Clinical and Translational Radiation Oncology 6 (2017) 7–14

Contents lists available at ScienceDirect

Clinical and Translational Radiation Oncology

journal homepage: www.elsevier.com/locate/ctro

Treatment constraints for single dose external beam preoperative partial breast irradiation in early-stage breast cancer

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ARTICLE INFO

Article history:
Received 31 May 2017
Accepted 14 June 2017
Available online 8 September 2017

Keywords:
Single dose
Breast cancer
Partial breast
Preoperative
Guidelines

ABSTRACT

Background: Following breast-conserving surgery and post-operative 3D-conformal accelerated partial breast irradiation (APBI), suboptimal cosmetic results have been reported. Preoperative radiation delivery to the intact tumor enables better target visualization and treatment volume reduction. Single dose preoperative APBI has the potential to improve toxicity profiles, reduce treatment burden and enable in vivo exploration of breast cancer radiogenomics.
Purpose: Develop practical guidelines for single dose external beam preoperative APBI.
Methods: Recommended dose constraints were derived from pooled dosimetry estimates from 2 clinical trials. In an American dose escalation trial, a uniform 15, 18 or 21 Gy dose has previously been evaluated for non-lobular cT1N0 or low/intermediate grade DCIS <2 cm in prone position ($n = 32$). In the Netherlands, the feasibility of ablative APBI (20 Gy to GTV, 15 Gy to CTV) to non-lobular cT1N0 in supine position, is currently being explored ($n = 15$). The dosimetric adherence to the developed constraints was evaluated in new APBI plans with a 21 Gy uniform dose but an extended CTV margin ($n = 32$).
Results: Dosimetric data pooling enabled the development of practical guidelines for single dose preoperative APBI.
Conclusion: The developed guidelines will allow further explorations in the promising field of single dose preoperative external beam APBI for breast cancer treatment.

Introduction

Accelerated partial breast irradiation (APBI) has been explored as an alternative to whole breast irradiation (WBI) following breast-conserving surgery [1–9]. In selected patients with early-stage breast cancer and low-risk of local recurrence, APBI efficacy appears to be equivalent to WBI with respect to local control and survival rates [3,6–10].

Several randomized controlled trials have evaluated different approaches to deliver APBI following breast-conserving surgery, each with its own advantages and disadvantages. Interstitial multicatheter brachytherapy (IMB) is the technique with the longest clinical follow-up available and good clinical results when compared to WBI with equivalent efficacy, and comparable toxicity profiles [6,9]. However, due to the invasiveness of the technique, the required physician's expertise and brachytherapy equipment, IMB has not been widely implemented. Second, intra-operative radiotherapy (IORT) is an appealing technique due to the single treatment approach at the time of surgery but requires costly and cumbersome equipment. External beam APBI has the advantage of widespread equipment availability and expertise, but when compared to the previous techniques, larger treatment volumes have typically been utilized. As a result, an increase in soft tissue fibrosis and suboptimal cosmetic outcomes has been seen with 3-dimensional conformal external beam radiation therapy (3D-CRT) [4]. However, more dose conformal techniques such as intensity-modulated radiotherapy (IMRT), have the potential for superior toxicity and cosmetic outcome profiles when compared to WBI, suggesting that the results of external beam APBI could be improved upon [8].

In an effort to overcome the disadvantages and capitalize on the advantages of the previous APBI techniques, the concept of MRI-guided single dose external beam partial breast irradiation

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http://dx.doi.org/10.1016/j.ctro.2017.06.003

delivered prior to surgical resection has been developed [11–13]. The single dose concept of IORT using a non-invasive external beam technique can minimize the treatment duration and burden for patients, without the purchase of any supplementary radiotherapy equipment. In addition, the delivery of radiation (RT) preoperatively to the intact tumor allows more precise targeting when compared to post-surgery, resulting in significantly smaller treatment volumes and possibly less RT-induced toxicity [11,14]. Another advantage of preoperative APBI concerns the uniformity of treatment volume definition, with less interobserver variation in target volume delineation when compared to a postoperative approach [15]. MRI-guided preoperative target definition can further improve the tumor visualization (i.e. tumor spiculae) [16]. This could facilitate dose escalation, enabling an ablative, definitive treatment approach for early-stage breast cancer. Finally, preoperative APBI allows the direct evaluation of RT effects in breast tumors, aiming at the identification of radiation response predictors and biomarkers, which may help to guide personalized treatment for future patients [17].

Single dose external beam preoperative APBI has great potential in clinical practice to deliver a precise and uniform, minimally burdensome treatment with less associated toxicity, and opens a new window of opportunity in radiogenomics. Based on the clinical experience with this approach in two university medical centers, this manuscript introduces practical guidelines for the delivery of single dose external beam preoperative radiotherapy.

Methods

Study population

The current study includes data from 2 pre-existing studies and was approved by the Institutional Review Boards of the participating institutes.

In both trials, toxicity was prospectively evaluated at predefined, overlapping time points using the Cancer Institute's Common Terminology Criteria for Adverse Events (CTCAE version_4.03).

At Duke University Medical Center, Durham, Unites States of America, a phase I dose escalation trial (ClinicalTrial.gov NCT00944528) was conducted between August 2010 and March 2013 in order to determine the maximum tolerated dose of single dose preoperative APBI in prone RT position. A total of 32 patients $\geq$55 years with cT_1N_0 invasive ductal carcinomas or DCIS $\leq$2.0 cm were included [12]. A lumpectomy was performed within 10 days following RT. The updated treatment toxicity at a median of 37 months follow-up is in line with the previous published results, with chronic grade 1–2 local fibrosis, dermatitis and breast pain being the most common toxicities. In all patients treated with single dose APBI only, good to excellent cosmetic outcomes were assessed by the treating physician.

At the University Medical Center Utrecht, The Netherlands, an ongoing trial evaluates the clinical feasibility of a radiosurgical approach for early-stage breast cancer (ClinicalTrial.gov NCT02316561). A lumpectomy is performed at 6 months following RT in the supine position, in order to evaluate the primary endpoint, the pathological response. The current study included the first 15 study patients $\geq$50 years with $cT_1N_{0(sn)}$ invasive ductal carcinoma. At time of analysis, eleven (of the planned 25) patients had a lumpectomy performed, and only grade 1–2 toxicity has been observed at a median follow-up of 7 months (Appendix Table A1).

Treatment planning

At Duke, IMRT was used to deliver 15 Gy, 18 Gy or 21 Gy to the gross tumor volume (GTV) and the clinical target volume (CTV) (Eclipse®version 10). At Utrecht, a single dose Volumetric Modulated Arc Therapy (VMAT) treatment was concomitantly prescribed to deliver two dose levels, 20 Gy to the GTV and 15 Gy to the CTV (Monaco®version 19). Study details have been previously published [12,13,18]. Table 1 and Fig. 1 illustrate treatment planning characteristics.

Guidelines development

Since the initial dosimetric parameters of interest differed between the institutions, a new protocol for treatment plan evaluation was reached in consensus. Using the original treatment plans, this protocol evaluated target volume coverage and dose to organs at risk (OAR) with respect to NSABP B39/RTOG 0413 and QUANTEC guidelines for target and normal tissue constraints, converted to a single-dose prescription [13,19]. Furthermore, in order to achieve a uniform evaluation between institutions the chest wall delineation was adjusted, and two different skin definitions were assessed (i.e. first 3 and 5 mm subcutaneous tissue).

Since no dose limiting toxicity has been encountered, no normal tissue complication probability curves were developed. Reasonable constraints were pragmatically defined based on descriptive statistics of the pooled dosimetric parameters in the clinical cohorts. Overall median, interquartile range (IQR) and 10th and 90th percentile doses were determined for target volume and OAR parameters. Optimal and acceptable dosimetry was defined as an OAR value that did not exceed the 75th (upper IQR) and 90th percentile of the pooled dosimetric parameter, respectively.

Dosimetric feasibility guidelines

To determine the feasibility of these new dose constraints for future studies, new treatment plans were performed for the patients in the dose escalation cohort ($n = 32$) using Eclipse®version 13.6. Given the variation in breast delineations, some ipsilateral and contralateral breast contours were adjusted, following consensus [20]. A uniform 21 Gy dose was prescribed to the intact tumor with a 2.0 cm margin in order to assess our guidelines using a larger CTV margin that more closely approximates existing post-operative external-beam APBI data. Due to the 0.5 cm CTV extension from the initial treatment plans, this would more often align the skin. Adequate target volume coverage was therefore defined as $\geq$95% of prescription dose to $\geq$98% of the CTV. Table 1 illustrates RT planning characteristics for this replanned cohort. The new plans were evaluated for adherence to the previously defined optimal or acceptable dosimetry from the clinical cohorts.

Results

Dosimetry across cohorts

The median GTV and CTV receiving $\geq$95% of the prescribed dose (PD) was $\geq$99% in all 3 cohorts. The median PTV receiving $\geq$95% of the PD was $\geq$97% in the clinical cohorts and 95% in the replanned cohort. Table 2 gives an overview of the treatment volumes. In the integrated boost cohort treatment volumes are larger compared to the dose escalation cohort, given the 0.5 cm additional CTV extension. When evaluating PTV overdosage in relation to the CTV PD in the integrated boost cohort, the median $V_{110\%}$ and $V_{105\%}$ was 29% and 43%, respectively. Table 3 illustrates the dosimetry across the various clinical cohorts. Higher mean ipsilateral breast and skin dosimetry are encountered with higher PD. Lower PD fall-off is observed in the integrated boost cohort.

Optimal or acceptable plan dosimetry

Optimal and acceptable dosimetry was defined from the clinical cohorts as a value up to the 75th percentile (i.e. upper IQR) and

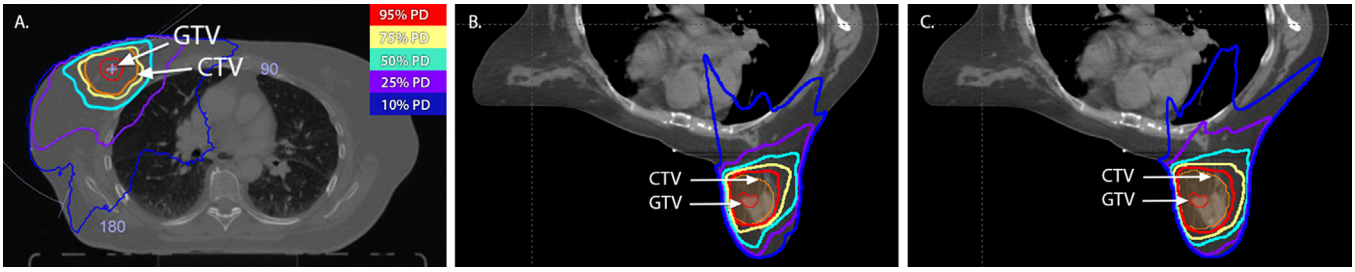

Fig. 1. Dose distributions treatment. (A) VMAT plan in supine treatment position with 20 Gy prescription dose (PD) to the gross tumor volume (GTV) and 15 Gy PD to the clinical target volume (CTV). Isodose illustrate the GTV prescription dose. (B) IMRT plan in prone treatment position plan with 21 Gy prescription dose (PD) and a 15 mm CTV margin. (C) IMRT plan in prone treatment position plan with 21 Gy prescription dose (PD) and a 20 mm CTV margin.

Table 1
Overview of treatment planning in the different cohorts.

	Dose escalation cohort 15, 18 or 21 Gy (total $n = 32$)	Integrated boost cohort 20/15 Gy ($n = 15$)	Replanned cohort 21 Gy ($n = 32$)
Set-up	Prone*	Supine	Prone*
Gross tumor volume (GTV)	Delineated based on fused CT-MR findings and intratumoral fiducial marker	Delineated based on fused CT-MR findings and intratumoral fiducial marker	Delineated based on fused CT-MR findings and intratumoral fiducial marker
Clinical target volume (CTV)	15 mm around GTV, excluding the first 5 mm from the body as well as chest wall, if greater than 1 cm from the GTV	20 mm around GTV, excluding the first 5 mm from the body as well as the chest wall	20 mm around GTV, excluding the first 5 mm from the body as well as the chest wall
Evaluated planning target volume (PTV)	3 mm margin from CTV, excluding the first 5 mm of subcutaneous tissue	– 3 mm margin from CTV, excluding the first 5 mm of subcutaneous tissue ($PTV_{(CTV)}$) – 3 mm margin from GTV, excluding the first 5 mm of subcutaneous tissue (PTV_{GTV})	3 mm margin from CTV, excluding the first 5 mm of subcutaneous tissue and chest wall
Prescription dose (PD)	15, 18 or 21 Gy to the CTV	15 Gy for the CTV 20 Gy for the GTV	21 Gy for the uniform CTV
Definition adequate coverage	At least 95% of PD to 100% of CTV	At least 95% of PD to at least 99% of PTV_{CTV} or PTV_{GTV}, respectively	At least 95% of PD to at least 98% of CTV Secondary objective: 95% of PD to 95% of PTV_{CTV}
Treatment planning approach	Intensity modulated radiation therapy with 5–7 (non)coplanar beam arrangement	Volumetric modulated arc therapy with 2 partial arcs	Intensity modulated radiation therapy with 4–7 noncoplanar beam arrangement

* 2 patients were treated supine.

Table 2
Treatment volume characteristics in the clinical and replanned cohorts.

	Dose escalation prone cohort 15, 18, 21 Gy ($N = 32$) median (IQR)[a]	Integrated boost supine cohort 15/20 Gy ($N = 15$) median (IQR)[a]	Replanned prone cohort 21 Gy ($N = 32$) median (IQR)[a]
Affected breast n (%)			
Left	18 (56%)	7 (47%)	18 (56%)
Right	14 (44%)	8 (53%)	14 (44%)
Ipsilateral breast volume (cc)	1589.6 (1098.1–1887.0)	1099.9 (821.1–1245.0)	1470.9[b] (974.7–1727.3)
Treatment volumes			
Gross tumor volume (cc)	0.9 (0.5–1.3)	1.3 (1.0–2.9)	0.9 (0.5–1.3)
Clinical tumor volume (cc)	43.2 (35.0–49.3)	74.1 (69.4–96.0)	75.6 (64.2–88.4)
Planning target volume (cc)	63.3 (54.3–73.5)	107.4 (97.0–154.9)	101.4 (85.3–122.6)
Ratio PTV to ipsilateral breast volume (%)	4.6 (2.9–5.5)	12.8 (8.5–13.8)	8.1 (4.9–9.5)
Overdosage			
$V_{105\%}$ PTV (%)	7.3 (0–35.8)	0[c] (0–0)	0 (0–0.2)
$V_{110\%}$ PTV(%)	0 (0–0)	0[c] (0–0)	0 (0–0)
D_{max} PTV(%)	106.8 (105.6–109.7)	104.5[c] (104.0–105.5)	103.2 (101.8–104.7)

[a] Unless otherwise specified.
[b] Represents consensus breast volumes.
[c] 105% (21 Gy) and 110% (22 Gy) respectively of the prescription dose to the GTV in the $PTV_{(CTV)}$ (thereby excluding the GTV).

90th percentile of the pooled dosimetric parameter, respectively (Table 4). Table 5 summarizes treatment recommendations for single dose preoperative APBI.

Dosimetric adherence to constraints

In the replanned cohort, at least acceptable $V_{100\%}$ and $V_{50\%}$ PD in the ipsilateral breast was achieved in 100% and 91% of the cases despite smaller consensus breast volumes (Table 2). An acceptable mean ipsilateral breast dose was evaluated in 56% of the patients. Optimal dosimetry was achieved for the contralateral breast, ipsilateral lung and chest wall in 97%, 94% and 97% of cases, respectively. At least acceptable D_{max} and D_{mean} heart was encountered in 97% and 100% of patients. For the first 3 mm of subcutaneous tissue, at least acceptable skin dosimetry was achieved for the D_{1cc} and D_{10cc} in 19% and 63% of cases, respectively. For the first

Table 3
Dose to organs at risk across the clinical cohorts.

	Dose escalation prone cohort 15 Gy (N = 8) median (IQR)	Dose escalation prone cohort 18 Gy (N = 8) median (IQR)	Dose escalation prone cohort 21 Gy (N = 16) median (IQR)	Integrated boost supine cohort 15/20 Gy (N = 15) median (IQR)
Ipsilateral breast				
$V_{100\%}$ CTV prescription dose (%)	4.2 (3.1–4.9)	3.2 (2.2–3.7)	4.2 (2.5–5.9)	10.2 (6.8–11.0)
$V_{50\%}$ CTV prescription dose (%)	14.4 (10.3–17.6)	11.6 (8.7–14.1)	14.2 (10.1–19.7)	27.3 (19.6–30.7)
$V_{100\%}$ GTV prescription dose (%)	**	**	**	0.4 (0.3–0.8)
$V_{50\%}$ GTV prescription dose (%)	**	**	**	21.9 (15.8–24.0)
Mean dose (Gy)	2.9 (2.2–3.3)	2.8 (2.4–3.0)	3.8 (2.8–4.7)	5.0 (4.0–5.4)
*Skin (3 mm)**				
D_{1cc} (Gy)	8.8 (7.1–10.9)	10.6 (9.1–11.9)	12.5 (10.9–15.8)	12.9 (11.6–13.3)
D_{10cc} (Gy)	5.9 (4.4–6.6)	7.2 (6.2–8.3)	7.8 (7.0–9.1)	9.7 (7.7–10.5)
*Skin (5 mm)**				
D_{1cc} (Gy)	12.1 (9.0–12.9)	12.9 (11.4–15)	17.1 (15.9–18.8)	14.5 (13.3–15.8)
D_{10cc} (Gy)	7.9 (6.3–8.9)	9.5 (8.5–10.4)	11.6 (10.6–13.9)	12.3 (10.4–12.7)
Heart				
D_{max} (Gy)	3.1 (1.0–4.0)	1.6 (0.5–3.0)	0.8 (0.3–2.4)	3.0 (1.9–3.9)
Mean dose (Gy)	0.1 (0.0–0.2)	0.2 (0.0–0.5)	0.1 (0–0.2)	0.7 (0.5–1.2)
Other				
D_{max} contralateral breast (Gy)	1.2 (0.2–2.2)	0.3 (0.2–1.1)	0.4 (0.3–0.7)	1.5 (0.8–3.1)
Mean dose ipsilateral lung (Gy)	0.2 (0.1–0.5)	0.2 (0.1–0.4)	0.4 (0.2–0.6)	1.4 (0.9–1.6)
D_{20cc} dose chest wall (Gy)	2.8 (1.7–7.7)	2.4 (1.0–4.0)	3.9 (2.4–5.0)	12.3 (9.4–13.4)

* The first 3 mm or 5 mm of subcutaneous tissue from body surface.
** CTV prescription dose is GTV prescription dose.

5 mm of subcutaneous tissue, this was achieved in 19% and 28% of patients, respectively.

Discussion

The current study provides consensus recommendations for single dose preoperative APBI target and OAR constraints based on the clinical data from 2 university medical centers (Table 5, Appendix Fig. A1). Optimal and acceptable dose constraints were formulated from clinically correlated data. In patients treated with preoperative single dose APBI only, no dose limiting toxicity has been observed, possibly placing these constraints at the lower, safe end of the toxicity spectrum [12], Appendix Table A1. In addition, the dosimetric feasibility of single dose 21 Gy APBI with CTV margin expansion was evaluated. Acceptable and optimal OAR dosimetry could be achieved in the great majority of the cases, except for the skin, with at least acceptable metrics ranging from 19 to 63%. Additional target volume expansion would likely preclude use of skin constraint and require additional clinical investigation to determine the impact of high skin doses on acute and chronic toxicity (Appendix Fig. A2).

To our knowledge, no other centers have evaluated the feasibility of single dose preoperative external beam APBI. Single dose 18-21 Gy 3D-CRT based APBI following surgery has been previously reported for $pT_{1-2(max.3cm)}N_{0-1}$ non-lobular carcinoma (n = 64) [21]. The study stopped prematurely due to unexpected grade 2–3 subcutaneous fibrosis and fair-poor cosmesis in 44% and 41% of the patients, respectively. This is in contrast to our results and is likely due to our smaller preoperative target volumes. For example, our median PTV was 72.2 cc (30.1–203.7 cc) versus 96 cc (range 17–290 cc) compared to the post-lumpectomy APBI study. Furthermore, increased toxicity in the post-lumpectomy 3D-CRT based APBI could be explained by differences in techniques, with less dose inhomogeneity for the IMRT-VMAT approach used at our institutes [22]. Also, we hypothesize that preoperative APBI is more favorable with respect to the cosmesis because a portion of the breast tissue receiving high-dose RT prone to development of fibrosis will be excised. In the post-lumpectomy APBI study, a mean ipsilateral breast dose $\geq$9 Gy was the only factor associated with impaired cosmesis. Their mean dose was 9.7 Gy (range 4.4–14.1 Gy), whereas the pooled mean estimate in the clinical cohorts was 3.8 Gy (range 1.6–7.8 Gy) and 5.0 Gy (range 2.9–7.3 Gy) in the replanned cohort.

Table 4
Dose to organs at risk in the pooled (clinical) cohort of patients, and in the replanned 21 Gy cohort.

	Clinical cohorts 15, 18, 21 (prone) and 15/20 Gy (supine) median (IQR) [10th–90th percentile] (N = 47)	Replanned prone cohort 21 Gy median (IQR) (N = 32)
Ipsilateral breast		
$V_{100\%}$ CTV prescription dose (%)	4.6 (3.1–7.2) [2.1–10.8]	1.4 (0.1–6.6)
$V_{50\%}$ CTV prescription dose (%)	16.3 (12.1–20.9) [8.2–29.8]	20.0 (16.0–26.7)
Mean dose (Gy)	3.6 (2.8–4.8) [2.3–5.4]	5.2 (4.2–5.8)
*Skin (3 mm)**		
D_{1cc} (Gy)	11.7 (10.4–13.2) [8.2–15.3]	16.4 (15.6–17.0)
D_{10cc} (Gy)	7.7 (6.6–9.5) [5.7–10.6]	10.2 (9.1–11.0)
*Skin (5 mm)**		
D_{1cc} (Gy)	14.5 (12.5–16.3) [11.0–18.2]	19.0 (18.4–19.4)
D_{10cc} (Gy)	10.5 (9.0–12.4) [7.7–13.9]	15.4 (13.7–16.0)
Heart		
D_{max} (Gy)	2.3 (0.8–3.4) [0.2–4.2]	2.6 (1.0–3.3)
Mean dose (Gy)	0.2 (0.1–0.6) [0–1.0]	0.2 (0.1–0.4)
Other		
D_{max} contralateral breast (Gy)	0.5 (0.3–1.6) [0.2–2.4]	0.2 (0.2–0.5)
Mean dose ipsilateral lung (Gy)	0.4 (0.2–1.0) [0.1–1.6]	0.6 (0.3–0.7)
D_{20cc} dose chest wall (Gy)	4.6 (2.5–10.2) [1.3–13.2]	4.1 (3.1–5.6)

* The first 3 mm or 5 mm of subcutaneous tissue from body surface.

Table 5
Treatment planning recommendations for single dose preoperative external beam partial breast irradiation.

	DEFINITION	RECOMMENDATION or CONSTRAINTS	POOLED CONSTRAINT (IQR) [10^{th}-90^{th} percentile]
ELIGIBILITY			
Patient characteristics	-	- women ≥ 50 years of age - eligible for breast conservation treatment	-
Tumor characteristic	-	- unifocal non-lobular cT_1N_0Mx or low/intermediate grade $cT_{is}N_0Mx$ ≤2cm - ER or PR receptor positive - Her2 negative	-
TARGET VOLUMES			
Prescription dose (PD)	-	- 15 to 21 Gy uniform dose, in case of short interval (≤ 10 days) to surgery - the recommended dose and interval to surgery for a radiosurgical approach is currently under evaluation in the integrated boost cohort. (ClinicalTrial.gov NCT02316561)	-
GTV	Delineation according to findings on fused contrast-enhanced CT-MRI.	Aim at: - ≥ 95% dose to 99% volume - D_{max} ≤ 107%	
CTV	-uniform PD: 1.5 to 2.0cm -integrated boost approach: 2.0cm -first 5mm of subcutaneous tissue and chest wall are excluded.	Aim at: - ≥ 95% dose to 98% volume - uniform PD: D_{max} ≤ 110% - D_{max} ≤ 140% with an integrated boost approach	-
Planning target volume (PTV) [18, 32]	- uniform PD: 3mm expansion from CTV - integrated boost approach: additional 3mm expansion from GTV.	Aim at: - ≥ 95% dose in ≥97% volume - D_{max} < 110%	-
	- first 5 mm of subcutaneous tissue are excluded.		
ORGANS AT RISK			
Ipsilateral breast [20]	According to radiopaque wire markings of breast tissue following palpation, as well as breast contouring atlas guidelines	Aim at: - ≤ 8.5% PTV to breast ratio - ≤ 4.8Gy mean dose - $V_{100\%}$ CTV PD ≤7.2% - $V_{50\%}$ CTV PD ≤20.9%	Ratio PTV/breast (3.5-8.5); [2.0-13.8] Mean breast dose (2.8-4.8); [2.3-5.4] $V_{100\%}$ CTV PD (3.1-7.2); [2.1-10.8] $V_{50\%}$ CTV PD (%) (12.1-20.9); [8.2-29.8]
Skin	The first 3 to 5 mm of subcutaneous tissue of the ipsilateral breast.	Aim at: - D_{max} ≤ 100% PD - 3 mm: D_{1cc} ≤ 13.2Gy - 3 mm: D_{10cc} ≤ 9.5Gy - 5 mm: D_{1cc} ≤ 16.3Gy - 5 mm: D_{10cc} ≤ 12.4Gy	Skin 3 mm D_{1cc} (10.4-13.2); [8.2-15.3] D_{10cc} (6.6-9.5); [5.7-10.6] Skin 5 mm D_{1cc} (12.5-16.3); [11.0-18.2] D_{10cc} (9.0-12.4); [7.7-13.9]
Chest wall	Sternum, ribs and (intercostal, pectoralis) muscles aligning the ipsilateral breast.	Aim at: - D_{20cc} ≤ 10.2Gy	D_{20cc} (2.5-10.2) [1.3-13.2]
Heart [33]	The heart contour starts below the pulmonary trunk bifurcation and includes the pericardium.	Aim at: - mean dose ≤0.6Gy - D_{max} ≤3.4Gy	Mean dose (0.1-0.6); [0-1.0] Max dose (0.7-3.4); [0.2-4.2]
Contralateral breast [20]	According to findings on CT-scan as well as breast contouring atlas guidelines, not extending past midline.	Aim at: - D_{max} ≤1.6Gy	D_{max} (0.3-1.6) [0.2-2.2]
Lungs	Delineation of ipsilateral, contralateral and both lungs according to CT findings.	Aim at mean dose: - ipsilateral lung ≤ 1.0Gy - contralateral lung ≤ 0.4Gy - both lungs ≤ 0.7Gy	Mean dose ipsilateral (0.2-1.0); [0.1-1.6] Mean dose contralateral (0-0.4); [0-0.5] Mean dose both lungs (0.2-0.7); [0.1-1.0]
Value: optimal organ at risk constraint		Value: acceptable organ at risk constraint	

(See above-mentioned references for further information.)

Van der Leij et al. evaluated preoperative multiple fraction APBI for $cT_{1-2(max.3.0cm)}N_0$ (n = 70) by delivering forty Gy in 10 fractions over 2 weeks with 3D-CRT, IMRT or VMAT, followed by lumpectomy at 6 weeks [23]. Interestingly, induration fibrosis actually declined over time and cosmetic outcome improved. At 24 months, 46% and 2% of the patients experienced mild-moderate local

fibrosis and 80% were satisfied to very satisfied with the cosmetic result. A phase 2 trial by Nichols et al. evaluated 3D-CRT preoperative APBI for $T_{1-2(max.3.0cm)}N_0$ ($n = 27$) with 38.5 Gy in 3.85 Gy fractions twice daily and lumpectomy performed ≥21 days after RT [24]. At a median follow-up of 3.6 years, good–excellent cosmetic outcome was reported by 78% of women. Expected grade 0–1 toxicity (CTCAE_version_3), such as fatigue, skin erythema, hyperpigmentation, fibrosis, breast discomfort, edema and dyspnea was encountered. A direct comparison with our cohorts is difficult due to fractionation and/or RT technique differences, nonetheless, these studies show that preoperative APBI is a feasible option for low-risk breast cancer patients and give a sense of expected clinical outcomes.

Furthermore, our clinical preoperative irradiated cohorts illustrate a great advantage in target volume reduction compared with postoperative APBI. In the APBI-arm of the RAPID trial, women ≥40 years with $pT_{1-2(max\ 3.0cm)}N_0$ were treated to a total of 38.5 Gy in twice daily 10 fractions following breast-conserving surgery [4,25]. The mean volume receiving 95% of PD was 332 cc (standard deviation (SD) 153 cc), with a mean ratio to ipsilateral breast of 22% (SD 7%). In our clinical cohorts, the mean PTV volume was 72 cc (SD 37 cc) with a mean 7% (SD 4%) PTV to ipsilateral breast ratio. Even in the replanned cohort with an extended CTV margin, the mean PTV was 99 cc (SD 31 cc) with a mean 8% (SD 3%) ratio PTV to ipsilateral breast. We therefore believe that preoperative external beam APBI has great potential in clinical practice to deliver a precise treatment with smaller treatment volumes, enabling a reduction in RT associated toxicity and improvement in treatment burden.

To our knowledge, no other clinical studies assessed skin toxicity following single dose RT. Setting constraints based on data from hyperfractionated or multiple fraction hypofractioned treatment would not be appropriate from a radiobiological point of view. If acceptable skin dosimetry cannot be achieved in clinical practice, a reduction of the CTV margin from 20 to 15 mm could provide an alternative in order to still deliver a single dose treatment. Another option to consider when skin constraints cannot be achieved, is accepting a higher dose given that no dose limiting toxicity has been observed so far. It should be noted though that additional single dose RT clinical studies are needed to determine whether larger target volumes with higher associated skin doses maintain clinically acceptable skin toxicity.

With postoperative APBI, the CTV definition has mainly evolved from Holland's work in mastectomy specimens, where even in small tumors ≤2.0 cm, 92% of microscopic disease extended up to 30 mm from the index lesion [26]. Nowadays, an MRI of the breasts is typically utilized to assess the possibility of extensive disease in APBI candidates, resulting in 11% of patients eventually deemed ineligible [27]. An MRI and histopathology correlation study showed that in the absence of extensive intraductal component, no subclinical invasive disease was present in 93% of lumpectomy cases more than 10 mm beyond the edge of the lesion as measured on MRI [28]. In a recent prospective pathology study on the appropriate CTV margin for APBI, the maximum radial extension of residual carcinoma was assessed in 133 women requiring re-excision or completion mastectomy after initial lumpectomy [29]. In the 58% patients with non-involved initial margins, residual disease, if present, was ≤10 mm in 97.4% of the cases. In the 42% patients with involved margins, disease extended beyond 20 mm in 10.7% of cases. Large extension of microscopic disease was associated with involved margins, tumorsize ≥30 mm and premenopausal status, which are characteristics that do not apply to our patient population. We acknowledge that the appropriate preoperative CTV margin is a subject up for debate, however for low-risk patients with biologically favorable and limited extent of disease assessed on MRI, we perceive 15 mm as a minimum, up to 20 mm, as a recommended CTV margin [30,31], Table 5. This is also supported by our clinical outcomes with only 1 local recurrence so far in our dose-escalation cohort at a median follow-up of 37 months.

Similarly, the optimal time between surgery and resection is not known. In the dose escalation 'proof of principle' trial, the investigators did not wish to delay definitive surgical resection and therefore surgery was performed ≤10 days. In the integrated boost cohort where a radiosurgical approach is currently explored, surgery is undertaken 6 months after RT in order to evaluate the complete pathologic response. Given that the latter approach is still under investigation, we suggest a short interval to surgery.

The current study has certain drawbacks that should be addressed. First, the recommended constraints originate from a heterogeneous population, treated in the prone or supine position, with a VMAT or IMRT technique, different optimization techniques and various fractionation schedules. Nonetheless, we believe that the radiobiological impact of single dose highly-conformal APBI ≥15 Gy is sufficiently similar, and rare, to justify this pooling of data. Combining the scarce experience will eventually define the safety aspects of this treatment approach. Also, this heterogeneous population reveals variation across different medical centers and illustrates current clinical practice, that should be considered in study design. We expect that ongoing and future trials will provide a sufficient number of patients to enable subgroup analysis. Second, the patients in the simultaneous boost cohort have a limited 229 days follow-up. Though toxicity has been limited thus far, additional data will be required to confirm the safety of treatment planning with the suggested constraints. Nonetheless, given the scarce experience with single dose APBI, guidelines to ensure consistent treatment planning will be critical for ongoing assessment of clinical feasibility with this technique.

We believe single dose preoperative RT is a compelling treatment approach and our practical recommendations could reach further than a low-risk APBI eligible population. Future studies could focus on locally advanced breast cancer in conjunction with immunotherapy, for example [34]. Furthermore, if single dose RT proves to be ablative for early-stage breast cancer, future studies could focus on the minimally invasive treatment for functionally impaired, medically inoperable breast cancer patients. However to minimize the possibility of adverse events for study patients, carrying out single dose ultra hypofractionated RT studies should be confined to stringent protocols, taking pre-existing experience into account. We perceive our current experience and recommendations a basic, but helpful foundation for future explorations in the promising field of single dose preoperative RT.

In conclusion, dosimetric data pooling acquired from clinical cohorts of 15 Gy, 18 Gy, 21 Gy, and simultaneous integrated 15/20 Gy boost, enabled the development of practical guidelines for single dose preoperative APBI in women ≥50 years of age with low-risk cT_1N_0 non-lobular breast cancer or limited DCIS. The dosimetric adherence to developed OAR constraints was demonstrated in new APBI plans with a 21 Gy uniform dose but an extended CTV margin. However, caution remains warranted and possible adaptation of skin constraints might be required following future single dose APBI clinical trials. Our short-term results support the importance of further developments in the field of single dose preoperative APBI which has the potential to further minimize treatment burden, reduce target volumes and treatment toxicity, and allow the in vivo exploration of breast cancer radiogenomics.

Conflict of interest

None.

Acknowledgements

The ABLATIVE study (ClinicalTrial.gov NCT02316561) was supported by a grant from the Pink Ribbon Association. Author JH was supported by K12HD043446 – Building Interdisciplinary Research Careers in Women's Health, Susan G. Komen for the Cure CCR12225923, and Varian Medical Systems. The funding sources had no role in study design, data collection, analysis of interpretation.

Appendix A

Table A1
Overview of main treatment toxicities and post-operative complications following single dose preoperative accelerated partial breast irradiation in the integrated boost cohort (ClinicalTrial.gov NCT02316561).

	Percentage toxicity $n = 15$ (%)
Toxicity grade 1 (%)	
Local fibrosis	87%
Fatigue	80%
Breast discomfort	67%
Dermatitis	0%
Toxicity grade 2 (%)	
Pain breast*	13%
Post-operative complications (%)	
Haematoma (grade 2)	7%
Chronic seroma	**

* Resolved following analgesic treatment and lymphedema therapy.
** Chronic seroma rates cannot be reported due to the limited median follow-up of 69 days following surgery.

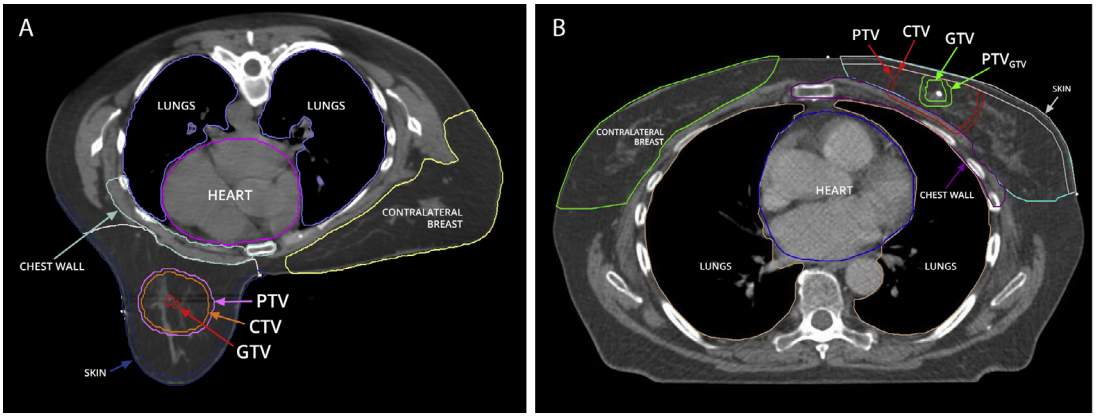

Fig. A1. Recommended delineations organs at risk and target volumes in prone (A) and supine treatment approach (B).

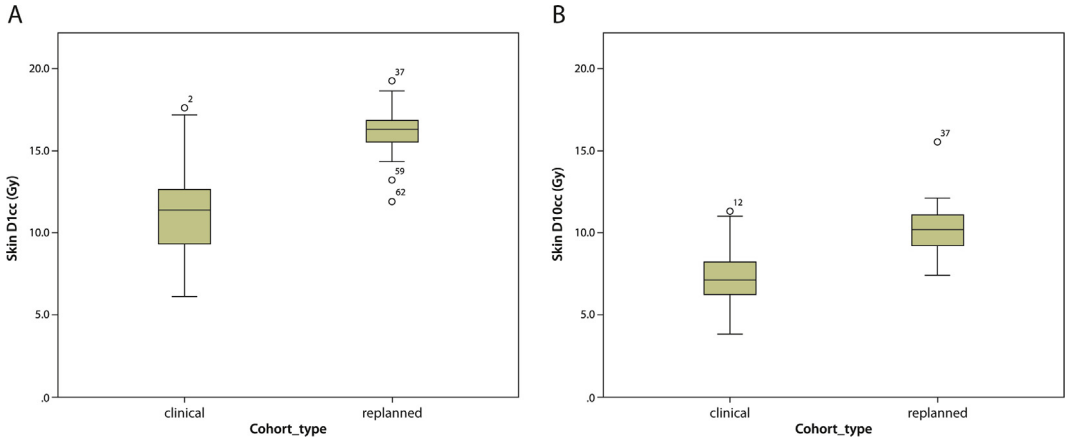

Fig. A2. The impact of CTV increase (from 15 to 20 mm) and 21 Gy prescription dose in the clinical versus replanned prone cohort for D_{1cc} (A) and D_{10cc} (B) in the first 3 mm of subcutaneous tissue.

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