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Original article

Early initiation of external beam radiotherapy (EBRT) may increase the risk of long-term toxicity in patients undergoing intraoperative radiotherapy (IORT) as a boost for breast cancer

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Abstract

Background: Intraoperative radiotherapy (IORT) during breast-conserving surgery is increasingly used. We analyzed the influence of the interval between an IORT boost and external beam radiotherapy (EBRT) on late toxicity.
Methods: Forty-eight patients received 20 Gy IORT (50 kV X-rays (Intrabeam, Carl Zeiss, Oberkochen, Germany) followed by 46–50 Gy EBRT with a median interval of 36 days (14-197). Late toxicity was assessed with the modified LENT SOMA score after a median of 36 months.
Results: Twelve patients developed a higher grade fibrosis (°II–III), three teleangiectases, one a breast edema grade °II, six retractions, four hyperpigmentations and five pain (°II–III). The median interval between IORT and EBRT was significantly shorter in these patients ($n = 18$) compared to the 30 patients without higher grade toxicity (29.5 days vs. 39.5 days, $p = 0.023$, Mann–Whitney U-test).
Conclusion: Starting EBRT about 5–6 weeks after IORT appears to be associated with a decreased risk of chronic late toxicity compared with a shorter interval. The impact on local recurrence of prolonged gaps between IORT and EBRT is not known.

Keywords: Intraoperative radiotherapy; Breast cancer; Boost; Toxicity; Fibrosis

Introduction

Intraoperative radiotherapy (IORT) is currently being evaluated as a novel approach for partial breast irradiation. IORT can be used during breast-conserving surgery either as a tumor bed boost followed by external beam radiotherapy (EBRT[1–8]) or as single treatment. Several studies investigating single dose IORT or accelerated partial breast irradiation (APBI) for early breast cancer are ongoing, e.g. TARGIT, ELIOT or NSABP B-39.[9,10]

When IORT is given as a boost during breast-conserving surgery followed by EBRT and/or chemotherapy, timing and sequencing of the modalities may become crucial for the outcome of the patients as to local tumor control and toxicity. A long interval between IORT and EBRT may decrease local control rates because of tumor cell proliferation during the split. On the other hand, a too short interval may lead to increased chronic toxicity, e.g. tumor bed fibrosis when the overall treatment time is too short.

We evaluated the patients who were treated during the first two years after initiation of IORT for breast cancer in our institution for whom a 3-year follow-up is available. This is the first report analyzing the influence of the time interval

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between IORT and EBRT on the occurrence of late tumor bed fibrosis and other chronic toxicities.

Materials and methods

Between March 2002 and March 2004, 59 patients were treated with IORT during breast-conserving surgery followed by EBRT at the University Medical Center, Mannheim. Five patients died and six were lost to follow-up. The current analysis includes 48 patients with a median follow-up of 36 months after the end of EBRT (minimum 30 months, maximum 56 months, see Table 1).

IORT was given as previously reported.[1–4] In short, a dose of 20 Gy of 50 kV X-rays prescribed to the applicator surface was delivered using the Intrabeam system (Carl Zeiss Surgical, Oberkochen, Germany) during breast-conserving surgery performed as segmentectomy and sentinel node biopsy. Axillary clearance was done when the sentinel node was positive. EBRT was initiated after completion of wound healing and/or chemotherapy. Using CT-based 3D treatment planning (Brilliance CT Big Bore, Philips, Cleveland, OH, USA; Oncentra MasterPlan, Nucletron, Veenendaal, The Netherlands) a dose of 46–50 Gy in 2 Gy fractions was delivered using standard tangential treatment portals (6 MV, Synergy, Elekta, Crawley, UK). Patients were advised to avoid unnecessary irritation of the skin, to reduce water exposure, to avoid soap and to use powder at least twice per day. Patients were seen weekly by the treating radiation oncologist to monitor skin reactions. Systemic therapy was prescribed according to the St. Gallen consensus recommendations. Chemotherapy ($n = 9$) was routinely given before EBRT. Six of the chemotherapy patients with more than three involved lymph nodes received 50 Gy to the breast and supra-/infraclavicular fossa. Due to the small number of patients receiving chemotherapy ($n = 9$) and the low number of toxicities in these patients ($n = 1$), the influence of chemotherapy on the outcome could not be analyzed separately. Forty-five patients received endocrine therapy, which was started 8–14 days after surgery or after completion of chemotherapy.

Patients were recalled every 6–12 months for follow-up visits. Clinical late toxicity was scored by the treating physician (FW, FV, UKT) according to the modified LENT SOMA scoring system (see Table 2[11,12]).

Table 1
Patients' characteristics

Mean age (years)		62.7 ± 9.1
Tumor size	T1b	8
	T1c	28
	T2	12
Receptor	Positive	45
	Negative	3
Endocrine therapy	$n = 45$	
Nodal involvement	N0	38
	N1	8
	N2	2
Chemotherapy	$n = 9$	
6× CMF ($n = 2$), 6× FEC, 3× FEC, 4× EC, 6× EC ($n = 2$), 4× EC + 4× DOC ($n = 2$)		

Statistical analysis was performed using Statistica 7.1. (StatSoft Inc., Tulsa, OK, USA). As there was no normal distribution and no homogeneity of variance of the data, the group difference was calculated using the Mann–Whitney *U* test.

Results

In general, late toxicity after IORT and EBRT was mild. Thirty out of 48 patients (63%) had no or only minor changes, i.e. toxicity °I at 3-year follow-up. Table 3 shows the complete list of side effects scored according to the LENT SOMA system. Chronic skin toxicity, especially telangiectasia and hyperpigmentation, was seen in less than 10% of the patients.

The rate of higher grade fibrosis was low with 11/48 patients having fibrosis °II–III of the tumor bed at 3-year follow-up. Any degree of induration around the surgical scar was scored as fibrosis regardless of the contribution of surgery or radiotherapy. In one of these patients the fibrosis was not restricted to the tumor bed. One additional patient underwent mastectomy due to fibrosis °III at 12 months after EBRT. For the sake of this analysis, this patient was scored as chronic higher grade fibrosis at 3-year follow-up, but could not be scored for other breast toxicities.

The median time interval between IORT and EBRT in the 48 patients was 36 days (see Fig. 1). Eight of 12 patients with higher grade fibrosis had a time interval below the median. Five of 12 patients (42%) in the shortest quartile (14–28 days) developed a fibrosis °II–III. Only 4/24 patients receiving EBRT after more than 36 days following IORT developed a fibrosis °II–III (see Fig. 2). The median time interval between IORT and EBRT was 29 days for the 12 patients with higher grade fibrosis and 37 days for the group of patients without fibrosis. The time interval between IORT and EBRT was 20, 20 and 97 days for the three patients with fibrosis °III.

Table 2
Modified LENT SOMA scale for late breast toxicity[11,12]

Fibrosis	°0	None
	°I	Barely palpable/increased density
	°II	Definite increased density and firmness
	°III	Marked density, retraction, fixation
Retraction	°0	Absent
	°I	Present
Ulceration	°0	Absent
	°I	Present
Hyperpigmentation	°0	Absent
	°I	Present
Pain	°0	Absent
	°I	Rarely, minimal
	°II	Sometimes, tolerable
	°III	Permanent, strong
	°IV	Always, excruciating
Teleangiectasia	°0	Absent
	°I	Present
Breast edema	°0	No edema
	°I	Asymptomatic
	°II	Symptomatic
	°III	Secondary dysfunction

Table 3
Summary of late toxicity after IORT and EBRT

	% at 36 months			
	0	°I	°II	°III
Fibrosis	51	26	19	4
Teleangiectasia	94	6		
Breast edema	89	9	2	
Retraction	87	13		
Ulceration	100	0		
Hyperpigmentation	92	8		
Pain	77	13	8	2

Please note that any degree of induration around the surgical scar was scored as fibrosis regardless of the contribution of surgery or radiotherapy.

There were also increased other late side effects when EBRT was initiated early after IORT. The median intervals for the patients with teleangiectases ($n = 3$, interval: 28 days, 37 days, 37 days), breast edema °II ($n = 1$, 20 days), retraction ($n = 6$, 20 days, 25 days, 28 days, 30 days, 34 days, 97 days), hyperpigmentation ($n = 4$, 20 days, 22 days, 37 days, 97 days) and chronic breast pain °II–III ($n = 5$, 20 days, 28 days, 29 days, 34 days, 97 days) was below the median for the whole group (see Fig. 1). As can be clearly seen from the distribution of events in Fig. 1, with the exception of one patient, there were no higher grade toxicities when the interval between IORT and EBRT was about 7 weeks or more. This patient suffering from fibrosis °III, retraction, hyperpigmentation and pain °II is depicted in Fig. 3. She was one of the first patients being treated at our institution. Her interval between IORT and EBRT was 97 days. Fig. 3 demonstrates an early and persistent erythema due to a too small distance between the applicator and the skin (<5 mm), which was followed by the development of a fibrosis °III, hyperpigmentation, pain °II and retraction.

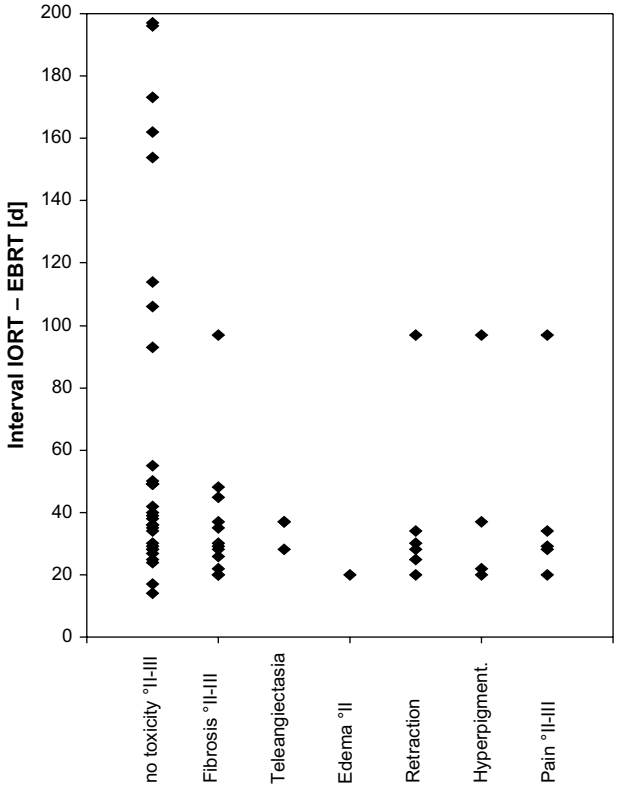

Fig. 1. Most toxicity events were seen in patients with a short interval between IORT and EBRT. Eight out of 12 higher grade fibroses, 5 out of 6 retractions and 4 out of 5 breast pains were found when the IORT–EBRT interval was below the median of 36 days.

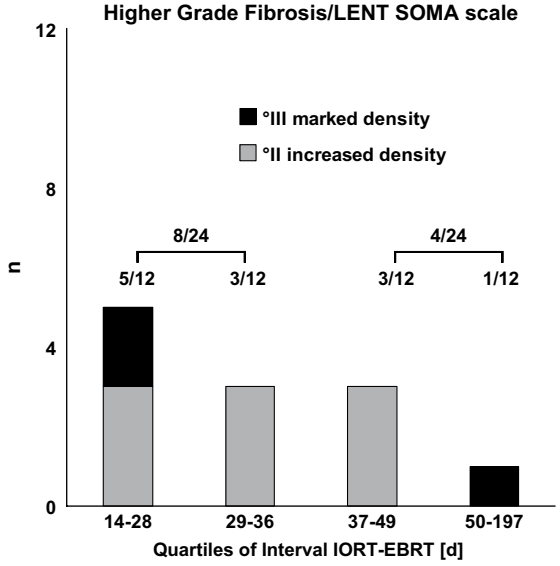

Fig. 2. The frequency of fibrosis °II–III decreases with a longer IORT–EBRT interval. The cohort of 48 patients was divided into quartiles ($n = 12$).

The median interval (29.5 days) between IORT and EBRT in these 18 patients with chronic and higher grade toxicity (fibrosis °II–III, telangiectasia, edema °II, retraction, hyperpigmentation, pain °II) was significantly shorter ($p = 0.023$, Mann–Whitney U test) than in patients without this type of toxicity ($n = 30$, median 39.5 days).

Discussion

IORT either as a boost followed by EBRT to the whole breast or as single modality APBI is increasingly used.[1–10] However, little is known up to now about the long-term toxicity[1] and factors influencing cosmetic outcome. The interval between IORT and EBRT may be relevant for tumor cell kill and the development of normal tissue complications. Although we have previously reported the low local recurrence rate using this approach,[6] this is the first report on toxicity after IORT using low-energy X-rays followed by EBRT analyzing the relevance of the IORT–EBRT interval for late toxicity. Although the patient number and follow-up time are limited up to now using this novel approach, a finding of clinical relevance is reported.

Cosmetic outcome is a relevant endpoint in breast-conserving treatment and depends to a substantial degree on subjective assessments. There is an ongoing debate about how and when to score the cosmetic outcome. We therefore concentrated on the objective items being part of the LENT SOMA classification and used only permanent and higher grade changes for statistical consideration (see Table 2[11,12]). Because many studies investigating cosmetic outcome report

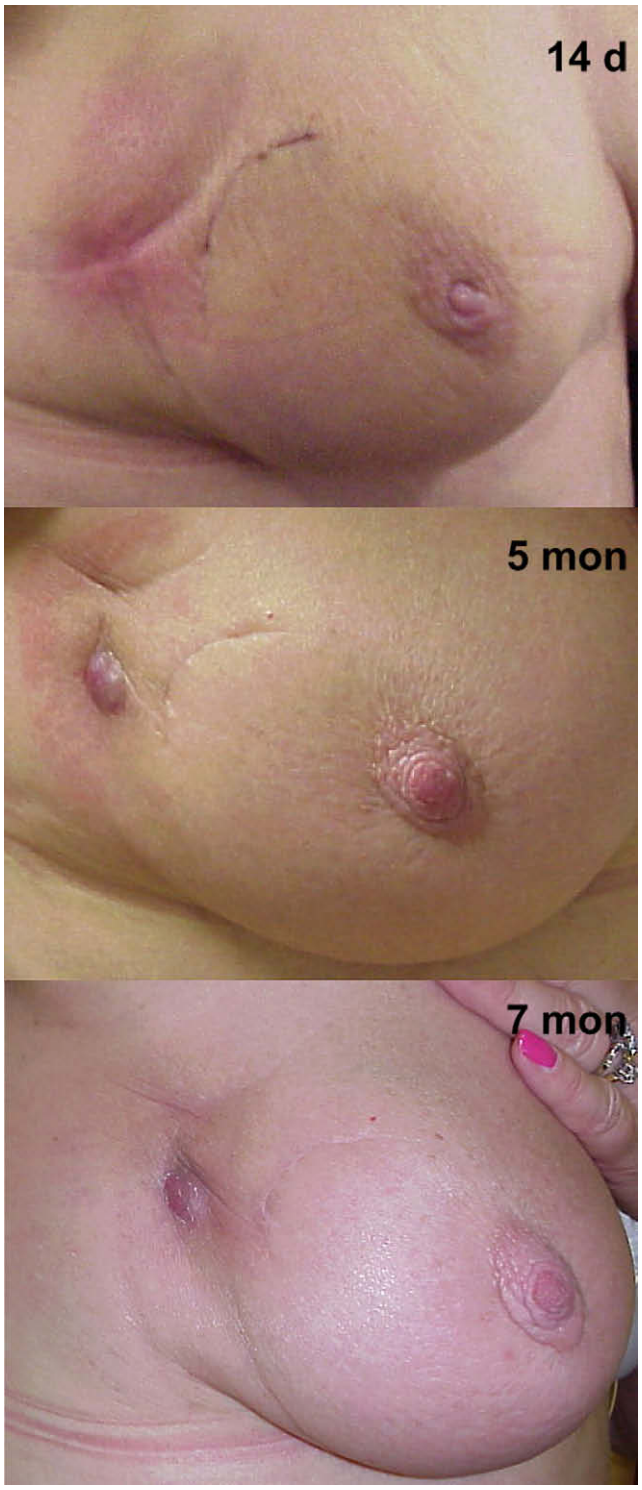

Fig. 3. A patient with an IORT–EBRT interval of 97 days developed fibrosis °III, retraction, hyperpigmentation and breast pain °II because the distance between skin and applicator surface was too small.

a stabilization of the results after 3 years, we used a median follow-up of 3 years after the end of EBRT.[13–22] In contrast to what is known after EBRT, there are reports after APBI (e.g. Chen et al.[23]) describing a peak of chronic toxicity at 2 years after therapy followed by a decline in frequency and severity.

We showed in this analysis that after 3 years of follow-up most higher grade toxicities occurred, when the interval between IORT and EBRT was too short, i.e. below about 5–6 weeks. Although toxicity was in general mild, the rate of side effects can obviously be further reduced by prolonging the initiation of EBRT.

We previously reported[2,3] that perioperative antibiotics can reduced the risk of acute mastitis. Vaidya et al.[5,9] published a case of skin necrosis when the skin was not kept away from the applicator shaft. In our series, we experienced one case of fibrosis °III, hyperpigmentation, retraction and pain °II in a patient in whom the distance from the applicator surface to the skin was far below 5 mm resulting in a skin dose >>10 Gy. It is therefore recommended to have at least 5 mm of breast tissue between the applicator and the skin. Alternatively, superficial tumors can be excised with a skin spindle excision to avoid overdosing of the skin during IORT. We have reported on toxicity after a median follow-up of 25 months (range 18–44 months) in 73 patients.[1] Twenty-one percent of the patients (4/19 patients) with a follow-up of 36 months had a fibrosis °II–III. At that time point no teleangiectases and two hyperpigmentations were seen. In the meantime with 48 patients with 3 years of follow-up, three patients developed teleangiectases and two more hyperpigmentations were seen, whereas the percentage of higher grade fibroses restricted to the tumor bed remained fairly constant at about 25%.

The rate of reported side effects in this study is in the range of current publications from our and other groups after EBRT following breast-conserving surgery. We have previously reported radiation induced fibroses °I, °II and °III in 55%, 6% and 1% respectively in a patient cohort of 421 followed for a median of 51 months after EBRT alone.[24] Scar induration, most likely due to surgery and not to radiation, was not counted in that study. Teleangiectasia was seen in 51% and breast pain was reported in 34%. Hoeller et al.[21] reported an assessment of late toxicity after a median follow-up of 8 years according to the LENT SOMA scale in 259 patients. They reported telangiectasia in 20% of the patients (9% °I, 4% °II, 7% °III), fibrosis in 38% (29% °I, 8% °II, 1% °III) and hyperpigmentation in 22% (14% °I, 8% °II). Increasing the radiation dose to the tumor bed by 16 Gy is beneficial for almost all patients with breast cancer; however, more than 20% of the patients experienced severe or moderate fibrosis after 3 years.[25] Therefore, IORT as a boost may be an alternative to an external beam electron boost. Skin toxicity, especially telangiectasia and hyperpigmentation, appears to be lower after this approach and the rate of higher grade fibrosis is acceptable and mainly limited to the tumor bed as is expected from radiobiological modeling studies[26,27] and early imaging follow-up.[28,29] Other groups (e.g. Chen et al.,[23] Shah et al.[30]) have reported after APBI tumor bed fibrosis rates of 10–48% and telangiectasia in up to 34% after 1–6 years of follow-up. The underlying radiobiological mechanisms of high single doses to small volumes (e.g. IORT boost, radiosurgery boost) combined with a course of fractionated EBRT (e.g. whole breast, whole brain) are not completely understood although there is longstanding clinical experience using this

approach. Especially, no reliable formalism is available to predict the effect of the interval between the high single dose and the course of fractionated radiotherapy taking sublethal damage repair into account. Preliminary biophysical modeling attempts[31] have led to the expectation of considerably higher rates of late damage, which are fortunately not observed in clinical practice. This and the general limitations of biophysical models underline the necessity of careful clinical observation and follow-up when new treatment modalities or combinations are introduced.

Conclusion

In summary, although the number of toxicity events in this report is low, there was a clear, statistically significant and clinically relevant tendency for increased late toxicity when EBRT was initiated early after IORT. Eight out of 12 higher grade fibroses, 5 out of 6 retractions and 4 out of 5 breast pains were found when the IORT–EBRT interval was below the median of 36 days. Starting EBRT about 5–6 weeks after IORT appears to be associated with a decreased risk of chronic late toxicity compared with a shorter interval.

Conflict of interest statement

The authors state that they have no competing interests.

Authors' contribution

F.W. was responsible for design and conception, involved in patient selection, responsible for final data analysis, responsible for writing and finalizing of the manuscript. G.W. and A.K. were responsible for data analysis and editing of the manuscript. E.B. and F.V. were involved in patient follow-up, clinical assessment and data analysis, and received informed consent for radiotherapy. C.H. was responsible for radiobiological modeling and interpretation of the data. O.T. and M.S. were involved in patient selection and follow-up, performed parts of the surgeries, and received informed consent for surgery, U.K.T. was involved in patient selection and follow-up, coordination of the procedures, and the initial drafting and writing of the manuscript.

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