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ORIGINAL ARTICLE

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Oncological outcome, postoperative complications, and mammographic changes after intraoperative radiotherapy with electrons (IOERT) as a boost in a large single-institution cohort of breast cancer patients

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Abstract

Advantages of using intraoperative radiotherapy with electrons (IOERT) as a boosting modality in breast-conserving therapy include the direct visualization of the tumor bed, a reduced skin dose, and patient convenience. We report oncological outcome, postoperative complication rate, and mammographic changes on follow-up imaging in women treated at our institution with IOERT as a boost modality in breast-conserving therapy for early-stage breast carcinoma.

Between January 2007 and June 2018, 763 consecutive patients were enrolled. During breast-conserving surgery, an IOERT boost of 9 Gy was applied, followed by whole breast irradiation (WBI).

At a median follow-up of 62.2 months (range: 0.5-135), 13 in-breast recurrences were observed, yielding a local tumor control rate of 98.4% at 5 years. In multivariable analysis, high tumor grading was predictive for local recurrence (HR = 5.6; 95%CI: 1.19-26.2). A total of 27 (3.5%) patients developed any kind of postoperative complication. None of the tumor characteristics nor any of the IOERT technical parameters were predictive for development of a postoperative complication.

On follow-up imaging, 145 patients with mammographic changes BIRADS score ≥3 were found of which 50.3% required a biopsy. Only 17 patients had positive biopsies; none of the IOERT parameters were predictive for false-positive imaging.

A 9 Gy IOERT boost combined with postoperative WBI provided outstanding local control rates, was well-tolerated, with limited postoperative complications. However, radiologists must be aware of a presumable higher prevalence of mammographic changes after IORT as a boost.

KEYWORDS
breast cancer, IORT, mammography, postoperative complications, radiotherapy

1 | INTRODUCTION

The successful treatment of early-stage breast cancer with breast-conserving therapy (BCT) has been well established over the past decades. Several trials have indicated BCT as an equally effective treatment as is mastectomy with respect to survival.[1-3] For locoregional treatment, radiotherapy applied after local excision is regarded as standard of care. This consists of whole-breast radiation (ie, WBI; usual dosage 45-50 Gy equivalent in 3-5 weeks), followed by an additional boost to the tumor bed. Considering the tumor bed as the tissue at highest risk for residual subclinical tumor cells, a local dose escalation has been shown to decrease the in-breast recurrence rates most effectively.[4,5]

Advantages of using intraoperative radiotherapy (IORT) with electrons (IOERT) as a boosting modality include the ability to directly visualize the tumor bed, thereby avoiding marginal misses as opposed to boosting a CT-based volume. Furthermore, it attributes to patient convenience—because of the considerably lower number of visits to the radiotherapy department—and has possibly a biologic advantage (ie, low alpha/beta ratio of breast cancer and immediate effect on the tumor microenvironment by abrogation of the proliferative cascade induced by wound healing after surgery).

The development of structural alterations in the tumor bed on postoperative mammography after BCT and IORT with electrons or low-energy X-rays has been described.[6-8] Since radiologic follow-up plays a vital role in detecting breast recurrence, these induced mammographic changes may lead to a limited diagnostic value of the post-therapeutic imaging or unnecessary biopsies (ie, false-positive imaging).

All published results on mammographic changes and postoperative complications[9-13] involved small studies with limited patient numbers and short follow-up time, emphasizing the need to investigate this in a large cohort.

Awaiting the randomized TARGeted Intraoperative radioTherapy as a tumor bed Boost (TARGIT-B) trial (https://clinicaltrials.gov/ct2/show/NCT01792726), the present study aims to report on oncological outcome, postoperative complication rate, and mammographic changes in a large cohort of women enrolled at our institution after IOERT as a boost modality in BCT for early breast carcinoma or ductal carcinoma in situ (DCIS).

2 | PATIENTS AND METHODS

2.1 | Population

Between January 2007 and June 2018, the clinical records of 775 consecutive patients diagnosed with early-stage breast carcinoma or DCIS treated at the GZA Hospitals with IOERT as a boost during breast-conserving surgery (BCS) followed by WBI were retrospectively reviewed in our prospectively assembled database. Twelve patients were excluded for one of the following reasons: IOERT as re-irradiation for local recurrence (n = 4), patient's refusal of WBI (n = 3), and missing follow-up data following the WBI treatment (n = 5). In total, 763 patients were available for the current analysis. Patients' tumor and treatment characteristics are summarized in Table 1.

2.2 | Surgery

All patients were treated by certified breast cancer surgeons (GZA Hospitals, St Augustinus, Antwerp, Belgium) using state-of-the-art procedures, in accordance with the European Society of Breast Cancer Specialists (EUSOMA) quality guidelines.

Lumpectomy was performed either by palpation or guided by a localization procedure. Microscopic evaluation of the resection margins was perioperatively performed by a pathologist. If the tumor-free resection margin was not achieved in case of invasive disease or if a calcification-free margin <2 mm was seen on mammography in patients with DCIS, an additional margin was removed by the surgeon. If all tumor margins were found to be negative by perioperative pathology, IOERT was administered.

2.3 | Radiation treatment

Intraoperative radiotherapy with electrons was administered directly after lumpectomy using an IOERT dedicated mobile accelerator (Mobetron, Intraop). Prior to IOERT, the tissue surrounding the lumpectomy cavity was temporarily approximated by sutures to bring it into reach of the electron beam. The depth and width of the lumpectomy cavity were measured for individual depth dose prescription, choice of applicator tube, and electron energy. The applicator tube was placed under visual control to encompass the entire tumor bed and could range from 3 to 6 cm. No attenuator aluminum-lead disk was used since delivered dose was low. High-energy electron (6-12 MeV) beam radiotherapy was administered, with choice of energy depended on depth of the lumpectomy cavity, size, and angle of the applicator tube, aiming to deliver a total dose of 9 Gy (prescribed at the 90% isodose) to the lumpectomy cavity.

After surgery, adjuvant WBI was performed according to current guidelines at time of presentation, similarly used fractionation scheme was dependent on guidelines at time of presentation. At least 98% of the PTV was receiving ≥95% of the prescribed dose of 50 Gy or 40 Gy in 25 or 15 fractions, respectively, using an uni-isocentric 3D-conformal technique.

TABLE 1 Patient', tumor, and treatment characteristics

	Patients (n)	%		Patients (n)	%
Age			ALND performed		
≤40 y	15	2.0	Unknown	1	0.1
41-50 y	139	18.2	Yes	319	41.8
51-60 y	212	27.7	No	444	58.2
>60 y	404	52.2			
			Number of nodes examined		
Menopausal status			Unknown	0	0
Unknown	81	10.6	0	7	0.9
Premenopausal	135	17.7	1-5	540	70.8
Postmenopausal	507	66.4	6-10	47	6.2
Perimenopausal	40	5.2	11-15	88	11.5
			>15	81	10.6
Largest diameter (mm)					
Unknown	22	2.9	Number of positive nodes		
<10 mm	181	23.7	Unknown	0	0
10-20	372	48.8	0	587	76.9
21-30	168	22.0	1-3	138	18.1
>30	20	2.6	4+	38	5.0
Histologic type			Margins		
Unknown	2	0.3	Unknown	2	0.3
IDC	610	79.9	Radical excision en-bloc	459	60.2
ILC	90	11.8	Radical excision after additional resection	271	35.5
DCIS	42	5.5	Irradical excision	31	4.1
Other	19	2.5			
			Re-excision		
Tumor grade (if invasive) (DCIS = 42)			Unknown	0	0
Unknown	0	0	Yes	34	4.5
1	190	26.4	No	716	93.8
2	349	48.4	Mastectomy	13	1.7
3	182	25.2			
			WBI dose		
Presence of LVI (if invasive)			≥45 Gy EqD2	760	99.6
Unknown	16	2.2	<45 Gy EqD2	3	0.4
Yes	178	24.7			
No	527	73.1			
			RT target volume		
Presence of PNG (if invasive)			Breast only	600	78.6
Unknown	603	82.8	Breast + regional lymph nodes	163	21.4
Yes	20	2.7			
No	102	14.0			
			Endocrine therapy		
Hormone receptor status (if invasive)			Unknown	7	0,9

(Continues)

TABLE 1 (Continued)

	Patients (n)	%		Patients (n)	%
ER			None	110	14.4
Unknown	43	5.6	Tamoxifen	374	49.0
Positive (Allred > 2)	648	84.9	Aromatase inhibitor	141	18.5
Negative	72	9.4			
PR					
Unknown	41	5.4	Adjuvant chemo		
Positive (Allred > 2)	118	15.5	Unknown	0	0
Negative	159	20.8	Yes	317	41.5
			No	446	58.5
Her2					
Unknown	117	16.2			
1+	354	49.1			
2+	244	33.8			
3+	55	7.6			

Abbreviations: ALND, axillary lymph node dissection; DCIS, ductal carcinoma in situ; ER, estrogen receptor; IDC, invasive ductal carcinoma; ILC, invasive lobular carcinoma; LVI, lymphovascular invasion; PNG, perineural growth; PR, progesterone receptor.

2.4 | Evaluation

Patient demographics included age at the time of surgery, menopausal status, and date of last follow-up. Tumor characteristics included tumor histology, tumor size, hormone receptor status, presence of lymphovascular invasion, perineural growth, axillary nodal status, tumor grade, and margin status (ie, radical excision en-bloc, a radical excision after additional resections during the same surgery or an irradical excision requiring additional surgery such as mastectomy) are listed in Table 1. Treatment details included IOERT applicator parameters (energy, diameter used for IORT, angle, and need for bolus), interval between IOERT and WBI, necessity of immediate re-resection or conversion to mastectomy, and use of adjuvant systemic therapy. Recurrences were evaluated by clinical follow-up and imaging. Postoperative complications included development of hematoma, wound dehiscence, and/or infections requiring antibiotics within a month after IOERT. Mammographies were evaluated by three experienced radiologists, qualified with the European Diploma in Breast imaging (EDBI), according to the EUSOMA guidelines. Mammographic changes were defined as changes on follow-up mammography with a Breast Imaging Reporting an Data System (BI-RADS) score ≥3.

2.5 | Statistical analysis

All categorical variables were reported by frequency and percentages. Furthermore, for continuous variables, the median and range were computed. All events were measured from the day of IOERT to event (or to last contact if not applicable). Local recurrence-free survival, disease-free survival (DFS), and overall survival (OS) rates were estimated according to the Kaplan-Meier method.

Univariate and multivariate Cox proportional hazards regression models were used to estimate the influence of patients', tumor, treatment, imaging, or IOERT characteristics on the risk of local recurrence, postoperative complications, mammographic changes, or unnecessary biopsy for a 95% confidence level.

All statistical comparison was done using the R software (version 3.3.2 [2016]; R Foundation for Statistical Computing) with significance level $\alpha = 0.05$.[14,15]

3 | RESULTS

A median follow-up of 62.2 months (range: 0.5-135 months) was reached as of September 2018. The median time interval between IOERT to WBRT was 7.4 weeks (range 1.3-58.4 weeks). Over 94.5% of the patients received any additional systemic therapy, dependent on TN-stage, menopausal, hormonal, and Her2 status: 85.5% received an anti-hormonal treatment, 41.4% chemotherapy, and 8.8% trastuzumab, respectively.

Disease-free survival and OS at 5 years were 95.1% and 97.2, respectively. Furthermore, only 13 ipsilateral breast recurrences were observed, yielding an ipsilateral local tumor control rate of 98.4% at 5 years. Nine recurrences were located within the initially involved quadrant (IQ) (ie, involved quadrant recurrence [IQR]) and four outside this quadrant (ie, outer quadrant [OQ] recurrence [OQR]). One additional patient developed an ipsilateral DCIS and was not included in invasive local recurrence analysis. Of the 42 patients with DCIS-only disease at time of diagnosis, four developed a DCIS-only recurrence, yielding a local recurrence rate at 5 years of 8.4%. No invasive recurrences were seen in this group.

Of the invasive local recurrences (LR), 30.7% patients (4/13) were triple-negative cancers vs only 9.6% (73/762) in the whole

group. Because age has been repeatedly reported as the strongest predictive factor for local control,[4] LR analysis was also performed along four age groups (≤40; 41-50; 51-60; and ≥60) showing an ipsilateral local tumor control rate at 5 years of 95.2%, 97.7%, 99.1%, and 98.8% in patients <40 years; 41-50 years; 51-60 years; and ≥61 years, respectively.

To evaluate risk factors predictive for LR, we focused on all LR firstly and additionally tried to analyze IQRs separately. In univariate analysis for all LR, younger age, cN-stage, pN-stage, high tumor grading, and total number of positive lymph nodes were predictive for local recurrence, albeit in multivariable analysis only high tumor grading (ie, 3) reached significance (Table 2). To ascertain the role of a WBI delay following IOERT, two time slots were considered: WBI onset ≤12 weeks and >12 weeks after IOERT, respectively. Along these slots, no influence on local recurrence rates could be identified (HR = 0.402; 95%CI: −0.111-1.463). None of the other tumor nor treatment characteristics were predictive for LR.

For IQR (true local recurrences), no influence of any tumor nor treatment characteristic could be identified in univariate analysis.

3.1 | Postoperative complications

A total of 27 (3.5%) patients developed postoperative complications within a month after IOERT. Hematoma was the most occurring complication (20/27), followed by infections requiring antibiotics (5/27) and wound dehiscence (2/27). None of the tumor characteristics nor any of the IOERT parameters were predictive for the development of a postoperative complication. Patients' age had no significant effect on this risk, albeit a trend toward a higher complication rate was found with increasing age, most likely due to the frailty and increasing amount of comorbidities of older patients.

3.2 | Mammographic changes

Ninety-nine percent of patients received follow-up imaging with a median frequency of 0.92/y (range: 0-5.5). On follow-up imaging, 145 patients (19%) with mammographic changes (ie, BI-RADS ≥3) were found of which 50.3% (n = 73) or 9.5% of the total population required a biopsy (Figure 1, Table 3). Only 17 patients had positive biopsies, confirming recurrent disease, either local (13/17) or regional (4/17). This implicates that 7.3% of all patients had to cope with false-positive imaging and a subsequent unnecessary biopsy. The inability to perform a radical resection in 1 session (ie, necessity to perform a re-resection) was predictive for false-positive mammographic changes ($P = .036$). None of the observed imaging findings, nor tumor characteristics nor IOERT parameters were predictive for false-positive imaging (ie, unnecessary biopsy).

TABLE 2 Hazard ratio (HR) and 95% confidence intervals (CI) obtained from univariate and multivariate cox proportional hazard regression model for local recurrences

	Univariate analysis			Multivariate analysis		
Characteristic	HR	95% CI	*P*-value	HR	95% CI	*P*-value
Age (continuous)	1.46	0.78-2.64	.012	1.006	0.20-5.05	.915
Clinical N stage						
N0	1	Reference				
N+	3.604	1.07-12.1	.038	1.001	0.10-9.53	1.000
Pathological N stage						
N0	1	Reference				
N+	2.24	1.22-4.1	.006	1.168	0.38-3.51	.782
Grade						
Grade 1	1	Reference				
Grade 2	5.253	1.58-17.4	.007	3.788	0.83-17.1	.083
Grade 3	6.076	1.75-21.0	.004	5.603	1.19-26.2	.029
SNP						
Yes	1	Reference				
No	0.404	0.18-0.87	.021	0.786	0.16-3.78	.764
#LN+ (continuous)	0.324	1.08-1.75	.008	1.306	0.95-1.80	.105
ALND						
#LN+ (continuous)	0.096	1.03-1.17	.004	1.086	0.92-1.27	.315

Note: Only significant characteristics in univariate analysis are presented.

Abbreviations: ALND, axillary lymph node dissection; LN, lymph node; SNP, sentinel node procedure.

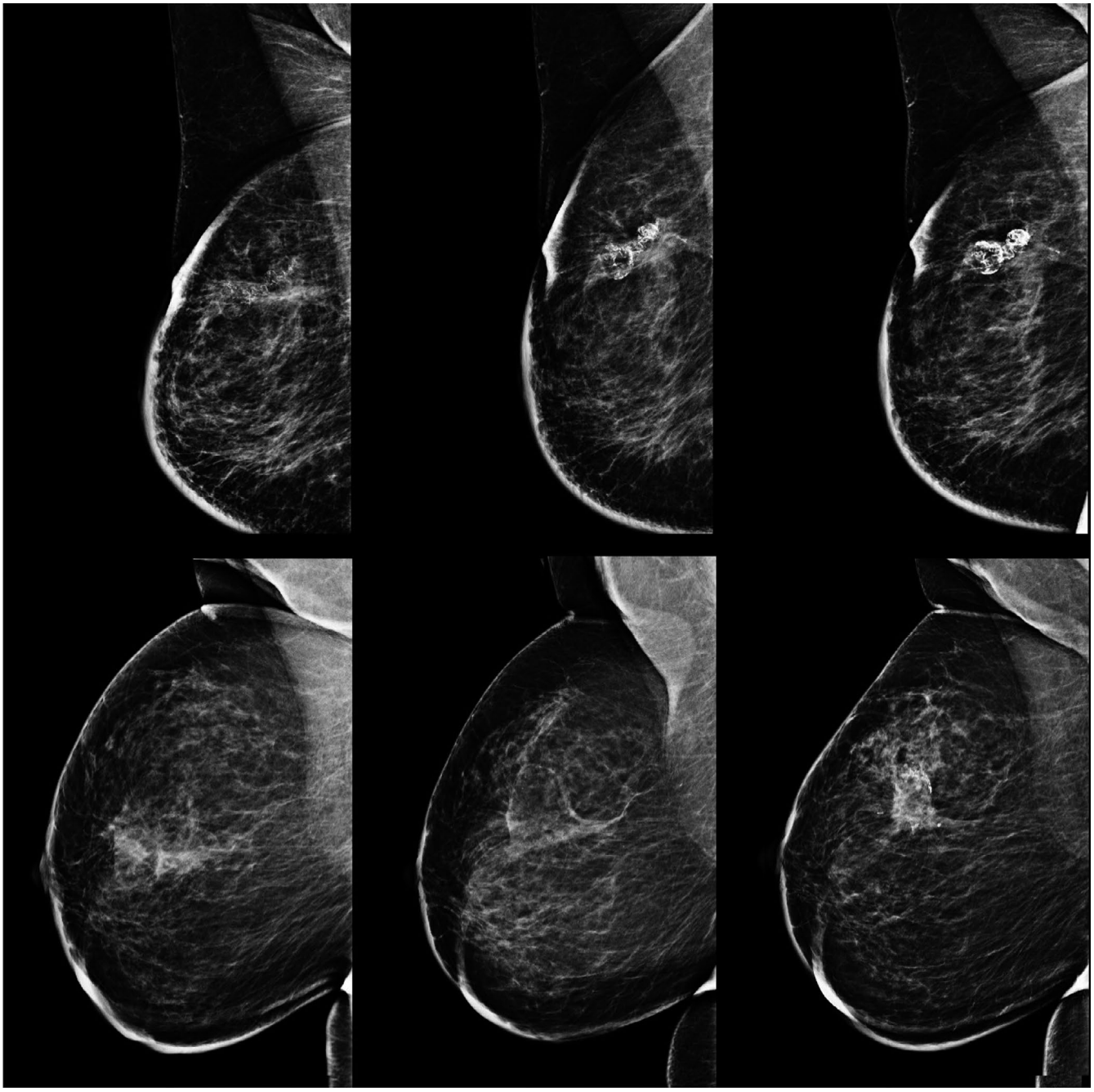

FIGURE 1 Exemplary right mediolateral oblique mammography of two patients (rows) with mammographic changes at 1 y (left column), 2 y (middle column), and 3 y after lumpectomy and IOERT, respectively. (A) The first post-treatment mammography of the first row (ie, patient) shows amorphous and coarse heterogeneous calcifications of intermediate concern (BI-RADS 3). Follow-up mammographies demonstrate progressive curvilinear macrocalcifications surrounding a radiolucent nodule compatible with the typical benign arc-like calcifications of fat necrosis (BI-RADS 2). (B) The first post-treatment mammography of the second row illustrates a typical post-surgical architectural distortion and diffuse skin thickening compatible with post-radiation skin edema (BI-RADS 2). Subsequent follow-up mammography after 2 y, however, reveals a developing density, new and larger than on the previous examinations, and peripheral coarse calcifications (BI-RADS 3)

4 | DISCUSSION

A 9 Gy IOERT boost combined with postoperative WBI provided outstanding local control rates and limited postoperative complications in our large single-center cohort.

True local recurrences are presumed to occur between 40 and 65 months after the primary diagnosis, so with a median follow-up of 62.2 months, we can consider our data to be mature.[16] IOERT boost recurrence rates have been reported previously in three large series, albeit all retrospective series.[17-19] Our local tumor control rate of

TABLE 3 Imaging findings on mammography and BI-RADS score for all 145 patients presenting with mammographic changes (≥BI-RADS 3) during follow-up

	Biopsy required (n = 73)		No biopsy required (n = 72)
Imaging findings	True local recurrence group (n = 17) n (%)	No local recurrence/false-positive imaging (n = 56) n (%)	n (%)
Axillary lymphadenopathy	4 (24)	5 (9)	15 (21)
Irregular/round or spiculated mass	5 (29)	19 (34)	4 (6)
Fine calcifications	5 (29)	10 (18)	11 (15)
Oval or circumscribed mass	2 (12)	17 (30)	12 (17)
Scar thickening/calcification	1 (6)	5 (9)	25 (35)
BI-RADS score			
3	1 (6)	33 (59)	68 (94)
4	14 (82)	23 (41)	4 (6)
5	2 (12)	0 (0)	0 (0)

Note: Some percentages do not total 100% because of rounding.
Abbreviation: BI-RADS, breast imaging reporting and data system.

98.4% at 5 years is similar to the local tumor control rates reported in previous IORT boost series with local control rate ranging from 99.2% at 6 years to 97% at 5 years.[17,18] Furthermore, our findings are also comparable to the recurrence rates reported in the EORTC studies and START-B trial, reporting recurrence rates at 5 years of 4.3% and 2.2% at 6 years, respectively.[4,20] In addition, similar to these studies unanimously reporting the influence of age on local control, our younger patients also had more ipsilateral breast tumor recurrences than older patients.[4,21] Then again, in the EORTC study only 34% of patients were aged >60 years, while in our study 52% of patients were aged >60 years, with current knowledge on reduced impact of a boost in this age, it is imaginable omission of a boost in this age group would have led to the same LR rates.

Rates of postoperative complications after conventional breast surgery followed by WBRT have been reported in different studies.[4,22,23] Infection rates of 19.7% and 13% are reported in the Cambridge Breast IMRT studies (n = 648 patients) and EORTC study.[4,22] Further, despite the widespread use of electrocautery, which has reduced the incidence of hematoma formation in the breast, this complication still occurs in 2-10% of cases.[22] In our IOERT series, only 3.5% of patients developed postoperative complications, which is considerably less than in previous studies and can be an underestimation. Postoperative complications related to breast procedures are relatively minor and frequently managed on an outpatient basis, and it can therefore be difficult to establish accurate incidence rates for these events in a retrospectively evaluated cohort. Moreover, throughout literature different time intervals for development of postoperative complication are used; subsequently, our prevalence rate of 3.5% within one month is most likely an underestimation.

Three small series reported earlier on postoperative complications after low-energy X-ray IORT as a boost.[9,10,24] Tuschy et al[10] demonstrated hematoma rates (24%) to be most prevalent, similar to our findings, the latter nonetheless occurring to a much lesser extent (2.6%), probably because of the possible underestimation we assume. Further, Kraus-Tiefenbaucher et al[9] studied the rates of seroma formation in 73 patients undergoing BCS and IORT as a boost and demonstrating that it was similarly occurring after IORT as it was after BCS without IORT. Sorrentino et al[24] demonstrated an overall risk for the development of complications of 1.22 compared to EBRT, albeit not significant ($P = .478$).

Taking these previous series and our findings into account, we can prudently conclude that IOERT as a boost does at least not increase the postoperative complication rate as is commonly thought.

From the radiologic perspective, the impact of IOERT on morphologic imaging changes during post-therapeutic follow-up is critical. After conventional BCS, it is well known that interpretation of follow-up imaging can be complicated because of the parenchymal alteration caused by the surgery and WBRT. With reported amounts ranging from 2%-6% of required additional diagnostic workup (ie, ultrasound, MR imaging or pathology)—and hence suggesting mammographic changes—during mammography surveillance after conventional BCS with external RT, this is less pronounced than the 19% of mammographic changes of which 9.5% required additional diagnostics seen in our IORT cohort. Wasser et al[25] showed mammographic incidence of fat necrosis and parenchymal scarring to be significantly higher after an IORT boost compared to conventional BCS. However, in their study, additional diagnostic procedures due to unclear findings were not more frequent in patients with IORT than in those of the control group. It might be plausible that our high amount of additional diagnostics is due to cautious radiologists, not acquainted with the more pronounced amount of structural scarring after IORT.

Another interesting finding was the predictive value of an irradical resection, requiring a re-resection, in terms of false-positive follow-up imaging. It might be probable that repeated

manipulation of the glandular tissue in a short time range in combination with IORT causes an even more pronounced structural parenchymal scarring.[26]

An apparent limitation of our study is its retrospective nature. Nonetheless in terms of evaluation of mammographic changes, the use of objective imaging data and the standardized documentation of the additional diagnostics and pathology findings. This retrospective evaluation does not strictly induce an error, this is not the case when evaluating postoperative complications, where most likely an underestimation of events occured.

The currently open TARGIT-B trial was designed to test whether indeed a tumor bed boost administered intraoperatively is superior to a tumor bed boost administered via EBRT for patients with breast cancer undergoing BCS followed by WBI, and their results are highly anticipated.

In conclusion, a 9 Gy IOERT boost combined with postoperative WBI provided outstanding local control rates, comparable to all trials with similar length of follow-up. Furthermore, this is the largest cohort reporting on postoperative complications and mammographic changes; our results demonstrate IOERT boost to be well-tolerated, with limited postoperative complications. However, radiologists must be aware of a presumable higher prevalence of mammographic changes after IORT as a boost.

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CONFLICT OF INTEREST

No disclosures.

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REFERENCES

1. Veronesi U, Cascinelli N, Mariani L, et al. Twenty-year follow-up of a randomized study comparing breast-conserving surgery with radical mastectomy for early breast cancer. *N Engl J Med*. 2002;347:1227-1232.
2. Fisher B, Anderson S, Bryant J, et al. Twenty-year follow-up of a randomized trial comparing total mastectomy, lumpectomy, and lumpectomy plus irradiation for the treatment of invasive breast cancer. *N Engl J Med*. 2002;347:1233-1241.
3. Litière S, Werutsky G, Fentiman IS, et al. Breast conserving therapy versus mastectomy for stage I-II breast cancer: 20 year follow-up of the EORTC 10801 phase 3 randomised trial. *Lancet Oncol*. 2012;13:412-419.
4. Bartelink H, Maingon P, Poortmans P, et al. Whole-breast irradiation with or without a boost for patients treated with breast-conserving surgery for early breast cancer: 20-year follow-up of a randomised phase 3 trial. *Lancet Oncol*. 2015;16:47-56.
5. Sanders ME, Scroggins T, Ampil FL, et al. Accelerated partial breast irradiation in early-stage breast cancer. *J Clin Oncol*. 2007;25:996-1002.
6. Engel D, Schnitzer A, Brade J, et al. Are mammographic changes in the tumor bed more pronounced after intraoperative radiotherapy for breast cancer? Subgroup analysis from a randomized trial (TARGIT-A). *Breast J*. 2013;19:92-95.
7. Elsberger B, Romsauerova A, Vinnicombe S, et al. Comparison of mammographic findings after intraoperative radiotherapy or external beam whole breast radiotherapy. *Eur J Surg Oncol*. 2014;40:163-167.
8. Della Sala SW, Pellegrini M, Bernardi D, et al. Mammographic and ultrasonographic comparison between intraoperative radiotherapy (IORT) and conventional external radiotherapy (RT) in limited-stage breast cancer, conservatively treated. *Eur J Radiol*. 2006;59:222-230.
9. Kraus-Tiefenbacher U, Bauer L, Kehrer T, et al. Intraoperative radiotherapy (IORT) as a boost in patients with early-stage breast cancer - acute toxicity. *Onkologie*. 2006;29:77-82.
10. Tuschy B, Berlit S, Romero S, et al. Clinical aspects of intraoperative radiotherapy in early breast cancer: short-term complications after IORT in women treated with low energy x-rays. *Radiat Oncol*. 2013;8:1-6.
11. Lemanski C, Azria D, Thezenas S, et al. Intraoperative radiotherapy given as a boost for early breast cancer: long-term clinical and cosmetic results. *Int J Radiat Oncol*. 2006;64:1410-1415.
12. Wenz F, Welzel G, Keller A, et al. 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. *Breast*. 2008;17:617-622.
13. Key S, Miglierini P, Dupré PF, et al. Cosmetic outcome and chronic breast toxicity after intraoperative radiation therapy (IORT) as a single modality or as a boost using the Intrabeam®device: a prospective study. *Ann Surg Oncol*. 2017;24:2547-2555.
14. Core R, Team R. *A language and environment for statistical computing*. Vienna, Austria: The R Foundation for Statistical Computing; 2013.
15. Bates D, Mächler M, Bolker B, et al. Fitting linear mixed-effects models using lme4. *J Statsitcal Softw*. 2015;67:51.
16. Gujral DM, Sumo G, Owen JR, et al. Ipsilateral breast tumor relapse: local recurrence versus new primary tumor and the effect of whole-breast radiotherapy on the rate of new primaries. *Int J Radiat Oncol Biol Phys*. 2011;79:19-25.
17. Fastner G, Sedlmayer F, Merz F, et al. IORT with electrons as boost strategy during breast conserving therapy in limited stage breast cancer: long term results of an ISIORT pooled analysis. *Radiother Oncol*. 2013;108:279-286.
18. Blank E, Kraus-Tiefenbacher U, Welzel G, et al. Single-center long-term follow-up after intraoperative radiotherapy as a boost during breast-conserving surgery using low-kilovoltage x-rays. *Ann Surg Oncol*. 2010;17:352-358.
19. Vaidya JS, Baum M, Tobias JS, et al. Long-term results of TARGeted Intraoperative radioTherapy (Targit) boost during breast-conserving surgery. *Int J Radiat Oncol Biol Phys*. 2011;81:1091-1097.
20. Haviland JS, Owen JR, Dewar JA, et al. The UK Standardisation of breast radiotherapy (START) trials of radiotherapy hypofractionation for treatment of early breast cancer: 10-year follow-up results of two randomised controlled trials. *Lancet Oncol*. 2013;14(11):1086-1094.
21. Vrieling C, Collette L, Fourquet A, et al. The influence of patient, tumor and treatment factors on the cosmetic results after breast-conserving therapy in the EORTC "boost vs no boost" trial. *Radiother Oncol*. 2000;55:219-232.
22. Mukesh MB, Barnett G, Cumming J, et al. Association of breast tumour bed seroma with post-operative complications and late normal tissue toxicity: results from the Cambridge Breast IMRT trial. *Eur J Surg Oncol*. 2012;38:918-924.
23. Ashraf M, Biswas J, Gupta S, et al. Determinants of wound infections for breast procedures: assessment of the risk of wound infection posed by an invasive procedure for subsequent operation. *Int J Surg*. 2009;7:543-546.
24. Sorrentino L, Fissi S, Meaglia I, et al. One-step intraoperative radiotherapy optimizes conservative treatment of breast cancer

with advantages in quality of life and work resumption. *The Breast*. 2018;39:123-130.
25. Wasser K, Ruch M, Brade J, et al. Do structural changes in the tumour bed after intraoperative radiotherapy (IORT) of breast cancer complicate the evaluation of mammograms in a long-term follow-up? *Eur J Radiol*. 2012;81:e255-e259.
26. Dershaw DD. Mammography in patients with breast cancer treated by breast conservation (lumpectomy with or without radiation). *Am J Roentgenol*. 1995;164:309-316.
27. Hasan S, Abel S, Simpson-Camp LS, et al. Short-term follow-up mammography in breast conservation therapy likely leads to unnecessary downstream workup: a longitudinal study. *Int J Radiat Oncol Biol Phys*. 2018;102:1489-1495.

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