



Original article

Health-related quality of life of breast cancer patients after accelerated partial breast irradiation using intraoperative or external beam radiotherapy technique



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ABSTRACT

Purpose: To compare health-related quality of life (HRQL) in elderly breast cancer patients between two types of Accelerated Partial Breast Irradiation: intraoperative radiotherapy (IORT) and external beam APBI (EB-APBI).

Methods: Between 2011 and 2016 women ≥ 60 years undergoing breast conserving therapy for early stage breast cancer were included in a prospective multi-centre cohort study. Patients were treated with electron IORT (1×23.3 Gy) or photon EB-APBI (10×3.85 Gy daily). HRQL was measured by the EORTC-QLQ C30 and BR23 questionnaires before surgery and at several time points until 1 year.

Results: HRQL data was available of 204 IORT and 158 EB-APBI patients. In longitudinal analyses emotional functioning and future perspective were significantly, but not clinically relevantly, worse in IORT-treated patients, and improved significantly during follow-up in both groups. All other aspects of HRQL slightly worsened after treatment and recovered within 3 months with an improvement until 1 year. Cross-sectional analysis showed that postoperatively fatigue and role functioning were significantly worse in IORT patients compared to EB-APBI patients who were not yet irradiated, but the difference was not clinically relevant. At other timepoints there were no significant differences. Multivariable analysis at 1 year identified comorbidity and systemic therapy as risk factors for a worse global health score (GHS). **Conclusions:** EB-APBI and IORT were well tolerated. Despite a temporary deterioration after treatment, all HRQL scales recovered within 3 months resulting in no clinically relevant differences until 1 year between groups nor compared to baseline levels.

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Introduction

Addition of whole breast irradiation (WBI) to lumpectomy in breast conserving therapy (BCT) results in a significant benefit in local control [1]. Accelerated partial breast irradiation (APBI) limits

radiotherapy solely to the tumour bed and shortens treatment time by further hypofractionation. APBI can be delivered using various techniques, such as brachytherapy, external beam APBI (EB-APBI), and intraoperative radiotherapy (IORT) with electrons or low-kilovoltage X-rays [2]. Depending on the APBI technique, treatment time varies from 1 day to 2 weeks.

“Low risk” patients are generally deemed suitable candidates for APBI but this definition varies slightly per guideline used and has been adapted over time [3–5].

In low-risk patients, local recurrence rates range from 0 to 4.4%

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at 5 years after APBI. Several randomised trials demonstrated that APBI is not inferior to WBI [6–13]. Nonetheless, recurrence rates in most studies were higher than after WBI, especially after intra-operative APBI. Results of these trials are difficult to interpret as they have been heterogenous regarding technique, control group and patient inclusion.

As the risk of local recurrence after APBI is low, other outcomes such as quality of life gained importance in this patient group with an excellent survival. Some RCT's on APBI measured Health-Related QoL (HRQL) and showed comparable or even better HRQL after APBI compared to WBI. As APBI can differ substantially in technique, dose and duration of treatment, knowledge on eventual differences in outcomes is important for deciding which APBI technique is most appropriate.

The APBI-study is the first study that compares outcomes of two APBI techniques (intraoperative radiotherapy (IORT) and external-beam APBI (EB-APBI)) in elderly early stage breast cancer patients [14]. The aim of this analysis is to compare health-related quality of life during the first year after treatment between IORT and EB-APBI.

Materials and methods

Patients

This is a prospective cohort study conducted in 2011 in two hospitals in the Netherlands. Detailed information on design, patient selection and treatment has been reported earlier [14]. Patients were included after providing informed consent, and treated with IORT in the Haaglanden Medical Centre and EB-APBI in the Haga Hospital. In 2015, patients were also accrued for the EB-APBI cohort at a third centre, the Isala Hospital. The last patient was included at the end of 2016.

Female patients aged 60 years and older who were classified as low or intermediate risk according to the GEC-ESTRO recommendations, were eligible for this study [4]. Neo-adjuvant chemotherapy was an exclusion criterion. This study was approved by the medical ethical committee (10-042 METC ZuidwestHolland; NTR2931).

Treatment

Breast-conserving surgery was performed according to at least level 1 oncoplastic surgery principles [15]. IORT was administered directly after lumpectomy after placement of a protection disc under the lumpectomy cavity [16]. High-energy electron (6–12 MeV) beam radiotherapy was administered, delivering a total dose of 23.3 Gy (prescribed at the 100% isodose, according to ICRU 71) to the lumpectomy cavity.

EB-APBI was delivered with photons (4–10 MV) within 6 weeks after surgery, to a total of 38.5 Gy in 10 daily fractions, 5 days a week using either Intensity Modulated Radiotherapy or 3D-Conformal Radiotherapy. Patients received adjuvant treatment consisting of hormonal or chemotherapy according to the current Dutch breast cancer guidelines [17].

Data collection and outcomes

Comorbidities were scored using ACE-27 questionnaires at baseline [18].

HRQL was assessed using the European Organization for Research and Treatment of Cancer (EORTC) QLQ-C30 (version 3) and breast cancer module (BR23) were used [19,20]. Scale scores were calculated according to the EORTC manual, if $\geq 50\%$ of the required questions were available [21]. The summary score of the QLQ C30 was calculated from the mean of 13/15 scales [22]. As very

little data was missing (2.5%), no imputation was performed.

For interpretation of the EORTC scale scores, the cut off points for clinical relevance of Cocks (C30) and Osoba (BR23) were used, and medium or moderate differences or changes are considered clinically relevant [23–25].

Quality of life questionnaires were sent to patients at baseline (before surgery), postoperatively, after EB-APBI treatment (only EB-APBI patients), and at 3, 6, and 12 months after last radiotherapy treatment. As the last fraction of EB-APBI was given approximately 7 weeks after surgery, the time points differ between groups. Questionnaires were included for analysis if received within 4 weeks after surgery (postoperative time point), within 4 weeks after the last fraction of radiotherapy (EB-APBI), or within half of the interval of the specified time point, i.e. at 3 months the questionnaire had to be received within 1.5–4.5 months after treatment.

Patients were included for this analysis if at least the baseline (before surgery) and one of the follow-up HRQL questionnaires were available, as well as information on comorbidity. In the case of a locoregional or distant recurrence or contralateral breast cancer, questionnaires filled in ≤ 3 months prior to the event were censored.

Statistical analysis and endpoints

The primary endpoint of this HRQL analysis was difference in Global Health Score between groups at 1 year after treatment, corrected for confounding by multivariable analysis. Secondary endpoints were differences in HRQL between treatment groups over time, and between treatment groups at the time points postoperative, at 3 months and 1 year after treatment.

Patient and tumour characteristics were described and compared using either the Mann-Whitney U test, independent samples T-test or chi-square test, depending on the type and distribution of the variable.

To evaluate the EORTC scales of HRQL between groups and over time, we used a linear mixed model (LMM). Patients were included as random effects and time, treatment and their interaction between time and treatment as fixed effects. The included time points were baseline, 3, 6 and 12 months after treatment. The postoperative time point was not included in the LMM, because only the IORT group had undergone their radiotherapy treatment at that time, whereas the EB-APBI group had only underwent part of their treatment. Hence, inclusion of this time point would result in an unbalanced comparison between the groups.

To evaluate the individual questions of the Breast Symptom scale between groups and over time, outcomes were dichotomised and analysed using generalized estimated equations (GEE) including the same fixed and random effects and time points as in the LMM.

In addition, HRQL was cross-sectionally analysed postoperatively, at 3 months and 1 year by univariable linear regression. In case of a significant difference, correction for confounding was performed by multivariable linear regression. Pre-defined possible confounders were: adjuvant systemic therapy, comorbidity (according to the ACE-27 grading system), axillary treatment (defined as axillary dissection or locoregional radiotherapy), pT stage and age.

Data was analysed using SPSS 23[®] for statistical analysis. A p-value of ≤ 0.01 was deemed significant for all analyses due to repeated measures and multiple testing, except for our primary outcome for which the level of significance was $p \leq 0.05$.

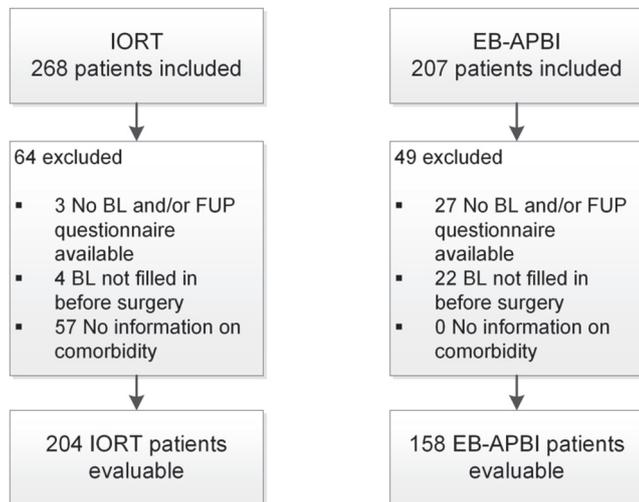


Fig. 1. Inclusion diagram for current analysis. The inclusion flow chart for this study has been reported previously [14]. IORT = intraoperative electron radiotherapy; EB-APBI = external beam APBI; BL = baseline; FUP = follow-up.

Results

Patients

A total of 475 patients were included in the APBI study (268 IORT, 207 EB-APBI) [14]. Of these, 362 patients (76%) were eligible

for this HRQL analysis (204 (76% of total) IORT, 158 (76% of total) EB-APBI) (Fig. 1). There were no significant differences in patient, treatment or tumour characteristics between the patients excluded and those included in this analysis (data not shown). Compliance of the 362 included patients was excellent, with response rates of 100%, 95%, 96%, 95%, 95%, and 94% at baseline, postoperative, after treatment (after IORT or after EBAPBI), 3 months, 6 months and 1 year after treatment, respectively. In general, <2.5% of the single items of the returned questionnaires were missing within scale scores at the different time points, with the exception of questions on sexual functioning where 17% to 24% of the items was missing.

Patient characteristics are shown in Table 1. With exception of pT and pN stage, patient and tumour characteristics were well balanced. Most patients had pT1 tumours, and 60% did not receive any systemic therapy.

HRQL

At one year GHS was not significantly different between groups (79.5 IORT vs 81.0 EB-APBI, $p = 0.45$) (Table 2, Table 3). In multi-variable analysis comorbidity (Grade 2 vs none $p = 0.031$; Grade 3 vs none $p < 0.0001$) and systemic therapy (combination of HT and CT vs none, $p 0.001$) were independent risk factors for a worse GHS at one year.

When comparing groups at several separate time points, cross-sectional analysis at baseline showed no significant differences (Table 2). Postoperative role functioning and fatigue were significantly worse in IORT-treated patients (Table 2). Financial difficulties were worse in EB-APBI-treated patients. However, none of these

Table 1
Patient characteristics.

		IORT, n = 204		EB-APBI, n = 158		p-value
		N; Median	%; Range	N; Median	%; range	
Age	Years	68	59–92	68	59–86	0.92
pT stage ^a	pTis	12	5.9	18	11.4	0.027
	pT1a	10	4.9	13	8.2	
	pT1b	63	30.9	35	22.2	
	pT1c	96	47.1	66	41.8	
	pT2	20	9.8	26	16.5	
	pT0*	3	1.5	0	0	
pN stage	pN0	179	87.7	138	87.3	0.033
	pN1a/mi	16	7.9	5	3.2	
	pNx	3	1.5	12	7.6	
	NA/unknown	6	2.9	3	1.9	
BR stage	Grade 1	57	27.9	50	31.6	0.56
	Grade 2	91	44.6	73	46.2	
	Grade 3	50	24.5	32	20.3	
	NA/unknown	6	2.9	3	1.9	
Estrogen receptor	Positive	179	87.7	130	82.3	0.72
	Not done	12	5.9	17	10.8	
Progesteron receptor	Positive	140	68.6	108	68.4	0.50
	unknown	13	6.4	17	10.8	
Her2neu	Positive	12	5.9	10	6.3	0.70
	NA/unknown	14	6.9	23	14.6	
Systemic therapy	No	121	59.3	95	60.1	0.89
	HT	68	33.3	50	31.6	
	CT	3	1.5	4	2.5	
	Combination ^b	11	5.4	9	5.7	
	Unknown	1	0.5			
Comorbidity (ACE 27)	Grade 0	62	30.4	60	38.0	0.40
	Grade 1	108	52.9	74	46.8	
	Grade 2	27	13.2	21	13.3	
	Grade 3	7	3.4	3	1.9	
Axillary treatment ^c	Yes	6	2.9	2	1.3	0.28

IORT = intraoperative electron radiotherapy; EB-APBI = external beam APBI; HT = hormonal therapy, CT = chemotherapy; NA = not applicable.

^a 3 patients in IORT group had pT0, biopsy positive tumours.

^b Combination of CT, HT, and/or trastuzumab.

^c Axillary treatment consists of axillary dissection and/or additional axillary RT. Significant p-values are marked bold.

Table 2

Cross-sectional comparison of IORT and EB-APBI of selected EORTC scales at different time points.

	Baseline	Postoperative	3 months	1 year
	p-value	p-value	p-value	p-value
<i>EORTC QLQ C30</i>				
<i>Functional scales</i>				
Global health status	0.28	0.08	0.25	0.45
Summary score	0.40	0.02	0.19	0.91
Physical functioning	0.99	0.02	0.66	0.60
Role functioning	0.99	0.001^a	0.56	0.18
Emotional functioning	0.02	0.69	0.68	0.06
<i>Symptom scales</i>				
Fatigue	0.44	0.004^a	0.70	0.85
Pain	0.96	0.40	0.07	0.75
Financial difficulties	0.24	0.009^b	0.64	0.66
<i>EORTC BR23</i>				
<i>Functional scales</i>				
Future perspective	0.08	0.18	0.88	0.02
Body image	0.18	0.69	0.59	0.11
<i>Symptom scales</i>				
Breast symptoms	0.79	0.12	0.27	0.82
Arm symptoms	0.74	0.93	0.11	0.95
Systemic therapy side effects	0.70	0.18	0.17	0.74

Due to multiple testing a p value < 0.01 is deemed to be significant. Significant p-values are marked bold.

^a Indicates a significant difference in favour of EB-APBI.

^b Indicates a significant difference in favour of IORT.

differences were clinically relevant (differences of 10.4, 8.5 and 4 points respectively) [25]. Cross-sectional analysis showed that there were no significant nor clinically relevant differences between groups anymore at 3 months and 1 year after treatment. Furthermore, HRQL at 1 year was not clinically relevantly different

compared to baseline.

The courses of the various aspects of HRQL over time are shown in Table 3 and Figs. 2 and 3. There were no significant differences between groups over time, meaning that the pattern of variation in functioning or symptoms was comparable during the first year in both groups. Several aspects of HRQL differed significantly over time only. For example, breast symptoms, fatigue, and pain increased after surgery and radiotherapy, but decreased from 3 months onwards. Breast swelling and breast oversensitivity differed significantly over time, showing the same pattern as breast symptoms. They did not differ significantly between groups or between groups over time (Fig. 3).

Emotional functioning and future perspective of the patients differed significantly over time ($p < 0.0001$) and between groups ($p = 0.005$ and 0.008 respectively). Regarding both emotional functioning and future perspective of the patients, baseline levels were lower for IORT patients, and this difference persisted until one year after treatment. However, the differences between groups were small and not clinically relevant, and functioning improved significantly over time in both groups.

Discussion

This study is the first to compare the HRQL outcomes after two types of accelerated partial breast irradiation; namely electron IORT and photon EB-APBI and shows that there are no clinically relevant differences in HRQL between patients treated with IORT or EB-APBI, during the first year after treatment.

Comparison of ABPI to WBI

Several previous studies have reported HRQL outcomes in

Table 3

Results of longitudinal analysis of selected EORTC scales per time point and their mean values.

<i>C30; Functional scales</i>		Baseline	3 months	6 months	1 year	P value over time	P value treatment	P value treatment*time
Global health status	IORT	80.0	80.8	78.4	79.5	0.75	0.30	0.28
	EB-APBI	82.1	78.6	81.2	81.0			
Summary score	IORT	89.0	87.5	87.7	88.2	0.006*	0.56	0.45
	EB-APBI	90.0	85.8	86.8	88.3			
Physical functioning	IORT	87.4	84.5	84.4	85.3	0.06	0.81	0.91
	EB-APBI	87.4	83.6	85.1	86.3			
Role functioning	IORT	90.6	85.3	85.2	84.5	0.001*	0.68	0.57
	EB-APBI	90.6	84.0	85.0	88.0			
Emotional functioning	IORT	72.8	84.0	84.7	84.0	<0.0001*	0.005*	0.49
	EB-APBI	78.0	84.9	86.6	88.0			
<i>Symptom scales</i>								
Fatigue	IORT	15.9	24.0	22.1	20.9	<0.0001*	0.78	0.89
	EB-APBI	14.3	25.0	21.8	20.4			
Pain	IORT	9.8	14.8	13.4	12.4	<0.0001*	0.03	0.37
	EB-APBI	9.9	18.7	17.6	13.1			
Financial difficulties	IORT	1.5	3.8	3.3	3.5	0.03	0.23	0.99
	EB-APBI	2.6	4.6	4.1	4.1			
<i>BR23; Functional scales</i>								
Future perspective	IORT	61.0	73.1	72.3	71.0	<0.0001*	0.008*	0.26
	EB-APBI	66.0	72.7	75.3	78.1			
Body image	IORT	94.2	93.5	93.1	93.6	0.42	0.03	0.89
	EB-APBI	95.8	94.2	94.3	95.8			
<i>Symptom scales</i>								
Breast symptoms	IORT	6.6	13.8	9.7	9.5	<0.0001*	0.08	0.27
	EB-APBI	6.9	15.6	12.8	9.2			
Arm symptoms	IORT	7.6	7.9	7.9	8.7	0.34	0.17	0.32
	EB-APBI	7.2	10.8	10.1	8.6			
Systemic therapy side effects	IORT	8.0	14.0	13.9	13.1	<0.0001*	0.10	0.35
	EB-APBI	7.6	16.5	16.4	13.6			

P values of linear mixed models are shown of selected scales. For functional scales, a higher mean score represents a better functioning. For symptom scales, a higher mean score represents a worse treatment burden.

* marks significant differences. Significant differences between groups are marked bold.

Abbreviations: IORT = Intraoperative electron radiotherapy, EB-APBI = External beam APBI.

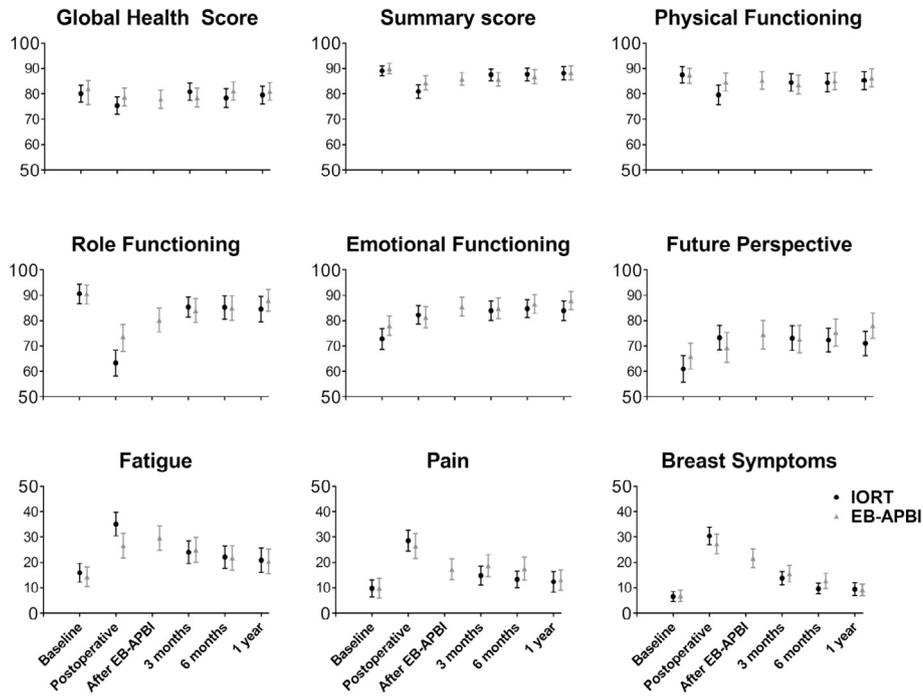


Fig. 2. Results of selected EORTC scale scores per treatment group over time. Mean per timepoint is shown with bars representing 99% confidence intervals. Scale scores range from 0 to 100 points. For functional scales, a higher mean score represents a better functioning. For symptom scales, a higher mean score represents a worse treatment burden. Abbreviations: IORT = intraoperative electron radiotherapy; EB-APBI = external beam APBI.

patients treated with APBI and compared these to outcomes after WBI. Table 4 provides an overview of these studies [12,26–35]. Although insightful, the comparison of these results need to be interpreted with caution as there is a heterogeneity in population, APBI and WBI techniques used, outcome measures, and

statistical approach between these studies. In general, there are few significant differences between APBI and WBI and those that are found are generally in favour of APBI. It remains to be determined whether the APBI technique used has a clinically relevant impact on HRQL.

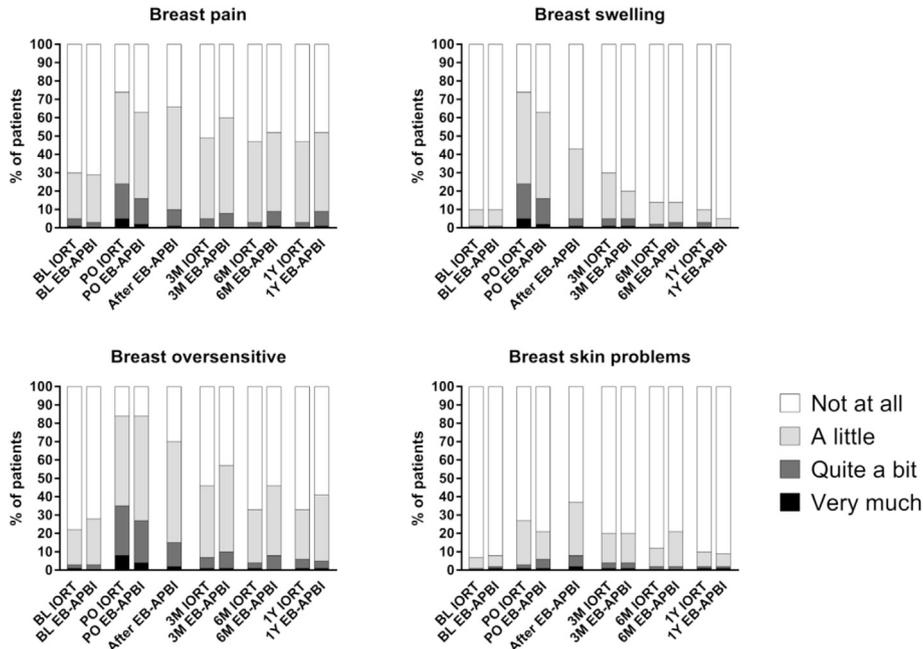


Fig. 3. Breast symptoms after IORT and EB-APBI (EORTC BR23 questionnaire). % of patients per time point reporting “not at all, a little, quite a bit or very much” symptoms are shown. For the GEE model outcomes were dichotomised, grouping “not at all” and “a little” together versus “quite a bit” and “very much”. p-values from GEE using time points BL, 3 M, 6 M and 1Y are: **Breast pain:** p over time 0.17; p between treatments 0.42; p treatment x time 0.13. **Breast swelling:** p over time 0.006; p between treatments 0.29; p treatment x time 0.73. **Breast oversensitivity:** p over time 0.007; p between treatments 0.59; p treatment x time 0.24. **Breast skin problems:** p over time 0.13; p between treatments 0.52; p treatment x time 0.89. Abbreviations: IORT = intraoperative electron radiotherapy; EB-APBI = external beam APBI; BL = baseline; PO = postoperative; 3 M = 3 months; 6 M = 6 months; 1Y = 1 year.

Table 4

Overview of studies comparing HRQL between (accelerated) partial and whole breast irradiation.

	Timepoint	GHS	PF	RF	FA	PA	FI	BS	AS	Other
Meattini 2017 [26]	Start of RT	=	=	=	=	=	=	=	=	
<i>Florence, RCT</i>	End of RT	↑	↑	↑	↑	↑	=	↑	↑	
<i>EB-APBI vs</i>	2Y	↑	↑	↑	↑	↑	↑	↑	↑	
<i>WBI + Boost</i>	Start RT vs 2Y	↑	↑	↑	↑	↑	↑	↑	=	
Schafer 2018 [27]	Before start of RT	=	=	=	=	=	=	=	↑	SUM: =
<i>GEC-ESTRO, RCT</i>	After end of RT	=	=	=	↑	=	↑	↑	↑	SUM: =
<i>BT vs WBI + Boost</i>	3 M	↑	=	↑	=	=	↑	↑	↑	SUM: =
	5Y	=	=	=	=	=	=	↑	↑	SUM: =
	Longitudinal	=	-	-	-	-	-	=	=	SUM: =
Coles 2017 [12]	5Y cumulative	-	-	-	-	-	-	=	=	BA/BH* ↑
<i>IMPORT-LOW, RCT</i>	5Y cross-sectional	-	-	-	-	-	-	=	=	BA/BH* ↑
<i>PBI vs low dose WBI + PB-boost vs WBI</i>										
Bhattacharya 2019 [35]	6 M, 1Y, 2Y, 5Y	-	-	-	-	-	-	-	-	Number of AE ↑
<i>IMPORT-LOW, RCT</i>										
<i>PBI vs low dose WBI + PB-boost vs WBI</i>										
Corica 2016 [28]	BL	↑	-	-	-	-	-	=	-	BIABC Arm =
<i>TARGIT, kV-IORT vs WBI</i>	3 M	↑	-	-	-	-	-	=	-	BIABC Arm =
	6 M	↑	-	-	-	-	-	↑	-	BIABC Arm =
	1Y	↑	-	-	-	-	-	↑	-	BIABC Arm ↑
	2Y – 5Y	-	-	-	-	-	-	↑	-	BIABC Arm -BIABC Arm ↑
	Longitudinal	-	-	-	-	-	-	↑	-	
Welzel 2010 [30]	47 M	=	=	=	=	↑	=	↑	=	
<i>TARGIT, kV-IORT vs kV-IORT + WBI</i>										
Welzel 2013* [29]	25 M	=	=	↑	=	↑	=	↑	↑	
Wadasadawala 2009 [33]	36 M	=	=	=	=	=	=	=	=	BRBI: ↑
<i>BT vs WBI + Boost</i>										
Albuquerque 2012 [31]	Longitudinal (Before RT, after RT, 6 weeks after RT)	-	-	-	-	-	-	-	-	FACT-F ↑
<i>BT vs WBI</i>										FACT-G ↑
He 2012 [32]	29/34 M	-	-	-	-	-	-	-	-	FACT-G ↓&
<i>EB-APBI vs WBI + Boost</i>										FACT-B =
Bitter 2016 [34]	1Y	-	-	-	-	-	-	-	-	FACIT:
<i>BT vs WBI + Boost</i>										Energy level ↑
										Lymphedema ↑

↑ = significant difference in favour of (A)PBI, ↓ significant difference in favour of WBI, = no difference between (A)PBI and WBI, - not applicable. *Protocol specific questions of IMPORT LOW trials added to EORTC questionnaire; †The questions included in the scale score BRBS and BRAS were analysed separately, showing no significant differences between groups.

% This study also compared groups treated outside of TARGIT-A study, these results are not shown in this table.

& Only the emotional scale. **Abbreviations:** RCT = Randomised controlled trial; RT = Radiotherapy; WBI = Whole Breast Irradiation; (A)PBI = (accelerated) partial breast irradiation; EB-APBI = External Beam APBI; kV-IORT = low-kilovoltage X-Ray Intraoperative Radiotherapy; BT = Brachytherapy. BL = Baseline (after surgery, before RT), M = Month(s), Y = Year(s). GHS = Global Health Score; PF = Physical Functioning; RF = Role Functioning; FA = Fatigue; PA = Pain; BS = Breast Symptoms; FI = financial difficulties; AS = Arm Symptoms; BRBI = Body image; SUM = Summary score (C30); BA/BH = breast appearance changed and breast harder or firmer; AE = Adverse Effects; BIABC Arm = Body Image After Breast Cancer questionnaire arm concerns; BRBI = Body image; FACT-G = Functional Assessment of Cancer Treatment – General; FACT-B = Breast; FACIT = Functional Assessment of Chronic Illness Therapy.

Global HRQL and common symptoms

We found that general HRQL of patients treated with APBI remained stable during 1 year after treatment. This is in accordance with results from APBI studies using brachytherapy or intra-operative low-kilovoltage X-rays as APBI modality [27,28,36]. In an RCT by Meattini et al. the HRQL of patients treated with EB-APBI (5 × 6 Gy fractions over 2 weeks) remained stable after treatment, whereas the HRQL of patients treated with WBI with a boost patients decreased. This may, amongst others, be caused by the large difference in treatment time (Table 4). When comparing two partial breast techniques, like in the current study, differences in HRQL may be smaller due to smaller differences in treatment burden and treated breast volume.

Even though the APBI treatments we investigated both have shorter treatment times than WBI and are limited to a more concise area of the breast, there are important differences in technique. Most important is that patients who received IORT completed radiotherapy on the same day as surgery. Postoperatively, patients treated with IORT were more fatigued than patients who underwent surgery without radiotherapy, but not to a clinically relevant extent. The most likely explanation for this is the addition of IORT to surgery, which slightly increases duration of surgery. However, confounding bias due to differences between the two cohorts

cannot be excluded. In the EB-APBI patients an increase in fatigue was also seen, but at a later timepoint, namely after completion of EB-APBI treatment. Temporary increase of fatigue is commonly seen after irradiation and is often self-limiting. Several studies show that shortening overall treatment time reduces fatigue, especially in the short term [37]. Importantly, in both our patient groups fatigue was decreased at 3 months after treatment and continued to improve thereafter.

Other common symptoms attributable to radiotherapy are breast symptoms such as pain and swelling. Several studies comparing WBI with a form of (A)PBI observed less breast symptoms in patients undergoing partial breast irradiation, both on the short- and on the long-term [12,27,28,35]. In our cohorts, severity of breast symptoms was highest directly postoperative and recovered within 3 months. Unlike fatigue, postoperative breast symptoms were not worse in the IORT group.

Other factors influencing HRQL

Knowledge on factors other than radiotherapy that influence HRQL is important when considering the different adjuvant radiotherapy treatment options with patients. We found that comorbidity (≥ grade 2) and systemic therapy (both hormone- and chemotherapy) were independent risk factors for a worse global

health-related quality of life after treatment. Age was not an independent risk factor in our study, although it has been identified as a risk factor in other studies [35,38,39]. This may be explained by our inclusion of only patients of ≥ 60 years.

Nowadays radiotherapy treatment after BCT is chosen with patients based on their personal preferences, for which both oncological outcome and effect of treatment on HRQL is important. Studies like ours provide essential information on the effect of adjuvant radiotherapy treatments on HRQL, and help to define which treatment fits the patient best.

Strengths and weaknesses

The main weakness of this study is its observational design of two prospective cohorts, which carries the intrinsic risk of residual confounding. This is illustrated for example in lower levels of emotional functioning at baseline in the IORT group. Another weakness is the timing of HRQL questionnaires, as these were collected at time points relative to the radiotherapy treatment instead of relative to baseline. This resulted in a time lag bias between groups as IORT patients received radiotherapy with surgery and patients in the EB-APBI group have had a longer time since surgery (approximately 7 weeks) at every time point, which influences HRQL due to longer surgical recovery time.

Strengths of our study are the excellent compliance until 1 year after treatment of 94%, use of validated questionnaires, and longitudinal analysis of HRQL that provides insight in HRQL patterns over time. Finally, we are the first to present a direct comparison of two APBI techniques.

Conclusion

Concluding, both IORT and EB-APBI are well tolerated and there are no differences in HRQL of patients between these groups until 1 year after treatment. Even though both APBI treatments caused symptoms, most patients only experienced a mild temporary decrease in HRQL after treatment and recovered rapidly; resulting in no clinically relevant differences in HRQL 1 year after treatment in both groups. Comorbidity and the combination of hormonal and chemotherapy have more impact on GHS than type of APBI treatment. Thus, regarding HRQL, both APBI treatments can be considered. Treatment availability and patient preferences, alongside oncological outcome, are crucial when choosing between these APBI treatment options.

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Conflicts of interest

All contributing authors declare no conflicts of interest.

Ethical approval

This study was approved by the medical ethical committee (10-042 METC ZuidwestHolland; NTR2931).

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