Author	Number of patients	Technique	Median follow-up (months)	Local recurrence (%)	Mortality (%)	Other findings
Kraus-Tiefenbacher [11]	21	kV IORT	26	0	5.9	No Grade 3/4 toxicities, 35.3% showed limited induration of the tumor bed, in 17.6% cases the moderate to severe induration of the area treated with IORT
Intra [18]	43	IORT with electrons	52	9	9.2	4.7% developed slight induration (fibrosis) in the irradiated area, further 4.7% had moderate slight field contracture
Blandino [19]	30	IORT with electrons	47	3.4	10.3	62.0% grade 2/3 subcutaneous toxicity (fibrosis) at last follow-up according to RTOGEORTC
Current analysis	41	kV IORT	58	7.9	18.4	No grade 3 or 4 acute toxicity, higher grade fibrosis 27%, chronic skin toxicity < 7%

follow-up of 5 years and may, therefore, differ concerning the overall survival and the metastasis-free survival.

Intra et al. examined patients with breast cancer and previous external beam therapy due to Hodgkin's disease. These patients underwent BCS and intraoperative radiotherapy with electrons. The colleagues reported a similar local recurrence rate. A local recurrence occurred in 9% after a median follow-up of 52 months [20].

Recently, Blandino et al. also confirmed a good local control in patients with IBTR and previous irradiation as well as in patients with irradiation due to Hodgkin's disease. They reported a local recurrence-free survival of 92, 3% at 5 years [21]. Table 3 shows all discussed data and gives an overview.

Conclusion

Our results of a pooled cohort with a follow-up up to 10 years and more show that BCS in combination with 50 kV X-ray IORT in in-breast tumor recurrence cancer after external beam therapy is a feasible method in selected patients to avoid radical surgery with less side effects, good local control and overall survival in this high-risk population.

Compliance with ethical standards

Conflict of interest FT, JH, RS, SK, SM, PM and ES do not have any conflict of interest to declare. WM works as a consultant for Carl Zeiss AG. FW receives research funding from Carl Zeiss AG and works as a consultant for this company.

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