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CLINICAL INVESTIGATION

Accelerated Partial Breast Irradiation Using External Beam or Intraoperative Electron Radiation Therapy: 5-Year Oncological Outcomes of a Prospective Cohort Study

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Purpose: To evaluate the ipsilateral breast tumor recurrence (IBTR) after 2 accelerated partial breast irradiation (APBI) techniques (intraoperative electron radiation therapy [IOERT] and external beam APBI [EB-APBI]) in patients with early-stage breast cancer.

Methods and Materials: Between 2011 and 2016, women ≥60 years of age with breast carcinoma or Ductal Carcinoma In Situ (DCIS) of ≤30 mm and cN0 undergoing breast-conserving therapy were included in a 2-armed prospective multicenter cohort study. IOERT (1 × 23.3 Gy prescribed at the 100% isodose line) was applied in 1 hospital and EB-APBI (10 × 3.85 Gy daily) in 2 other hospitals. The primary endpoint was IBTR (all recurrences in the ipsilateral breast irrespective of localization) at 5 years after lumpectomy. A competing risk model was used to estimate the cumulative incidences of IBTR, which were compared using Fine and Gray's test. Secondary endpoints were locoregional recurrence rate, distant recurrence, disease-specific survival and overall survival. Univariate Cox regression models were estimated to identify risk factors for IBTR. Analyses were performed of the intention to treat (ITT) population (IOERT n = 305; EB-APBI n = 295), and sensitivity analyses were done of the per-protocol population (IOERT n = 270; EB-APBI n = 207).

Results: The median follow-up was 5.2 years (IOERT) and 5 years (EB-APBI). Cumulative incidence of IBTR in the ITT population at 5 years after lumpectomy was 10.6% (95% confidence interval, 7.0%-14.2%) after IOERT and 3.7% (95% confidence interval, 1.2%-5.9%) after EB-APBI ($P = .002$). The locoregional recurrence rate was significantly higher after IOERT than EB-APBI (12.1% vs 4.5%, $P = .001$). There were no differences between groups in other endpoints. Sensitivity analysis showed similar results. For

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both groups, no significant risk factors for IBTR were identified in the ITT population. In the per-protocol population, surgical margin status of the DCIS was the only significant risk factor for developing IBTR in both treatment groups.
Conclusions: Ipsilateral breast tumor recurrences and locoregional recurrence rates were unexpectedly high in patients treated with IOERT, and acceptable in patients treated with EB-APBI.

Introduction

Radiation therapy after breast-conserving therapy is standard of care for patients with early stage breast cancer and has proven to be essential for the prevention of local recurrence.[1,2] As conventional whole breast irradiation (WBI) is time consuming and burdensome, efforts to hypofractionate radiation therapy have successfully been applied, shortening treatment duration from 5 to 6 weeks to 3 to 4 weeks with similar or less treatment-related toxic effects.[3] Recently, a fractionation schedule of only 5 daily fractions has been implemented in the United Kingdom.[4] With (accelerated) partial breast irradiation ([A]PBI), radiation therapy is limited to the tumor bed as opposed to the whole breast because most local recurrences occur at the site of the tumor bed. This approach has been shown to be feasible in selected patients at low risk of recurrence and facilitates further hypofractionation resulting in shorter treatments. APBI has proven to be advantageous for toxic effects and quality of life owing to the decrease in irradiated volume.[5-7] Various APBI techniques are available, ranging from single-fraction intraoperative electron radiation therapy (IOERT) to short course (1-2 weeks) external beam APBI (EB-APBI). Reported oncological outcomes differ between studies and techniques. In a recent meta-analysis including 9 randomized trials comparing APBI to WBI (14,514 patients), APBI was associated with increased odds of local recurrence at 5 years compared with WBI (odds ratio [OR], 1.69; $P < .001$). External beam APBI techniques had the lowest magnitude of inferiority (OR, 1.08) and intraoperative techniques (either electron- or photon-based IORT) the highest (OR, 3.10).[8-16] However, absolute differences in local recurrences are small and improve with better patient selection, and APBI does not influence overall survival in these patients. APBI could be an attractive alternative to WBI because of the shortened treatment time and lower risk of toxic effects.

In 2008, results of IOERT in 1246 patients of the Cancer Institute in Milan were published and showed a local recurrence rate of 1.9% after a median of 24 months follow-up.[17] Simultaneously, APBI was being investigated using external beam radiation therapy (mostly in 10 twice-daily fractions to a total dose of 34-38.5 Gy) also with promising first results showing no recurrences at 24 months follow-up.[18,19] Based on this, EB-APBI was introduced in 2 hospitals in the Netherlands in 10 fractions of 3.85 Gy. Fractions were given daily instead of twice-daily because this study aimed at older patients and twice-daily irradiation could be too burdensome. At the same time, in another hospital treatment with 1 fraction of 23.3 Gy to the tumor bed with IOERT was initiated. Because both the IOERT and EB-APBI techniques were new in the Netherlands at the time, a prospective cohort study for selected patients ≥60 years of age with early-stage breast cancer was initiated in a collaboration of these 3 teaching hospitals in the Netherlands, aiming to evaluate outcomes of both techniques.

Toxic effect and quality of life outcomes of this cohort study on IOERT and EB-APBI have been previously reported and showed limited toxic effects and excellent quality of life.[20,21] In this article, we present the oncological outcomes of a prospective cohort study at 5 years after treatment for IOERT and EB-APBI in a clinical setting.

Methods and Materials

Study design and patients

Methods and procedures have been described in an earlier publication.[21] In short, this is a prospective cohort study with 2 treatment arms investigating clinical outcomes after IOERT and EB-APBI. Patients included at the Haaglanden Medical Center (HMC) were treated with IOERT, and patients included at the Haga Hospital and Isala Clinics were treated with EB-APBI. Patients who, although intended, did not undergo IOERT but were still eligible for EB-APBI, were treated with EB-APBI in the HMC. The study opened in 2011 and accrual was completed in November 2016. Inclusion criteria were female patients ≥60 years of age with invasive or in situ breast tumors of ≤30 mm (cT1 and any receptor status or cT2 and ER [estrogen receptor]/PR [progesterone receptor]−positive and HER2/neu −negative [human epidermal growth factor receptor 2] −negative), clinical N0 status, and eligibility for breast conserving therapy with a sentinel node procedure. Exclusion criteria were multicentric or multifocal tumors, extensive intraductal carcinoma or lymphovascular invasion, positive surgical margins (ink on tumor, perioperatively in the IOERT group and on definitive pathology analysis in the EB-APBI group), >pN1a after sentinel node procedure (or a positive sentinel node perioperatively in the case of IOERT), neoadjuvant chemotherapy, previous malignancy in the past 5 years, and previous radiation therapy on the ipsilateral breast. Eligibility was assessed preoperatively based on the tumor characteristics determined on the biopsy and imaging. These eligibility criteria correspond to patients classified

as low or intermediate risk according to the 2010 GEC-ESTRO (Groupe Européen de Curiethérapie—European Society for Radiotherapy and Oncology) recommendations.[13] The intention to treat (ITT) population for each treatment arm includes all patients deemed eligible preoperatively regardless of treatment received. The per-protocol (PP) population includes all preoperatively eligible patients who received either IOERT or EB-APBI, and patients were assigned to the arm of the treatment they had received (Fig. 1). In the EB-APBI arm, final treatment choice also depended on definitive pathology analysis performed postoperatively. Definitive pathology analysis of the lumpectomy specimen was performed for all patients. A positive surgical margin was defined as ink on invasive tumor or Ductal Carcinoma In Situ (DCIS). In the IOERT arm, treatment was applied during surgery before definitive pathology analysis was available, and the definitive treatment choice was made during surgery. The study was approved by the medical ethical committee ZuidWestHolland (10- 042; NTR2931); all patients provided written informed consent for participation.

Procedures

Surgery

Surgical localization was performed by palpation or needle localization. In the EB-APBI group, it was determined on the radiology specimen radiogram if a tumor-free margin could be expected. In the IOERT group, perioperative inspection of margins was performed directly on the fresh lumpectomy specimen on which macroscopic margins were measured. The removed sentinel node was evaluated perioperatively by a pathologist with frozen sections. If macroscopic surgical tumor margins were ≥2 mm wide and the sentinel node was deemed negative by the pathologist, IOERT was administered. If the tumor-free resection margin was <2 mm macroscopically, additional breast tissue was removed by the surgeon, and IOERT was applied if margins were expected to be adequate. If IOERT was deemed not possible, further treatment was chosen at the discretion of the treating physician, which included EB-APBI.

IOERT

IOERT was administered directly after lumpectomy using a dedicated mobile accelerator (Mobetron, INTRAOP). A protection disk was placed inside the lumpectomy cavity in front of the pectoralis muscle to protect underlying organs at risk. The electron applicator diameter covered a total of 20 mm laterally of the lumpectomy cavity or clips and ranged from 4 to 6.5 cm with a majority of 5 cm applicators used (41%).[21] A total dose of 23.3 Gy (prescribed at the 100% isodose according to ICRU [International Commission on Radiation Units & Measurements] Report 71) was delivered using high-energy electron (6-12 MeV) beam radiation therapy, which is sufficient to deliver 21 Gy at the 90% isodose for the full thickness of the glandular tissue.[22]

EB-APBI

EB-APBI was delivered within 6 weeks after surgery, in 10 daily fractions of 3.85 Gy. Daily instead of twice-daily fractionation was chosen to decrease the burden for the older study population, assuming an a/b ratio of 4 for breast tumor and no repopulation factor, this resulted in an equivalent dose of 50.4 Gy. Patients were treated in supine position using either intensity modulated radiation therapy (n = 53) or 3-dimensional (3D) conformal radiation therapy (n = 153) and was mostly performed with 4 to 5 coplanar fields with use of >4 MV photons. The clinical target volume was defined as the region between the gold or titanium markers plus the seroma cavity, with an additional margin of 15 mm minus the smallest tumor-free resection margin. The planning target volume was obtained by adding a 7 mm margin to the clinical target volume, trimmed at 5 mm under the skin surface. At least 90% of the planning target

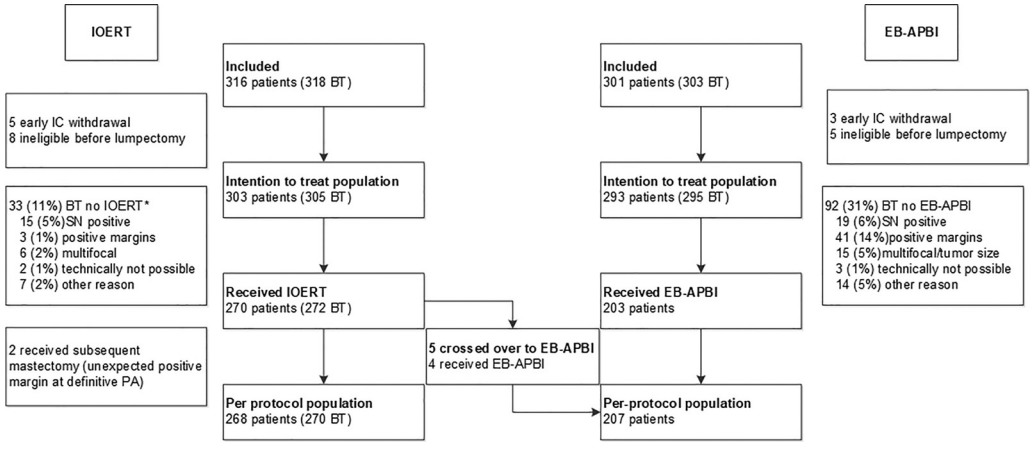


Fig. 1. Inclusion flowchart for IOERT and EB-APBI cohorts. Percentages represent percentage of total intention to treat population (IOERT 305, EB-APBI 295). *Abbreviations*: BT = breast tumors; EB-APBI = external beam accelerated partial breast irradiation; IC = informed consent; IOERT = intraoperative electron radiation therapy; PA = pathology analysis; SN = sentinel node. *Decision for IOERT was made perioperatively for all items in this box.

volume had to receive 90% of the prescribed dose, and the maximum dose should not exceed 120% of the prescribed dose. Patients could only be treated if the treatment planning showed that ≤35% of the ipsilateral breast volume would receive 100% of the prescribed dose. If this constraint was exceeded, the patient did not receive EB-APBI and further treatment was chosen at the discretion of the treating physician. Dose constraints were applied for the contralateral breast, lungs, heart, thoracic wall and thyroid gland, details are provided in Appendix E4.

Additional radiation therapy and systemic therapy

In both treatment groups, patients received additional regional radiation therapy (ipsilateral axillary level 1-4) if there was an indication by local protocol. Systemic therapy (hormonal therapy, chemotherapy or trastuzumbab) was administered according to national Dutch guidelines and it was documented if a patient had started the assigned systemic therapy.

Endpoints and events

The primary endpoint of this study is the cumulative IBTR at 5 years after treatment (from the date of first lumpectomy) in both cohorts. An IBTR was defined as a recurrence anywhere in the ipsilateral breast. In case of concomitant presence of ipsilateral axillary nodes or distant metastases (within 3 months before or after IBTR) the IBTR was included in the analysis. Secondary endpoints were regional recurrence (recurrence in ipsilateral axillary levels), locoregional recurrence (LRR; IBTR and/or regional recurrence), distant recurrence, disease-specific survival, and overall survival. Additionally, we aimed to identify risk factors for developing IBTR. All analyses were performed on the ITT population and analysis were repeated on the PP population as sensitivity analyses.

All IBTR cases underwent extensive pathologic and radiologic review by a specialized pathologist and radiologists to classify IBTR into (1) in-field recurrence (occurring in the irradiated field or within ≤20 mm thereof), (2) new ipsilateral breast tumor (recurrence elsewhere in the ipsilateral breast), or (3) a recurrence along the biopsy or localization tract. This subanalysis was performed only for the IBTRs in the PP population.

Statistical analyses

This study was designed as a prospective observational cohort study with 2 separate treatment arms. The aim of the study was to confirm adequate IBTR rates after breast-conserving surgery and accelerated partial breast irradiation using IOERT or EB-APBI techniques. Based on the literature, we expected a recurrence rate similar to that after WBI of 4% at 5 years and that should not exceed 10% at 5 years.[23] Patients were censored at 5 years after surgical treatment (lumpectomy date).

Patient, tumor, and treatment characteristics were compared between groups using either the χ^2 test or Mann-Whitney *U* test. Median follow-up was calculated using the reverse Kaplan-Meier method. The cumulative incidence of IBTR and LRR for each treatment were estimated using a competing risk model with death and distant recurrence as competing events.[24] The cumulative incidence for distant recurrence for each treatment were estimated using a competing risk model with LRR and death as competing events. To assess the difference between the cumulative incidence for each treatment modality, Fine and Gray's test was applied.[25] The Kaplan-Meier method was used to estimate actuarial disease-specific survival and overall survival at 5 years. Univariate cause−specific Cox regression models were estimated to identify possible risk factors for IBTR for IOERT and EB-APBI separately. A *P* value ≤.05 was deemed statistically significant. All analyses concerning the competing risk models were performed in R with the mstate library.[26] All other analyses were performed in SPSS Statistics 25 (IBM).

Results

Patients

Figure 1 shows the inclusion of patients in both cohorts. For IOERT, 303 patients with 305 breast tumors were included in the ITT population. Eventually, 268 patients with 270 breast tumors were treated with IOERT and included in the PP population. The most common reason for not receiving IOERT was a positive sentinel node peri-operatively (5% of ITT population). For EB-APBI, 293 patients with 295 breast tumors were included in the ITT population, and 207 patients were eventually treated with EB-APBI and included in the PP population. The most common reason for not receiving EB-APBI was positive resection margins (14% of ITT population). In the IOERT group only 11% of patients deemed eligible did not receive IOERT, in the EB-APBI group 31% of patients did not receive EB-APBI. Patients who were excluded from the PP population had significantly more often larger (≥20 mm) tumors, ≥pN1a status, positive surgical margins, and consequently additional systemic treatment or axillary treatment.

Baseline characteristics

Patient, tumor, and treatment characteristics of the ITT populations are shown in Table 1. In the ITT population, there were significantly more patients with positive surgical resection margins (ink on invasive tumor or DCIS) in the EB-APBI group on definitive microscopic pathology analysis (Table 1). The majority of patients in both groups had pT1N0, ER-positive, HER2-negative tumors, and slightly more than half of patients did not receive systemic therapy. Sensitivity analysis among the PP population showed the

Table 1 Patient, tumor, and treatment characteristics of the intention to treat population

		IOERT n = 305 (%)	EB-APBI n = 295 (%)	*P* value
Age	**60-69 y**	**189 (62)**	**173 (58.6)**	**.41**
	≥70 y	116 (38)	122 (41.4)	
Tumor histology	Invasive ± DCIS	281 (92.1)	260 (88.1)	.10
	DCIS	24 (7.9)	35 (11.9)	
	DCIS	24 (7.9)	35 (11.9)	
pT	pTis	24 (7.9)	35 (11.9)	.73
	pT1	245 (80.3)	210 (71.2)	
	≥ pT2	36 (11.8)	50 (16.9)	
pN*	pN0	243 (86.5)	216 (83.1)	.18
	≥ pN1mi	36 (12.8)	37 (14.2)	
	Not done	2 (0.7)	7 (2.7)	
ER*	Positive	260 (92.9)	241 (93.4)	.80
	Missing	1	2	
HER2*	Negative	260 (92.5)	235 (90.4)	.80
	Missing	4	11	
Grade of invasive component†	Grade 1	86 (31.4)	78 (30.7)	.34
	Grade 2	123 (44.9)	134 (52.8)	
	Grade 3	65 (23.7)	42 (16.5)	
	Missing	7	6	
Grade of in situ component†	Grade 1	27 (27.8)	29 (20.1)	.35
	Grade 2	43 (44.3)	73 (50.7)	
	Grade 3	27 (27.8)	42 (29.2)	
	Missing	4	8	
Subtype*	Luminal A	200 (72.7)	196 (80)	.06
	Luminal B HER2−	42 (15.3)	25 (10.2)	
	Luminal B HER2+	14 (5.1)	10 (4.1)	
	HER2+	3 (1.1)	4 (1.6)	
	Triple negative	16 (5.8)	10 (4.1)	
Margin invasive tumor‡	Positive	4 (1.5)	21 (8.1)	<.001
	<2 mm	17 (6.2)	45 (17.4)	
	≥2 mm	253 (92.3)	192 (74.4)	
	Missing	7	2	
Margin DCIS component‡	Positive	8 (7.7)	25 (16.2)	.026
	<2 mm	19 (18.3)	34 (22.1)	
	≥2 mm	77 (74.0)	95 (61.7)	
	Missing	3	10	
Re-excision during lumpectomy	Yes	74 (24.3)	28 (9.7)	<.001
	No	231 (75.7)	260 (90.3)	
	Missing	0	7	
Systemic therapy	None	169 (55.6)	158 (53.9)	.56
	Hormonal therapy	106 (34.9)	101 (34.5)	
	Chemotherapy	8 (2.6)	8 (2.7)	

(*Continued*)

Table 1 (*Continued*)

		IOERT n = 305 (%)	EB-APBI n = 295 (%)	*P* value
Age	**60-69 y**	**189 (62)**	**173 (58.6)**	**.41**
	Combination	21 (6.9)	26 (8.9)	
	Missing	1	2	
Regional radiation	Yes	22 (7.2)	29 (9.8)	.25
	No	283 (93.8)	266 (90.2)	
Received allocated treatment	Yes	272 (89.2)	203 (68.8)	<.001

Abbreviations: DCIS = Ductal Carcinoma In Situ; EB-APBI = external beam accelerated partial breast irradiation; ER = estrogen receptor; HER2 = human epidermal growth factor receptor 2; IOERT = intraoperative electron radiation therapy.
* In tumors with invasive component only.
† Grading according to Bloom-Richardson.
‡ Microscopic margin based on definitive pathology analysis. Positive margin is defined as ink on tumor or DCIS.

same differences between groups, although the differences were less pronounced (Appendix Table E1).

Events

Median follow-up was 5.2 years (95% confidence interval [CI], 5.1-5.2) in the IOERT group and 5.0 years (95% CI, 4.9-5.1) in the EB-APBI group. The cumulative incidence of IBTR in the ITT population at 5 years after lumpectomy was 10.6% (95% CI, 7.0%-14.2%) in the IOERT group and 3.7% (95% CI, 1.2%-5.9%) in the EB-APBI group (P = .002; Fig. 2). In the PP population, the cumulative incidence of IBTR was 11.9% (95% CI, 7.9%-15.9%) after IOERT and 4.3% (95% CI, 1.4%-7.2%) after EB-APBI (P = .005; Table 2, Appendix Fig. E1). Only in the IOERT group was the IBTR rate higher than the prespecified limit of 10% at 5 years. Most (85%) of the IBTRs occurred more than 2 years after surgery.

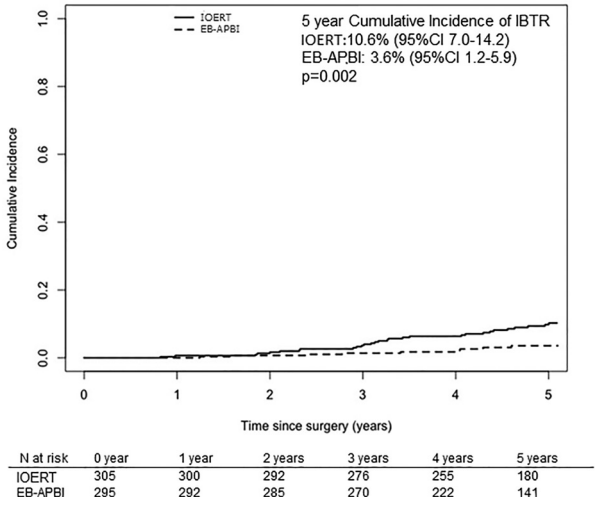


Fig. 2. Five-year cumulative incidence of ipsilateral breast tumor recurrence of intraoperative electron radiation therapy (IOERT) and external beam accelerated partial breast irradiation (EB-APBI) in the intention-to-treat population. *Abbreviations*: 95% CI = 95% confidence interval; IBTR = ipsilateral breast tumor recurrence.

Locoregional recurrence was significantly higher in the IOERT group than in the EB-APBI group (ITT 11.6% vs 3.6%, P = .001; PP 12.6% vs 5.2%, P = .003; Table 2). In the IOERT group, there were 9 regional recurrences combined with IBTR and 3 solitary regional recurrences. In the EB-APBI group, there was 1 regional recurrence combined with IBTR and 1 solitary regional recurrence. There was no difference in distant recurrence or overall survival between the groups at 5 years after treatment (Table 2). Four of the 20 deaths in the IOERT group were breast-cancer related, versus 3 of 20 in the EB-APBI group. Disease-specific survival at 5 years was 98.4% (95% CI, 95.9%-99.4%) and 98.5% (95.4%-99.5%) in the IOERT and EB-APBI groups, respectively. Sensitivity analysis among the PP population showed similar results for distant recurrence, overall survival and disease-specific survival (Table 2).

IBTR analysis

An explorative analysis was performed in the PP population to determine whether an IBTR was an in-field recurrence, new ipsilateral breast tumor or recurrence in the biopsy or localization tract (Table 3). In the IOERT group 12 of 30 (40%) of IBTRs appeared to be an in-field recurrence, 10 of 30 (33%) were new ipsilateral breast tumors, and 8 of 30 (27%) were recurrences in the biopsy or localization tract, with respective 5-year absolute rates of 4.4%, 3.7%, and 2.9%. In the EB-APBI group, 2 IBTRs could not be classified. The remaining 6 IBTRs were all new ipsilateral breast tumors, resulting in a 5-year absolute rate of 2.9%.

Risk factors

Figure 3 shows the relation between clinical factors and IBTR in the ITT population. For both IOERT and EB-APBI, we did not identify significant risk factors that predict IBTR.

Table 2 Events and deaths observed during follow-up in intention-to-treat and per-protocol populations

	IOERT n = 305			EB-APBI n = 295			
Intention-to-treat population	**Events, n**	**5-y outcomes, %**	**95% CI, %**	**Events, n**	**5-y outcomes, %**	**95% CI, %**	***P* value**
IBTR	30	10.6	7.0-14.2	9	3.6	1.2-5.9	.002
Locoregional recurrence	33	11.6	7.8-15.3	10	3.6	1.2-5.9	.001
Distant recurrence	10	2.8	.9-4.7	6	2.3	.5-4.1	NS
Regional recurrence	12	3.7		2	.7		
Overall survival	20	92.1	88.2-94.7	20	92.1	87.9-94.9	NS
Disease-specific survival	4	98.4	95.9-99.4	3	98.5	95.4-99.5	NS
Deaths	20			20			
Breast cancer related	4			3			
Other cause	10			16			
Unknown	6			1			
Per-protocol population	**IOERT n = 270**			**EB-APBI n = 207**			
IBTR	30	11.9	7.9-15.9	8	4.3	1.4-7.2	.005
Locoregional recurrence	33	12.5	8.4-16.6	9	5.2	1.8-8.5	.003
Distant recurrence	7	2.0	.2-3.8	2	1.0	.0-2.4	NS
Regional recurrence	12	4.4		2	1.0		
Overall survival	18	92.8	88.8-95.4	14	92.1	86.9-95.3	NS
Disease-specific survival	3	98.7	96.0-99.6	1	99.2	94.0-99.9	NS
Deaths	18			14			
Breast cancer related	3			1			
Other cause	10			12			
Unknown	5			1			

Abbreviations: CI = confidence interval; EB-APBI = external beam accelerated partial breast irradiation; IBTR = ipsilateral breast tumor recurrence; IOERT = intraoperative electron radiation therapy; NS = not significant.

Sensitivity analysis among the PP population showed that margin status of DCIS on definitive pathology analysis was the only significant risk factor for developing IBTR both after IOERT and EB-APBI (Appendix Table E2). IOERT applicator diameter was not significantly associated with IBTR (data not shown).

Discussion

Our aim was to evaluate published favorable treatment results in patients ≥60 years of age, for whom APBI can be a convenient alternative to WBI. We also aimed to compare the outcomes of 2 different APBI techniques, but

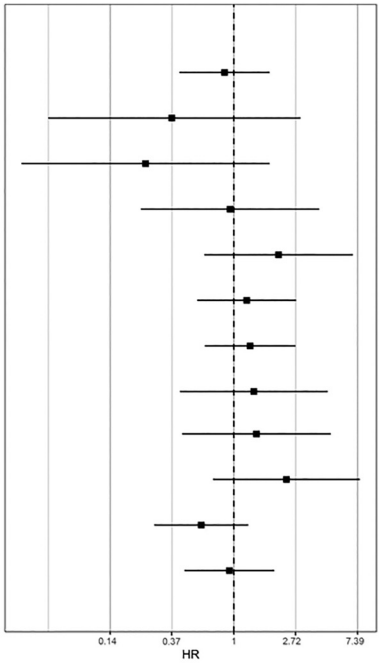
Table 3 Characteristics of ipsilateral breast tumor recurrences in per-protocol population

	IOERT n = 270)			EB-APBI n = 207		
Type of IBTR	**n**	**% of IBTR total (n = 30)**	**Absolute incidence, %**	**n**	**% of IBTR total (n = 8)**	**Absolute incidence, %**
In-field	12	40.0	4.4	0		-
New ipsilateral breast tumor	10	33.0	3.7	6	75.0	2.9
Along biopsy/ localization tract	8	27.0	2.9	0		
Unknown	0			2	25.0	1.0
IBTR total	30	100.0	11.1	8	100.0	3.8

Abbreviations: EB-APBI = external beam accelerated partial breast irradiation; IBTR = ipsilateral breast tumor recurrence; IOERT = intraoperative electron radiation therapy.

(A)

Risk factor	N ref	Events ref	N	Events	HR	95% CI	p-value
Age (>=70 vs. 60–69)	116	12	189	18	0.86	0.41–1.78	0.68
Histology (invasive +/- in situ vs. in situ)	281	29	24	1	0.38	0.05–2.81	0.35
pN (pN0 vs. >=pNmi)	243	28	36	1	0.24	0.03–1.78	0.16
ER (positive vs. negative)	260	27	20	2	0.94	0.22–3.97	0.94
Her2Neu (negative vs. positive)	260	25	17	3	2.06	0.62–6.84	0.24
Subtype (luminal A vs luminal B/HER2pos/tr)	200	19	75	9	1.23	0.56–2.73	0.60
Grade (1–2 vs. 3)	219	20	84	10	1.30	0.60–2.70	0.56
Tumor size (<=20 mm vs >20mm)	280	27	24	3	1.38	0.42–4.55	0.60
Margin invasive component (>=2mm vs. <2mm or irradical)	253	25	21	3	1.44	0.44–4.78	0.55
Margin DCIS component (>=2mm vs. <2mm or irradical)	71	6	27	5	2.34	0.71–7.66	0.16
Systemic therapy (none vs. any)	169	20	135	10	0.59	0.27–1.26	0.17
ASTRO (suitable vs. cautionary or unsuitable)	169	17	136	13	0.93	0.45–1.92	0.85
Excluded from PP population (yes vs. no)	270	30	35	0			



(B)

Risk factor	N ref	Events ref	N	Events	HR	95% CI	p-value
Age (>=70 vs. 60–69)	173	5	122	4	0.83	0.22–3.10	0.79
Histology (invasive +/- in situ vs. in situ)	260	6	53	3	3.61	0.90–14.45	0.07
pN (pN0 vs. >=pNmi)	216	37	37	0			
ER (positive vs. negative)	241	6	17	0			
Her2Neu (negative vs. positive)	235	6	14	0			
Subtype (luminal A vs luminal B/HER2pos/tr)	196	6	49	0			
Grade (1–2 vs. 3)	226	7	65	2	1.00	0.20–4.70	0.98
Tumor size (<=20 mm vs >20mm)	265	8	26	1	1.30	0.16–10.40	0.80
Margin invasive component (>=2mm vs. <2mm or irradical)	192	4	66	2	1.65	0.30–9.03	0.56
Margin DCIS component (>=2mm vs. <2mm or irradical)	90	3	52	4	2.66	0.59–11.93	0.20
Systemic therapy (none vs. any)	158	8	135	1	0.14	0.02–1.14	0.07
ASTRO (suitable vs. cautionary or unsuitable)	116	5	179	4	0.55	0.15–2.04	0.37
Excluded from PP population (no vs. yes)	203	8	92	1	0.35	0.04–2.81	0.32

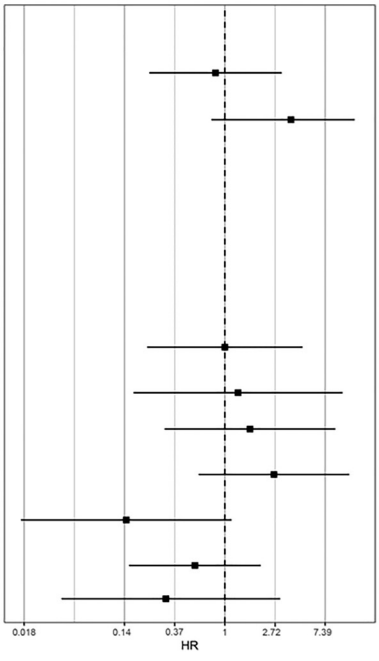


Fig. 3. (A) Forest plot of risk factors for ipsilateral breast tumor recurrence (IBTR) for patients treated with intraoperative electron radiation therapy. Results of univariate Cox regression models in intention-to-treat population. (B) Forest plot of risk factors for IBTR for patients treated with external beam accelerated partial breast irradiation. Results of univariate Cox regression models in intention-to-treat population. A hazard rate (HR) of >1 indicates an increased risk of IBTR compared with the reference category. The reference category is the first group presented in the column labeled "Risk factor." "Irradical" indicates a positive surgical margin (ink on tumor or Ductal Carcinoma In Situ [DCIS]) on definitive pathology analysis. *Abbreviations*: ASTRO = American Society for Radiation Oncology; CI = confidence interval; ER = estrogen receptor; HER2neu = human epidermal growth factor receptor 2; PP = per-protocol.

conducting a randomized trial was not feasible because these treatments were already clinically implemented. We therefore conducted a 2-armed prospective cohort study, and we found a significantly higher IBTR rate of 10.6% at 5 years after electron intraoperative radiation therapy compared with 3.6% after external beam APBI. Furthermore, regional recurrence was more frequent in patients undergoing IOERT compared with EB-APBI. Overall survival at 5 years after treatment did not differ between groups.

Several international randomized studies have compared (A)PBI to whole breast irradiation. Appendix Table E3 describes the inclusion criteria and outcomes of these trials. All, with 1 exception, showed noninferiority of (A)PBI to WBI regarding IBTR rate.[9-16,27-30] Across studies, different APBI techniques were applied: external-beam radiation therapy, brachytherapy, or intraoperative electron or kV radiation therapy. These techniques all differ significantly regarding dosimetrical and physical properties, leading to marked differences in dose distribution and irradiated volume in the treated breast and overlying skin. This hampers comparison of clinical outcomes between these studies as these properties might influence IBTR rate. For external-beam PBI, the randomized IMPORT-LOW (partial-breast radiotherapy after breast conservation surgery for patients with eartly breast cancer) trial demonstrated noninferiority of EB-PBI compared with WBI with a 5-year IBTR rate of 0.5% after PBI and 1.1% after WBI in patients with node-negative, grade 1 to 2 breast cancer.[11] Other randomized trials comparing EB-APBI with WBI also showed low recurrence rates after EB-APBI.[9,13] When APBI is given intraoperatively with electrons, dose-distribution is more concise and less homogeneous compared with EB-APBI. This technique was applied in the randomized ELIOT (intraoperative irradiation for early breast cancer) trial. In that trial, 5-year IBTR rates were higher but still noninferior after APBI compared with WBI: 4.4% after IOERT and 1.1% after WBI at 5 years.[12] Differences between techniques can partly explain the difference in local recurrence rates. Besides technique, patient selection plays an important role. In studies including more patients with high-risk characteristics, IBTR rates are higher. Over time the selection criteria for APBI became more restricted, and recurrence rates have decreased accordingly.[12,28] Thus, radiotherapeutic techniques as well as patient selection determine clinical outcome after APBI, and APBI shows favorable IBTR rates in adequately selected patients.

The results of trials investigating APBI thus far hint toward differences in clinical outcome depending on APBI techniques. However, no randomized study has compared outcome between techniques. The randomized NSABP-B39 trial compared 2 APBI techniques (external beam radiation therapy 38.5 Gy, n = 1536 or brachytherapy 34 Gy, n = 571, in 10 fractions over 5 days) to WBI (n = 2109) in patients with early-stage breast cancer (tumor size ≤3 cm, all histologies and multifocal breast cancers, ≤3 positive axillary nodes). The 10-year IBTR rate was 4.6% in the APBI group and 3.9% in the WBI group, which did not meet equivalence criteria for APBI even though the absolute difference in IBTR was low (0.7%).[28] Although this trial did allow different APBI techniques, the study was not powered for subgroup analysis by APBI technique.

In the aforementioned ELIOT trial, 1305 patients aged ≥48 years with tumors of ≤25 mm and cN0 status were randomized to IOERT or WBI. At 5 years, IBTR rate was significantly higher in the IOERT group, but still noninferior to WBI.[12] Recently published 10-year results show that IBTR rate in the IOERT increased to 8.4%, whereas it remained low in the WBI group at 1.1%.[29] Still these percentages are lower than our 5-year IBTR rate. Technique and patient characteristics of our study are similar, if not slightly more favorable in our study due to inclusion of older patients, compared with the ELIOT study. The higher incidence of recurrences in our study may partly be explained by the relatively low proportion of patients having received adjuvant hormone therapy. This was 40% of patients in our study compared with 96% of patients in the ELIOT study.[12] Hormone therapy (HT) reduces the chance of an IBTR even in patients at low risk of recurrence.[31,32] In randomized APBI studies, use of HT varies from 65% to 96%, and in other, nonrandomized IOERT studies showing low IBTR risks, 82% to 98% of patients use HT.[11,13,16,27,29,33,34] Hence, the percentage of patients who had HT in our study is particularly low compared with the literature, which may partly explain the relatively high recurrence rates.

Some differences in IBTR rates after APBI compared with WBI can be expected owing to substantial reduction of the radiation therapy target volume. We found 33% of IBTRs were new ipsilateral breast tumors in the IOERT group, consistent with findings in IOERT literature.[12,35] All evaluable IBTRs in the EB-APBI group were classified as new ipsilateral breast tumors. Relatively, the percentages of new ipsilateral breast tumors in both IOERT and EB-APBI groups are similar (3.7% and 2.9%, respectively). Thus, APBI is not able to eradicate subclinical disease elsewhere in the mammary gland.

There were no in-field recurrences in the EB-APBI group, whereas 40% of IBTRs in the IOERT group were in-field. Even though we did not find that small applicator diameter increased risk of IBTR, perhaps resection margins and IOERT applicator diameter were insufficient to irradicate residual microscopic disease in the proximity of the tumor bed. Regarding surgery, the importance of obtaining adequate surgical margins is even more important when radiation therapy dose distribution is more concise, as is the case in IOERT. This is especially true for DCIS or invasive tumors with DCIS component with often multifocal growth. A comprehensive pathology analysis was performed in which the original lumpectomy pathology specimens were reexamined, focusing extensively on microscopic margins. It appeared that the reported surgical margins of tumors (especially those with a DCIS component outside of the tumor) were narrower and sometimes even focally positive at the comprehensive analysis compared with the initially reported surgical margin of the same pathology specimens

(data not shown). IOERT is discouraged in patients with pure DCIS due to high recurrence rates of 19% at 5 years.[36] At our centers, we discourage use of IOERT when mammography and/or biopsy shows accompanying DCIS.

A notable phenomenon in the IOERT group was the finding of recurrences in the biopsy or needle localization tract in more than one-fourth of patients with recurrence, whereas this was not seen in patients in the EB-APBI group. A possible explanation for this type of recurrence is the difference in target volume between APBI techniques: in IOERT, irradiated volume is more concise compared with pre- or postoperative EB-APBI where there is considerable spread-out dose owing to tangential fields, and with IOERT no skin is irradiated.[37] To the best of our knowledge, although seeding of tumor cells and subsequent recurrences in the biopsy tract have been identified in patients undergoing skin-sparing mastectomy or breast-conserving surgery, there is no mention of this phenomenon in IOERT literature.[38] In the preoperative accelerated partial breast irradiation (PAPBI) trial, which investigates preoperative EB-APBI, 2 of 4 recurrences occurred in the biopsy tract.[39] The reason for the higher regional recurrence rate in the IOERT cohort compared with the EB-APBI cohort may be found along the same lines. Several studies have found WBI to be protective of developing regional metastases compared with IOERT due to tangential field irradiation, and in randomized studies comparing EB-APBI to WBI no differences in regional recurrences were found.[40]

Another key aspect in achieving low recurrence rates after ABPI is adequate patient selection. Despite the consensus recommendations from the American Society for Radiation Oncology and the European Society for Radiotherapy and Oncology on eligibility for APBI, selection remains challenging.[35,41-43] Especially for IOERT, selection is impeded because not all required information is available before treatment and the decision to apply IOERT is made during surgery. In this study, 11% (33 of 303) of patients deemed eligible for IOERT preoperatively did not receive IOERT based on perioperative information. Although in the EB-APBI group 31% of patients did not receive the allocated treatment based on definitive postoperative pathology results. This selection procedure may have contributed to the lower IBTR rate in the EB-APBI group. In the literature, several factors have been identified to be associated with a significant risk of IBTR, such as tumor size of >2 cm, grade 3 tumors, Ki-67 of >20%, and luminal B or triple negative subtypes, as well as pure DCIS.[29,36] In the present study, we could not determine patient, tumor or pathologic factors that significantly identified patients at high risk of IBTR in either group. The American Society for Radiation Oncology classification does not distinguish patients at high risk of recurrence from those at low risk of recurrence in this study.

Optimal treatment for older patients is still a matter of debate. Omission of radiation therapy altogether seems feasible for a subgroup of patients and is currently evaluated in the TOP-1 study (Tailored treatment in Older Patients-1: Omission of radiation therapy in elderly patients with low-risk breast cancer). However, it should be taken into account that in studies investigating omission of radiation therapy, patients received HT, which negatively affects quality of life.[44] Current studies comparing only HT with only APBI will potentially facilitate further evidence for optimal treatment in older patients.[45]

In summary, factors contributing to the higher-than-expected IBTR rate in the IOERT cohort are possibly pre- and perioperative patient selection as opposed to selection based on definitive pathology outcomes postoperatively (leading to an inevitable selection difference between cohorts); recurrences in the biopsy tract (this is inherent to the IOERT technique but can be prevented by altered biopsy technique and surgical approach); narrow surgical margins; and a more concise radiation therapy target volume (compared with EB-APBI) and the relatively low proportion of patients receiving adjuvant HT, per Dutch national guidelines. Several of these aspects could be altered to achieve better outcomes. Currently at our institute, outside of this study, IOERT is offered to patients >50 years of age with low-grade, unifocal invasive (nonlobular) tumors of ≤2 cm that are ER/PR−positive, HER2-negative, Ki-67 <15% without a DCIS component, and cN0. Biopsy is now done with coaxial needles to prevent recurrences along the biopsy tract, and the overlying skin involving the biopsy tract is surgically removed. Furthermore, a surgical tumor-free margin of at least 2 mm is recommended and the applicator diameter has been increased to at least 5 cm to better ensure adequate coverage of the target volume and margins. Patients are now counseled about the higher risk of IBTR compared with WBI or EB-APBI. With these adaptions in selection, biopsy, and treatment, we expect lower recurrence rates. In our experience, some patients still choose IOERT despite a higher chance of IBTR because of the convenience of a single-day treatment and the availability of salvage options in the case of a recurrence, especially older frail patients.[46] Regarding EB-APBI, current regimens have evolved and 5 × 5.2 Gy PBI is now the standard in most centers in the Netherlands based on the recently published favorable 5-year results of the FAST FORWARD (hypofractionated breast radiotherapy for 1 week versus 3 weeks) for whole breast irradiation and IMPORT-LOW for partial breast irradiation.[11,47]

A limitation of this study is the lack of a control group treated with the standard of care, whole breast irradiation, during the same period. Because IOERT was not available at all centers, this study was designed as a nonrandomized cohort study, which intrinsically has selection bias, confounding by indication, and residual confounding. We aimed to minimize the effect of these biases by using identical inclusion criteria for both treatment arms. However, definitive pathology was available before EB-APBI treatment but not before IOERT, leading to more patients in the EB-APBI group not receiving the assigned treatment compared with the IOERT group.

Strengths of this study are the prospective nature of the study and the comparison of 2 different APBI techniques. Furthermore, we present complete oncological data at a median of 5-years follow-up in addition to previously published toxic effect and quality of life data, providing an overview of all aspects these APBI treatments.[20,21] The most important asset of this study is the fact that it is a prospective cohort study assessing efficacy of 2 APBI techniques in daily practice, that have already been tested in the setting of randomized controlled trials. As such, our study represents the final phase of clinical testing before wide-spread implementation should take place. Our results emphasize the importance of evaluating new techniques in a real-world setting and add to data that affirm this experience.[35,48]

Conclusions

We found unexpectedly high ipsilateral breast tumor recurrences and locoregional recurrence rates in patients treated with electron IORT, and acceptable IBTR rates in patients treated with EB-APBI. More than one-fourth of recurrences in the IOERT cohort were located in the biopsy or localization tract and 40% were in-field recurrences. Patient selection in IOERT is partly impeded by lack of definitive pathology analysis at the time of treatment. In clinical practice, IOERT should be reserved for patients at very low risk of recurrence preferring single-day treatment who have been counseled appropriately. Finally, we emphasize the importance of phase 4 studies when implementing treatments with encouraging outcomes in randomized trials in a real-world setting.

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