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Clinical Investigation

Intraoperative Tumor Bed Boost With Electrons in Breast Cancer of Clinical Stages I Through III: Updated 10-Year Results

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Summary

This study provides 10-year outcome data of 770 stage I through III breast cancer patients who received intraoperative electron radiation therapy (IOERT) as a tumor bed boost preceding whole breast irradiation. After a median follow-up period of 121 months, 21 in-breast recurrences (2.7%) occurred with triple-negative and HER2+ subtypes as negative predictors. As confirmed in long-term follow-up, IOERT has been demonstrated to be a viable boost strategy in any risk constellation.

Purpose: To assess retrospectively the role of an anticipated intraoperative tumor electron radiation therapy (IOERT) as a bed boost during breast-conserving surgery followed by conventional whole breast irradiation (WBI).

Methods and Materials: An unselected cohort of 770 breast cancer patients of all risk types was analyzed in terms of local control (LC) and survival outcome. Patients were treated by breast-conserving surgery, IOERT of 10 Gy, and WBI to total median doses of 54 Gy (range, 1.6-2). Patients were retrospectively analyzed for LC, locoregional control, metastasis-free survival (MFS), overall survival (OS), and breast cancer–specific survival (BCSS).

Results: After a median follow-up of 121 months (range, 4-200), 21 (2.7%) in-breast recurrences (IBRs) were observed, 107 patients (14%) died and 106 (14%) developed metastases. Ten-year rates of LC, locoregional control, MFS, OS, and BCSS amounted to 97.2%, 96.5%, 86%, 85.7%, and 93.2 %, respectively. In multivariate analysis, HER2+ and triple-negative breast cancer subtype (TN) turned out to be significant negative predictors for IBRs (hazard ratios, 15.02 and 12.87, respectively; $P < .05$). Sorted by subtypes, 10-year LC rates were observed in 98.7% (range, 96.7%-99.5%) (luminal A), 98% (range, 94%-99.3%) (luminal B), 87.9% (range, 66.2%-96%) (HER2+), and 89% (range, 76.9%-94.9%) (TN), respectively.

Conclusions: After 10 years, boost IOERT maintains high LC rates in any risk setting.

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Introduction

During the last few decades in-breast recurrences (IBRs) could be steadily reduced for numerous reasons, not least by routine whole breast irradiation (WBI) after breast-conserving surgery (1). A local dose escalation to the tumor bed as the region with highest recurrence risk (2, 3) was proven to be a viable strategy for decreasing IBRs if administered by fractionated external electrons or brachytherapy (4).

Since 1998 we have established an intraoperative single-shot delivery of electrons (intraoperative electron radiation therapy [IOERT]) as a standard boost technique, which we deemed to be advantageous in terms of maintaining accuracy (and, hence, local control [LC]), sparing tissues at risk, and shortening the overall treatment time. Meanwhile, this procedure is well established, causing no additional morbidity and providing good cosmetic outcome (5-7). Clinical data with respect to this approach were published in several articles (8-11), including a pooled analysis of 1109 patients with a heterogeneous risk profile of clinical stages I through III conducted by the European Group of the International Society of Intraoperative Radiotherapy (ISIORT-Europe) (12). After a median follow-up period of 6 years, an actuarial IBR rate of 0.8% was reported (8). For patients at higher risk for IBRs, for example locally advanced breast cancer with primary systemic treatment (10) or a triple negative subtype (TN) (13), IBR rates of 1.5% after 6 years (10) up to 11.5% after 8 years (11) were observed, respectively.

To gain more data maturity in long-term observation, a retrospective study was performed comprising all of our institutional patients who were treated between 1998 and 2005 and followed until December 2015. Emphasis was put on LC, survival outcome, and late toxicity for all histologic subtypes as well as initial clinical stages.

Methods and Materials

From 1998 to 2005, 770 clinical stage I through III breast cancer patients with a median age of 58 (range, 22-89) were treated by breast-conserving surgery, IOERT, and subsequent WBI. Patients with histologically confirmed invasive breast cancer suited for breast-conserving surgery and WBI were eligible. There were no limitations according to systemic treatment, age, histologic subclassification (including hormonal receptor status, Her2/neu positivity or KI 67), tumor size, or nodal status. Previous irradiation of the affected breast or carcinoma in situ were considered exclusion criteria. The study was approved by the local ethics committee; informed consent was given from all patients.

Breast-conserving surgery consisted of a lumpectomy and a dissection of axillary lymph node levels I and II after sentinel lymph node (SLN) biopsy sampling. Starting in 1999 SLN biopsy sampling was routinely performed at our clinic, which meant that all patients who were treated in 1998 (n = 9) received an axillary dissection upfront. Since the second half of 1999, axillary nodes were only dissected if SLN biopsy sampling was tumor-positive. Commonly, a median number of 17 (range, 4-43) and 2 (range, 1-10) nodes were removed in cases of an axillary dissection and SLN biopsy sampling only, respectively. For patients with positive nodes, a median number of 18 nodes (range, 1-43) were removed.

All but 9 patients (with RX status) were classified R0 with a median resection margin of 3 mm (range, 0.4-18). For 32% (n = 249), the dimension of free margin was not noted. After tumor removal, the tumor bed was treated by an IOERT boost with a median 10 Gy as Dose-maximum (range, 5-12) on a dedicated linear accelerator within the operation room. For this purpose the tissue adjacent to the resection site was fixed by temporary sutures and brought directly into the center of the electron beam. For depth dose measurement, intraoperative ultrasound was used. The planning target volume comprised a rim of tissue of at least 2 cm in all directions calculated from the former macroscopic tumor edge, with the exception of the skin and the anterior rib wall where the exit dose was limited to 5 Gy. Electrons were applied by tubes with a median diameter of 6 cm (range, 4-10) and a median energy of 6 MeV (range, 4-18), encompassing a median tissue volume of 7.5 mL (range, 2.2-105) with the prescribed 90% isodose.

After a median time gap of 43 days (range, 17-259), WBI was performed by tangential 3-dimensional conformal radiation therapy (6-MV photons) with the patient in the supine position and conventional daily fractionation between 1.6 and 2 Gy (5 fractions/wk) up to a median total dose of 54 Gy (range, 14-63). One patient was treated with a dose of up to 63 Gy as compensation for a radiation break due to seroma infection. In a second patient, WBI was stopped at 14 Gy because of axillary inflammation. With respect to their postoperative nodal status (1-3 positive nodes, 32% [n = 247]; >3 positive nodes, 4% [n = 30]; pN0, 64% [n = 491]) and other additional histopathologic risk factors (grading, hormonal receptor status, and Her2/neu positivity), 116 of 770 patients (15%; pN1, n = 83; pN2, n = 24; pN3, n = 6; ypN0/cN1, n = 2; pN0, n = 1) received an additional regional node irradiation (RNI) of the supra- or infraclavicular fossa. From these, 31 patients were additionally given conventional fractionation to the ipsilateral internal mammary chain of the first 3 intercostal spaces with median doses of 46.2 Gy (range, 22.4-54). In 1 node-negative patient (pN0) with RNI, characterized by a TN tumor located in the upper-inner quadrant and a young age (32 years), only the adjacent mammaria chain was treated. Furthermore, for patients with high (grade 3), low, or intermediate grading (grade 1/2) tumors, RNI was performed in 18% and 14% of cases, respectively. Patients with RNI were systemically treated as follows: 75 (64%) with chemotherapy, 86 (74%) with antihormonal treatment,

and 51 (44%) with both (chemotherapy and antihormonal treatment). Information on RNI was not available for 3 patients of the whole cohort.

Twenty-eight percent (n = 215) of all patients received additional courses of chemotherapy. Patients with high-grade tumors or positive nodes received more chemotherapy (grade 3, 59.5%; N+, 45%) compared with those with low or intermediate grading or negative nodes (grade 1/2, 17.6%; N0, 18.2%). In 22% of patients (n = 169), chemotherapy was administered in an adjuvant and in 6% (n = 46) in a neoadjuvant setting (rate of pathologic complete response, 19.5%). Clinical information regarding the administration of chemotherapy was not stated (ns) in 16 patients. Adjuvant chemotherapy mostly consisted of cyclophosphamide, methotrexate, and 5-fluorouracil or anthracycline-containing regimens, which starting in 2004 were gradually complemented or replaced by taxanes. Decisions to administer chemotherapy were made according to recommendations of the St. Gallen Consensus Conference, which was published regularly between 1995 and 2005. The most common substances for primary systemic treatment were summarized and reported previously (10). Furthermore, 622 patients (81%) were prescribed antihormonal treatment (not stated, n = 19), of whom 101 (13.1%) received additional chemotherapy (not stated, n = 1). Since 2000, Her2/neu status was routinely assessed. For the sake of this analysis, for all other patients a retrospective determination was attempted. In 59 patients Her2/neu status was missing; in 31 patients its definitive classification was unclear (score 2 positive). Six hundred six patients were classified as negative and 74 patients as positive (Table 1). Of these, only 18 received trastuzumab as targeted systemic therapy, including 1 patient with an unclear Her2/neu status.

Statistics

Actuarial 10-year rates for LC, locoregional control, metastasis-free survival (MFS), breast cancer specific survival (BCSS), and overall survival (OS) were calculated using the Kaplan-Meier method (14) based on the Kaplan-Meier product-limit estimator. Each clinical endpoint stands for the percentage of patients without any event for IBRs (LC), IBRs and regional recurrence (locoregional control), metastases (MFS), death caused by disease only (BCSS), and death due to all reasons (OS), respectively.

All data are presented with 95% confidence intervals (CIs) calculated by logarithmic transformation of Greenwood's variance estimate. Comparisons between subgroups were done with the Taron-Ware test because proportional hazard cannot be assumed. $P < .05$ was considered as statistically significant and not adjusted for multiple testing because of the explorative nature of the study. All calculations were done with NCSS 8 (Utah, USA). For graphical presentation, MedCalc 13.2 (Ostend, Belgium) was used. Cox regression analysis was done with MedCalc 13.2 (Ostend, Belgium). In a stepwise regression algorithm, variables with $P < .05$ were kept in the model, whereas those with $P > .1$ were not considered for such analysis. For multivariable Cox analyses, a backward regression model was performed.

Results

Of 827 patients who were designated for IOERT and subsequent WBI, 770 were eligible for statistical analysis. Nine of these had bilateral breast cancers with IOERT for both sides and were therefore counted twice. Patients were excluded from the study if immediate secondary mastectomy was performed as a consequence of repeatedly positive or close resection margins (n = 39), if WBI was declined by the patient (n = 7), if no further clinical information was available after the completion of WBI (ie, lost to follow-up; n = 5), or if IOERT was intended as palliative single treatment (n = 6). Patient and tumor characteristics are summarized in Table 1, including luminal subtype classification as proposed by the St Gallen consensus conference recommendations (15, 16).

After a median follow-up period of 121 months (range, 4-200), 21 IBRs were observed, 12 in the former index quadrant (true local recurrences) and 9 outside (out quadrant). Evaluation of all 21 relapses showed 5 patients with resection margins <2 mm (1 mm closest, no data for margins in mm for 6 patients), 3 (14%) with a positive nodal status N1 (all treated without RNI), and no cases positive for an extensive intraductal component. Furthermore, in 3 of all local recurrences, a reresection was performed until a negative margin status (R0) was obtained. Five patients developed regional recurrences in ipsilateral lymph node pathways (4 axillary, 1 supraclavicular), and 2 had received RNI to the supraclavicular fossa. The corresponding crude rate for IBRs and regional recurrences amounts to 2.7% and 0.65%, respectively. Furthermore, 106 patients (14%) developed distant metastases, and a further 107 patients (14%) died. A detailed summary on patients' clinical status (deaths, metastases, IBRs, and regional recurrences) is depicted in Table E1 (available online at www.redjournal.org).

For the whole cohort, 10-year rates for LC, locoregional control, OS, MFS, and BCSS were 97.2% (95% CI, 95.5-98.2), 96.5% (95% CI, 94.7-97.7), 85.7% (95% CI, 82.8-88.1), 86% (95% CI, 83.1-88.4), and 93.2% (95% CI, 90-94.9), respectively. After subanalysis, respective 10-year LC rates were observed for luminal A, luminal B, HER2+, and TN subtypes in 98.7% (95% CI, 96.7-99.5), 98% (95% CI, 94-99.3), 87.9% (95% CI, 66.2-96), and 89% (95% CI, 76.9-94.9), respectively. A detailed survey of 10-year actuarial rates by endpoint definition is illustrated in Table 2 for all study patients as well as the following subgroups: age (≥60, 50-59, 40-49, and <40 years), histologic subtypes (luminal A, luminal B, HER2+, TN), clinical stage (I, II, III), nodal status (N+, N0) and irradiation field arrangements (RNI yes, RNI no). In addition, for comparisons between subgroups, significant P values are stated.

Table 1 Patient characteristics

Characteristics	No. of patients	Percent of patients
Histology		
IDC	533	69
ILC	73	9.5
Mixed	76	10
others	61	8
Invasive + EIC-comp	26	3.4
Invasive + DCIS-comp	291	38
ns	1	0.1
Breast cancer subtypes		
Luminal A	422	55
Luminal B	182	23.6
HER2+	33	4.2
TN	76	9.9
ns	57	7.3
Grading		
Grade 1	92	12
Grade 2	487	63
Grade 3	189	24.8
Grade x	2	0.2
Her2/neu status		
Positive	74	9.6
Negative	606	78.7
ns/unclear	90	11.7
HR status		
Positive	657	85.3
Negative	113	14.7
Pathologic tumor stage		
T1	514	66.8
T2	206	26.8
T3	3	0.4
Tx	1	0.1
Pathologic nodal stage		
N0	471	61.2
N1	225	29.3
N2	21	2.7
N3	6	0.8
Nx	1	0.1
Clinical stage*		
I	384	50
II	354	46
III	32	4
Systemic treatment		
AH	622	81
Adjuvant CTX	169	22
Neoadjuvant CTX (PST)	46	6
CTX ns	16	2
AHT/CTX	101	13
Age, y		
≥60	340	44
50-59	234	31
40-49	157	20
<40	39	5
Neoadjuvant chemotherapy	46	
y pathologic tumor stage (PST)		
T1	22	2.8
T2	10	1.3
Tx	1	0.1
T0	10	1.3
Tis	3	0.4
y pathologic nodal stage (PST)		
N0	20	2.6
N1	22	2.8
N2	3	0.4
Nx	1	0.1
pCR	9	19

Abbreviations: AH = antihormonal treatment; CTX = chemotherapy; DCIS comp = ductal in situ components positive; EIC-comp = extensive intraductal component; HR = hormonal receptor; HER2+ = negative HR status and positive for Her2-neu; IDC = invasive ductal; Invasive + DCIS-comp = invasive tumors with DCIS comp (inclusively positive for EIC); ILC = invasive lobular; IDC/ILC = mixed; Invasive + EIC-comp = invasive tumors with DCIS comp exclusively defined as EIC; ns = not stated; pCR = pathologic complete response; PST = primary systemic treatment; TN = triple negative.

y: identification of pathological tumor (T) and nodal (N) - stage after neoadjuvant chemotherapy (PST).

* According to "TNM Classification of Malignant Tumours", J.D Brierley, M.K Gospodarowicz, Ch. Wittekind (eds.), 8th Edition, publisher: John Wiley & Sons, 2017.

The median time gap between the end of WBI and the first progression averaged 83 months (range, 19-185) for IBRs and 54 months (range, 5-181) for systemic failure. Results for subtype classification (LC, OS, BCSS) are illustrated in Figure 1a-c. For patients positive for Her2/neu receptor status (ie, HER2+ and luminal B/Her2/neu+, n = 74), crude rates for LC, BCSS, OS, and MFS amounted to 94.6% (4 relapses), 90.6% (7 patients died of primary disease), 86.5% (10 patients died), and 79.8% (15 patients developed metastases), respectively.

Time gap between IOERT and WBI

Because the median time gap of 43 days between IOERT and WBI comprised a wide range between 17 and 259 days, the time interval was also analyzed according to breast cancer subtypes. For patients with TN or HER2+ tumors we observed a median time span of 108 days (range, 21-224) and for those with luminal classification (luminal A and B) 42 days (range, 17-208).

Independent prognostic factors for IBRs

By Cox proportional hazards regression, HER2+ and TN were independent prognostic factors for developing an IBR in multivariate analysis (hazard ratio [HR], 15.02 [95% CI, 2.9-77.78] and 12.87 [95% CI, 3.37-49], respectively; $P < .05$) compared with luminal A subtypes. Interestingly, this was not true for tumor grading 3 (crude IBRs, grade 3, 4.2%, versus grade 1 or 2, 2.2%; $P = .19$) or a positive nodal status, both showing a trend toward

Table 2 Ten-year results per endpoint definition

Endpoint	All patients			
LC	97.2% (95.5-98.2)			
LRC	96.5% (94.7-97.7)			
MFS	86% (83.1-88.4)			
BCSS	93.2% (90.0-94.9)			
OS	85.7% (82.8-88.1)			
Endpoint	**≥60 y**	**50-59 y**	**40-49 y**	**<40 y**
LC	97.6% (94.7-98.9)	97.2% (93.4-98.8)	97.2% (92.7-98.9)	93.5% (76.5-98.3)
LRC	96.9% (93.9-98.5)	96.8% (92.9-98.6)	96.3% (91.2-98.4)	93.5% (76.6-98.3)
MFS	85.9% (81.1-89.6)	87.7% (82.6-91.4)	84.4% (77.2-89.4)	80.8% (63.8-90.4)
BCSS	95% (91.6-97)	91.8% (87.1-94.8)	90.3% (83.8-94.2)	88.6% (72.5-95.5)
OS	82% (77.1-85.9)	87.7% (82.4-91.4) $P^{\Phi} = .034$	90.3% (83.8-94.2) $P^{\Phi} = .005$	86.3% (70.2-94.1)
Endpoint	**luminal A**	**luminal B**	**HER2+**	**Triple negative**
LC	98.7% (96.7-99.5)	98% (94-99.3)	87.9% (66.2-96) $P^{\Psi} = .0002$ $P^{\Omega} = .02$	89% (76.9-94.9) $P^{\Psi} < .0001$ $P^{\Omega} = .008$
LRC	97.6% (95.2-98.8)	98% (94-99.3)	87.9% (66.2-96) $P^{\Psi} = .009$ $P^{\Omega} = .039$	89 % (76.9-94.9) $P^{\Psi} = .001$ $P^{\Omega} = .01$
MFS	89.9% (86.2-92.7)	80.4% (73.2-85.9) $P^{\Psi} = .004$	77.9% (59.2-88.8) $P^{\Psi} = .01$	76.8% (65.4-84.9) $P^{\Psi} = .0001$
BCSS	95.5% (92.6-97.3)	93.4% (87.6-96.5)	80% (60.5-90.5) $P^{\Psi} = .0001$ $P^{\Omega} = .004$	81.7% (70.5-88.9) $P^{\Psi} < .0001$ $P^{\Omega} = .0007$
OS	89.1% (85.3-92)	83.2% (76.4-88.2) $P^{\Psi} = .04$	77.2% (57.9-88.5) $P^{\Psi} = .03$	71.5% (59.7-80.4) $P^{\Psi} < .0001$ $P^{\Omega} = .01$
Endpoint	**Stage I**	**Stage II**	**Stage III**	
LC	95.5% (92.5-97.3)	97.8 (95.2-99)	100%	
LRC	95.2% (92.2-97.1)	97.5% (94.8-98.8)	100%	
MFS	91.4% (87.8-94)	82% (77.2-86) $P = .0003^{¥}$	68.4% (47.3-82.5) $P < .0001^{¥}$	
BCSS	95.6% (92.7-97.4)	91.4% (87.5-94) $P = .02^{¥}$	89.9% (63.6-97.5)	
OS	88.6% (84.6-91.6)	84.2% (79.7-87.7) $P = .04^{¥}$	74.3% (52.3-87.2) $P = .04^{¥}$	
Endpoint	**N+**	**N0**		
LC	98.4% (95.1-99.5)	95.8% (93.3-97.4) $P = .02$		
LRC	98% (94.7-99.3)	95.6% (93-97.2) $P = .04$		
MFS	78.6% (73-83.3)	90.5% (87.2-93) $P < .0001$		
BCSS	89.7% (85-93)	95.6% (93-97.2) $P = .002$		
OS	82.6% (77.3-86.8)	87.9% (84.4-90.7) $P = .02$		
Endpoint	**RNI yes**	**RNI no**		
LC	95.3% (92.9-96.9)	96.3% (94.3-97.6)		
LRC	98.1% (92.6-99.5)	96.2% (94.1-97.5)		
MFS	69.3% (59.2-77.4)	89.2% (86.3-91.5) $P < .0001$		

(*continued on next page*)

Table 2 (*continued*)

Endpoint	RNI yes	RNI no
BCSS	88.5% (80-93.6)	94.3% (92-96) $P = .01$
OS	79.4% (70.2-86)	87.2% (84.1-89.7) $P = .009$

Abbreviations: BCSS = breast cancer–specific survival; LC = local control; LRC = locoregional control; MFS = metastasis-free survival; OS = overall survival; P^{Φ} = compared with age > 60; P^{Ψ} = compared to luminal A; P^{Ω} = compared to luminal B; $P^{¥}$ = compared to stage I. RNI = regional node irradiation.

Values in parentheses are 95% confidence intervals (CIs).

lower risk of relapse if compared with grade 1 or 2 (HR, 0.39; $P = .11$) and node-negative patients (HR, 0.3; $P = .068$). Furthermore, positivity for ductal in situ components also showed a trend for a higher recurrence risk (HR, 2.11; $P = .11$) (Table 3). However, other potential parameters, like age, tumor size and multifocality, tube size, systemic treatment (chemotherapeutic or antihormonal), or the time gap between IOERT and WBI (time slot <70 vs ≥70 days), were not statistically assessable by a complete Cox regression analysis (ie, univariate and multivariate) because of the low number of events in these respective groups.

Acute treatment tolerance and late cosmesis

Of all patients, 38 (4.9%) were registered with wound complications. A second operation was necessary in 28 patients (3.6%), 22 due to postoperative bleeding at the resection site of the breast or the SLN area (n = 1) and 6 patients due to wound infection. A further 9 patients were treated conservatively for local inflammation (n = 8) or delayed shoulder mobilization of the affected side (n = 1).

Late cosmetic outcome assessment was not provided for the whole cohort and is available for a subset of 261 patients after a median follow-up of 56 months. According to

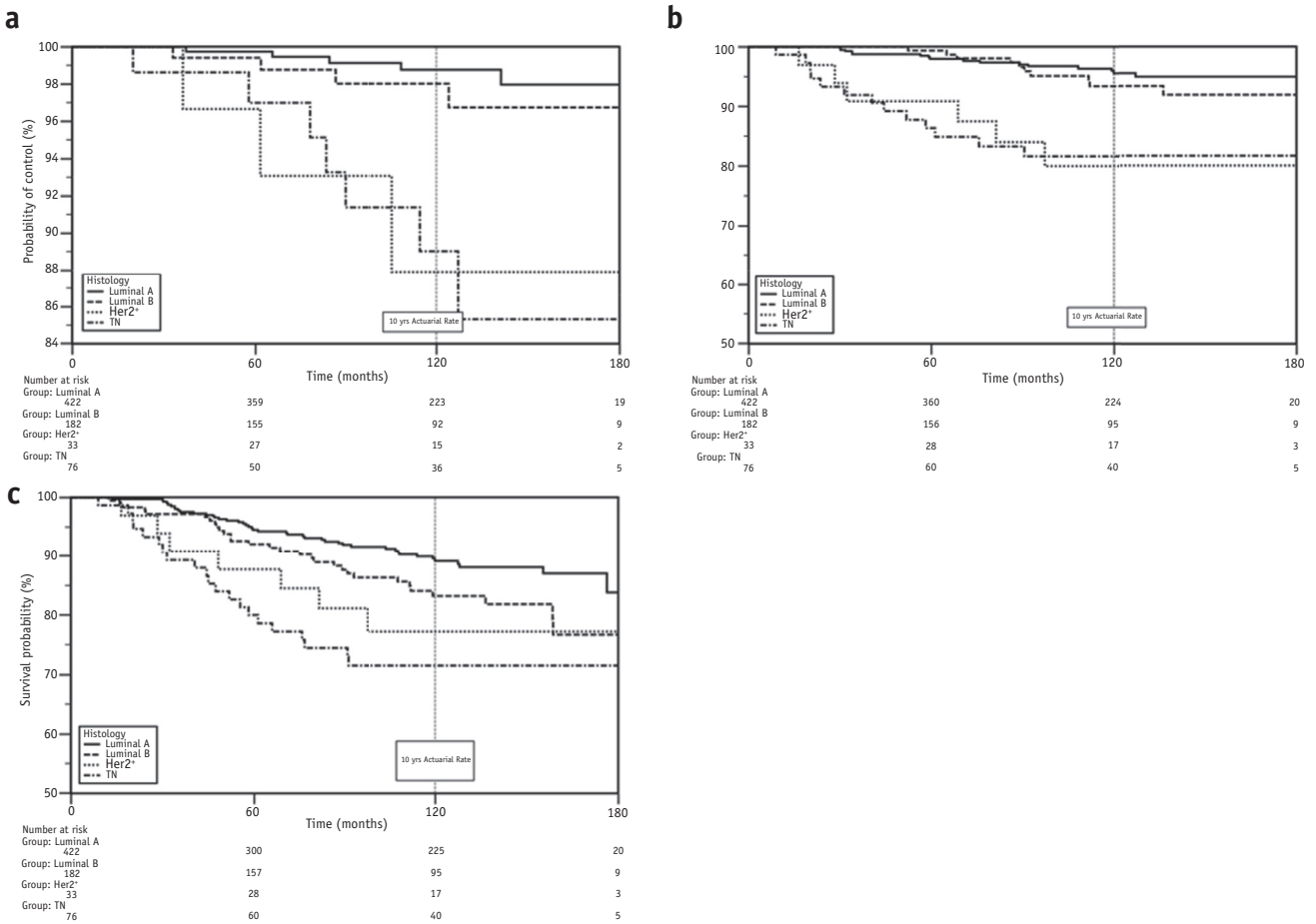

Fig. 1. Probability of survival and local control by subtype classification. (a) Local control, (b) breast cancer–specific survival, and (c) overall survival. *Abbreviation:* TN = triple-negative subtype.

Table 3 Cox proportional hazards regression

			Univariate		Multivariate	
Characteristics	Patients (n = 770)	IBRs (n = 21)	*P* value	Hazard ratio (95% confidence interval)	*P* value	Hazard ratio (95% confidence interval)
Grading						
Grade 1/2	579	13		1		1
Grade 3	189	8	.14	1.92 (0.79-4.64)	.11	0.39 (0.12-1.24)
Grade x	2	0				
Nodes						
N0	491	18		1		1
N+	277	3	.05	0.29 (0.086-1)	.068	0.3 (0.087-1.09)
Nx	2	0				
DCIS-comp						
Negative	479	10		1		1
Positive	291	11	.08	2.16 (0.89-5.24)	.11	2.11 (0.83-5.37)
BC subtypes						
Luminal A	422	6		1		1
Luminal B	182	4	.48	1.56 (0.44-5.53)	.25	2.13 (0.57-7.96)
HER2+	33	3	.006	6.99 (1.74-28)	.0012	15.02 (2.9-77.78)
TN	76	7	.0005	6.91 (2.31-20.63)	.0002	12.87 (3.37-49)
ns	57	1				

Abbreviations: BC = breast cancer; DCIS-comp = ductal in situ components; IBRs = in-breast recurrences; ns = no statement; TN = triple negative.

a scoring system established by Van Limbergen et al (17), 91% of patients rated their breast cosmesis as satisfactory (excellent/good) and 95% as acceptable (excellent/good/moderate), whereas physician ratings turned out be a bit more critical, with 64% satisfactory and 95% acceptable results (7, 18). Of note, telangiectasia were not described.

Secondary malignancies

In total, 103 patients (13.4%) with a median age of 61 years (range, 29-86) developed secondary cancers, 19 (2%) before treatment of the affected breast and all others (84 patients, 10.9%) after treatment. For the latter, we observed a median time gap between IOERT and the first diagnosis of a secondary malignant disease of 71.6 months (range, 3.8-174). Most of these patients (n = 31, 4%) developed contralateral breast cancer alone (n = 26) or in combination (n = 5) with other malignancies. All other tumor origins (n = 62) are summarized in Table E2 (available online at www.redjournal.org). In summary, 8 patients were identified with 2 or more combinations of all registered tumor sites.

Cardiac toxicity

To estimate a possible influence on cardiac toxicity, we investigated the distribution of right- and left-sided breast cancers treated in the whole cohort with respect to reported fatal cardiac events (ie, death caused by myocardial infarction). Of 397 left-sided breasts treated, no death was related to a cardiac event, in contrast to 4 of 373 right-sided breasts. These 4 patients were treated between 1999 and 2000, had a median age of 70.5 years (range, 65-81), and received WBI without RNI. The median time gap from IOERT to the cardiac events was 86 months (range, 44-190). Because complete Computer tomography data sets are no longer available for exact recalculation of cardiac exit doses for these patients, we estimated dose contributions by comparing them with present patients with similar anatomies, irradiated with the same tangential field technique, and in the supine position. Clinical and technical information for patients with a fatal cardiac event (n = 4) are summarized in Table E3 (available online at www.redjournal.org).

Discussion

Several clinical trials demonstrated that after breast-conserving surgery and consecutive WBI, up to 80% of all first IBRs will occur in the index quadrant (2, 3). The most likely explanation is based on histopathologic studies on subclinical tumor cell distribution, revealing that up to 90% of all microscopic tumor cells are found within a distance of 4 cm and 60% at 2 cm, calculated from the macroscopic tumor edge (19). This fact made it plausible to augment the dosage in the tumor bed as the area with the highest probability of remnant cancer burden.

Clinical results of the last European Organisation for Research and Treatment of Cancer (EORTC) boost trial (4) corroborated a steady and significant reduction of the 20-year IBR rates in the age group $\leq$50 years after a local dose escalation to the tumor bed (primarily performed with external electrons) even though no boost effect was shown for OS. However, in this trial no subanalysis was undertaken to investigate a possible boost

effect in dependency of breast cancer subtypes (15, 16), which significantly influence both LC and survival (13, 20-23). In several studies, TN and HER2+ subtypes showed worse results for both endpoints, which is consistent with our experience (13, 20-23). Of note, patients with TN and HER2+ breast cancers showed a longer time delay (median, 108 days; range, 21-224) compared with those with luminal ones (median, 42 days; range, 17-208), respectively. Such a longer gap can be explained by the fact that patients with TN or HER2+ breast cancer are frequently scheduled for a time-consuming chemotherapy preceding WBI. However, in the present study it was impossible to identify the influence of time delays between IOERT and WBI ($<$70 vs $\geq$70 days) as a negative predictor for IBRs because of the very low numbers of recurrences in both respective groups. This is in line with a previous analysis, where the time gap was not identified as arisk factor by univariable and multivariable Cox regression models (8).

However, because a negative influence of a timely delayed WBI onset cannot be entirely excluded, the time gap between IOERT and WBI should be kept as short as possible. Whether dose escalation of boost dosages up to ranges of about 15 Gy will provide better LC for patients with a TN or HER2+ histology will be a consideration for further clinical trials.

Surprisingly, no higher risk for IBR was seen for high-graded tumors (grade 3) and a positive nodal status. Patients with 1 of these characteristics had by trend lower risk to relapse compared with patients with grade 1/2 tumors (HR, 0.39; 95% CI, 0.12-1.24; $P = .11$) and negative nodes (HR, 0.3; 95% CI, 0.087-1.09; $P = .068$), respectively. Because of the very low number of recurrences and the retrospective nature of this study, a statistical bias (or even artifact) cannot be excluded. A possible clinical explanation might be that grade 3 and/or node-positive patients received more chemotherapy (grade 3, 59.5%, vs grade 1/2, 17.6%; N+, 45%, vs N0, 18.2%), which also contributes to better LC. Furthermore, grade 3 tumors were slightly more likely to receive RNI than those with grade 1/2 differentiation (grade 3, 18%; grade 1/2, 14%). It remains highly speculative if RNI in dependency on tumor grading could be of clinical relevance in terms of LC. Of all 21 IBRs, only 3 (14%) had shown a positive nodal status N1 (all without RNI), and all other relapses were node-negative. On the basis of these data, it was not surprising that an N1 status did not reach significance as a risk factor for IBRs in the present study population, which is in contrast to other reports (24). Ductal in situ components, which were shown as significant risk factors for local recurrences in the EORTC boost trial (25), were found in 38% (n = 291) of our cohort, correlating well with similar data by Cedolini et al (26). The negative predictive value of additional ductal in situ components for clinical endpoints (IBRs, OS, and disease-free survival) is conflicting (26). For IBRs, we observed an HR of 2.11 (not significant) in multivariate analyses (Table 3), which correlates with the EORTC boost data (25).

If compared with external or interstitial boost techniques, IOERT bears several advantages in terms of accuracy, dose delivery, and homogeneity, as described in detail in our previous reports (8, 10). Within the last decade, new biologic aspects of IORT-induced antitumor effects came into the focus of investigation (27, 28). Observations from in vitro studies suggested that wound fluid might play a key role for the proliferation of clonogenic tumor cells that can be blocked by a higher single dose (28). Furthermore, Herskind and Wenz (27) described a successively increasing complex cascade of inducible antitumor processes with rising single dosages. However, according to published results from clinical trials investigating intraoperative techniques with electrons or 50-Kv x-rays as partial breast irradiation (PBI) compared with WBI (29, 30), a subset of low-risk patients could be identified as suitable for intraoperative PBI alone (31). In particular for node-negative patients aged 50 years or older, small tumor sizes (T1), which are removed by a negative resection margin of at least 2 mm, and positivity for hormonal receptors, boost IOERT could be completely replaced by a full-dose PBI (32).

Late toxicity

Darby et al (33) assumed that every 1 Gy mean heart dose increases the risk for a serious cardiac event by 7.4%. Our results denoted an unlikely influence on a higher cardiac toxicity caused either by WBI or IOERT for the following reasons: all 4 cases with myocardial infarction occurred in patients who were irradiated on right-sided breasts with consecutive low (estimated) mean heart dosages, and 2 already suffered from coronary artery disease or chronic heart disease before radiation therapy.

Disregarding secondary breast cancers in the contralateral breast, 7.5% of all patients developed secondary cancers (Table E2; available online at www.redjournal.org). Of these, 1 showed an angiosarcoma of the affected breast, occurring 5.6 years after IOERT and WBI. This histology is generally assumed as potentially induced malignancy within a time period of 4 to 8 years after treatment completion (34). Additionally, 6 patients (median age, 58.9 years) were diagnosed with a consecutive lung cancer after a median time interval of 60.3 months (range, 35.7-156.3). Three occurred in the previously irradiated side (WBI without RNI). In the literature, lung cancer was assumed to be a probable tumor entity with a higher incidence after locoregional breast irradiation at a latency of at least 10 years (35) but also with contradictory results after longer follow-up (35, 36). Because of the very low numbers of patients with secondary lung cancers in our cohort (0.8% of all patients), with only half of them occurring on the same side, and a median latency of only 5 years, a radiation induction seemed unlikely.

Late cosmesis

Comprehensive data for late tissue reactions according to a generally accepted scoring system (eg, LENT-SOMA scoring scale) (37, 38) are not available for this analysis. Nevertheless, IOERT enables absolute skin protection and a small boost volume. This has the potential to minimize fibrosis rates and hence contribute to satisfactory cosmetic outcome (18). This assumption is supported by long-term data from the Research Cancer Center of Montpellier France of 2006 (5): After a median follow-up period of 9 years, only 6 of 42 patients (14%) after IOERT developed a subcutaneous fibrosis grade 2 directly within the boost region. Breast cosmesis was classified as good to excellent in all patients (5). The few clinical trials that compare cosmetic results after IORT (as boost or single treatment) with conventional WBI revealed no significant differences between these 2 strategies (6, 39, 40). Our own institutional experience has revealed that after an IOERT boost, increasing patient age or electron ube diameters >6 cm might be negative predictors for cosmetic impairment (18). However, despite the fact that physicians classified cosmetic outcome with excellent/good (satisfactory) in 64% of cases, this shows potential for further improvement. Hypofractionated external beam schedules, like 40 Gy in 15 fractions, provide excellent cosmetic results, which was shown in the Canadian as well as START trials for WBI (41, 42) and has now been corroborated in the IMPORT trial (43) for a PBI approach. Especially for a "low-risk" postmenopausal subgroup of patients (small tumor sizes, node-negative, ER-positve, and low-grade differentiation), hypofractionated PBI turns out to be a viable treatment option, with no cosmetic inferiority compared with WBI (43).

Because especially in low-risk cancer patients hypofractionated PBI achieves very high 5-year LC rates of >99% (43), it remains questionable whether these patients really benefit from boost IOERT when followed by WBI. However, IOERT with high single dosages also represents a kind of (extreme) hypofractionation. To date, hypofractionation for WBI is increasingly accepted to be at least isoeffective compared with conventional fractionation in terms of LC and late toxicity (41, 42) because of lower α/β values of breast cancer cells of around 4 (44). Using a linear-quadratic model to estimate biologic equivalence, a 10-Gy single-dosage equals about 23 Gy in normofraction equivalent dose in 2 Gy fractions. Therefore, it seemed logical to combine both boost IOERT and hypofractionated WBI, a setting first published by Ivaldi et al (45) in a phase 2 trial. This schedule showed acceptable treatment tolerance after short-term follow-up (45). Further conclusions regarding this regimen's effectiveness is awaited from the multicenter HIOB trial (ClinicalTrials.gov Identifier: NCT01343459) begun in January 2011 as an ISIORT investigator-initiated study.

Limitations to this study

Because of the retrospective study design and the extraordinary low numbers of recurrences, clinical interpretation of statistical results should be made with caution. Selection criteria for study eligibility was nonhomogeneous and not well adjusted, making it difficult to draw any definite clinical conclusions with respect to different risk constellations. Furthermore, our study was not a randomized trial comparing a "head-to-head" design of IOERT as a boost with external standard techniques (electrons, photons) or interstitial brachytherapy. Hence, on the basis of our current knowledge, boost techniques other than IOERT remain an alternative treatment option if an additional dose augmentation to the tumor bed seems to be beneficial. The clinical effect of systemic treatment in the form of chemotherapy, immunotherapy, or antihormonal treatment improved rapidly over time, which could possibly conceal the potential of IOERT on LC if administered according to recommendations of current guidelines. In the light of new clinical data regarding PBI, it remains unclear if all patients, especially those with a lower local recurrence risk, would still profit in terms of LC if IOERT is administered as a boost.

Conclusions

After long-term observation, IOERT as a boost consistently provides high LC rates in breast cancer patients in tumor stages I to III and all risk settings, with a prevalence for subsequent in-breast relapse in patients showing HER2+ and TN breast cancer subtypes.

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