

Original Research Article

Single dose partial breast irradiation using an MRI linear accelerator in the supine and prone treatment position



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ABSTRACT

Background: In selected patients with early-stage and low-risk breast cancer, an MRI-linac based treatment might enable a radiosurgical, non-invasive alternative for current standard breast conserving therapy.

Aim: To investigate whether single dose accelerated partial breast (APBI) to the intact tumor in both the prone and supine radiotherapy positions on the MRI-linac is dosimetrically feasible with respect to predefined coverage and organs at risk (OAR) constraints.

Material & methods: For 20 patients with cTis or low-risk cT1N0M0 non-lobular breast carcinoma, previously treated with single dose preoperative APBI in the supine (n = 10) or prone (n = 10) position, additional intensity modulated radiotherapy plans with 7 coplanar beams in the presence of a 1.5T magnetic field were generated. A 20 Gy and 15 Gy dose was prescribed to the gross tumor and clinical target volume, respectively. The percentage of plans achieving predefined organ at risk (OAR) constraints, currently used in clinical practice, was assessed. Dosimetry differences between the prone versus supine approach and the MRI-linac versus clinically delivered plans were evaluated.

Results: All MRI-linac plans met the coverage and predefined OAR constraints. The prone approach appeared to be more favorable with respect to the chest wall, and ipsilateral lung dose compared to the supine position. No dosimetric differences were observed for the ipsilateral breast. No treatment position was clearly more beneficial for the skin or heart, since dosimetry varied among parameters. Overall, the MRI-linac and clinical plans were comparable, with minor absolute dosimetric differences.

Conclusion: MRI-linac based single dose APBI to the intact tumor is a promising and a dosimetrically feasible strategy in patients with low-risk breast cancer. Preliminary OAR dosimetry favored the prone radiotherapy position.

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1. Introduction

Accelerated partial breast irradiation (APBI) following breast-conserving surgery has proven to be an alternative to whole breast irradiation (WBI) in early-stage low-risk breast cancer [1–6]. In current clinical practice however, APBI target volume definition can be difficult due to post-surgical breast tissue changes. The use of surgical markers and contouring guidelines improves the tumor bed delineation consistency among clinicians [7]. Nonetheless, a preoperative APBI approach with the tumor in situ has proven to be more beneficial with respect to target def-

inition and treatment volumes, compared to postoperative APBI [8,9].

For APBI, an MRI-based strategy enables adequate visualization of tumor extent and selection of eligible patients [10–12]. MR-guided CT-linac based single dose APBI delivered preoperatively in the prone treatment position has recently been evaluated as feasible for low-risk non-lobular carcinoma or ductal carcinoma in situ (DCIS) [13]. Furthermore, an MR-guided supine preoperative approach has also been shown to be dosimetrically feasible and is currently under clinical investigation with promising preliminary results [14,15]. This single dose preoperative RT delivery results in a burden minimizing treatment for patients, and opens a new window of opportunity to evaluate a radiosurgical approach for breast cancer patients [15–17].

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The MRI linear accelerator (MRI-linac) is a hybrid system, consisting of a 7MV linear accelerator (Elekta AB, Stockholm), and a 1.5 Tesla MRI scanner (Philips®) [18–20]. In contrast to MRI-guided CT-based RT currently employed in clinical practice, the MRI-linac provides on-line high soft-tissue contrast during the actual radiation delivery, thereby differentiating between target and non-target surrounding normal tissue. Furthermore, real-time target volume MR-imaging allows for potential plan adaptation strategies, such as smaller margins for target volumes and dose escalation. This may result in less radiotherapy-induced toxicity, while simultaneously enhancing the local tumor control probability. This might enable a radiosurgical approach to the intact tumor, possibly making breast conserving surgery and the subsequent radiotherapy (RT) schedule redundant for selected patients with early-stage low-risk breast cancer eligible for APBI. Also, due to real-time target volume MRI-imaging during RT, fiducial markers needed for position verification or a planning CT-might not be required, making single dose APBI MRI-linac based treatment less burdensome for selected breast cancer patients. Nonetheless, at least three major issues should be considered for treatment planning on the MRI-linac. First, the trajectories of secondary electrons are modified due to the presence of a magnetic field. As a result of a shorter build-up region and increased exit dose in the skin (i.e. due to the electron return effect), the dose distribution can be impacted [21,22]. Second, certain technical specifications of the MRI-linac such as the fixed collimator and fixed couch position relative to the isocenter, could impact treatment planning. Furthermore, both the prone and supine treatment position on the MRI-linac might have specific challenges in practical and dosimetric feasibility. The main objective of the current study was therefore to investigate whether single dose APBI in both the prone and supine treatment positions to the intact tumor is dosimetrically feasible on the MRI-linac with respect to predefined, currently used in clinical practice, coverage and organs at risk constraints.

2. Material & methods

2.1. Patient selection

This study was designed as a RT predicate study for evidence based-introduction of the MRI-linac according to the R-IDEAL framework for clinical evaluation of technical innovations in radiation oncology [23]. Twenty patients were selected from 2 earlier studies on MRI-guided preoperative single-dose partial breast irradiation. At Duke University Medical Center, Durham, United States of America, 32 women (≥ 55 years with cT_1N_0 ductal carcinoma or low-intermediate grade DCIS ≤ 2.0 cm) were treated in the prone position with a single dose of 15 Gy, 18 Gy or 21 Gy to the tumor plus margin [13]. At Utrecht University Medical Center, Utrecht, The Netherlands, a study on the feasibility of preoperative single dose ablative radiotherapy in the supine position has recently been completed (≥ 50 years of age with $cT_{1-2}(\max 3.0\text{cm})N_0$ non-lobular carcinoma), delivering 20 Gy to the tumor and 15 Gy to the clinical target volume. Details on these studies have been previously published [13,15,16,24].

For the current study, data was obtained from the first 10 patients treated in the supine position in the Dutch study and 10 patients treated with 21 Gy in the prone position, matched for breast size. A waiver exempting additional informed consent was acquired from the Institutional Review Boards of both participating institutes.

2.2. Treatment imaging and planning

For patients treated in the prone position, a preoperative diagnostic or treatment planning 1.5T or 3.0T contrast-enhanced

(CE)-MRI and planning CT-scan using a CDR® prone breast board were available. For patients treated in the supine position, a preoperative diagnostic 1.5T or 3.0T CE-MRI, and a CE-planning 1.5T MRI and CE-planning CT-scan in the supine position were available. The first two patients were scanned on a supine board at 10° incline on a C-qual® and MRI-compatible Thorawedge board®. The remaining 8 patients were scanned at 5° incline on an adapted MRI-compatible Macromedics® breast board. For all patients, the gross tumor volume (GTV) had been contoured previously on the planning-CT by the treating breast radiation oncologist based on the fused images with the diagnostic and/or planning MRI. The GTV was uniformly expanded by 20 mm to create a clinical target volume (CTV). The chest wall and the first 5 mm from the external body surface were excluded from the CTV. A 3 mm margin was employed to generate the planning target volume (PTV). The first 5 mm from the external body surface were excluded from the PTV. This PTV margin is in concordance to the PTV margin employed in the supine clinical study, aiming at an objective dosimetric comparison to the clinical plans. A PTV was defined for the GTV as well as the CTV, resulting in a PTV_{GTV} and PTV_{CTV} , respectively. Organs at risk (OAR) such as heart, lungs, breasts, and chest wall had been previously delineated [16]. The skin was defined as the first 5 mm of the external body surface in the ipsilateral breast.

Intensity modulated radiotherapy (IMRT) plans with 7 coplanar beams in the presence of a 1.5T magnetic field were created using Monaco® (version 5.19.01, Elekta AB, Stockholm, Sweden) on the planning CT-scans. The MRI-linac technical features are incorporated in this software. The linac is equipped with a multileaf collimator housing 160 leaves with a projected width of a single leaf of 0.72 cm at the isocenter [25]. In the MRI-linac, the flattening filter free 7MV photon beam can rotate a full 360° around the patient with maximum field size of 22 cm longitudinal and 57.4 cm lateral. The isocenter is fixed at 14.3 cm above the treatment couch.

All plans were generated by one experienced radiation dosimetrist. The maximum amount of segments in the treatment planning software was set at 100. Dose prescription, coverage requirements and organ at risk (OAR) constraints were utilized as currently employed in the Dutch study for single dose APBI in the supine position [15]. The rationale for this possibly ablative treatment approach, prescribed dose and development of the organs at risk constraints have been previously described [15]. An integrated boost was utilized, with 20 Gy delivered to the GTV and 15 Gy delivered to the CTV, since this is also the intended prescription dose for future MRI-linac treatments. Adequate coverage of the target volume with doses as low as reasonably possible to the OAR was prioritized. Adequate coverage was defined as at least 99% of the $PTV_{GTV/CTV}$ receiving at least 95% of the prescribed dose to the GTV or CTV, respectively. The employed OAR constraints were a $D_{\text{mean}} < 3.6$ Gy to the ipsilateral lung, a $V_{2.8\text{Gy}} < 10\%$ and $V_{4.7\text{Gy}} < 5\%$ to the heart, a $D_{20\text{cc}} < 16.3$ Gy to the chest wall, and a $D_{1\text{cc}} < 12$ Gy to the skin or a $D_{1\text{cc}} < 16$ Gy if the CTV aligned the skin [15]. Dose to the ipsilateral and contralateral breast was kept as low as possible.

2.3. Comparison to clinical treatment plans

In order to compare the MRI-linac plans to the actual delivered clinical plans in the prone or supine position, the OAR dosimetry was extracted from the clinical treatment planning systems. For the supine treatment position, the clinical plans attained the same prescription dose, target volume definition, and OAR constraints, however volumetric modulated arc therapy (VMAT) instead of IMRT was utilized for treatment plan optimization. For the prone position, the main differences compared to the MRI-linac treatment characteristics were a uniform dose prescription (i.e. 21 Gy to the GTV and CTV), a smaller CTV definition (i.e. 1.5 cm instead

of 2.0 cm from the GTV) and different OAR-constraints [24]. Given the variation in techniques and prescribed dose, a pairwise individual comparison was not applied between the MRI-linac and the clinical plans.

2.4. Statistical analysis

According to the R-IDEAL design for RT-based innovations, a sample size of 20 patients should be adequate for this predicate study [23]. The primary study endpoint was defined as the percentage of feasible plans with respect to target coverage and OAR constraints. Secondary study endpoints entailed the dosimetric differences between the prone versus the supine treatment position, and dosimetric differences between the MRI-linac plans versus the corresponding clinical treatment plans. These differences were described quantitatively; no statistical tests were performed given the limited number of 10 patients. Patient and treatment planning characteristics were evaluated using descriptive statistics. Medians and interquartile ranges (IQR) were employed for continuous variables and frequencies for discrete variables. All analyses were performed in IBM SPSS Statistics® version 22.

3. Results

3.1. Baseline characteristics

Tumor and target volume characteristics of the 20 patients are presented in Table 1. For the total group of patients (n = 20), the median GTV, CTV and PTV_{CTV} was 0.9 cc (IQR 0.5–1.4 cc), 73.4 cc (IQR 66.5–84.0 cc), and 103.0 cc (IQR 94.8–115.2 cc), respectively, with a median PTV_{CTV} to ipsilateral breast ratio of 9.0% (IQR 7.6–12.8%).

3.2. MRI-linac plans overall

Adequate target coverage and the predefined ipsilateral lung, heart, and chest wall constraints were achieved in all plans. The CTV extended to the first 5 mm of the external body surface (i.e. skin) in 19 out of 20 patients. The D_{1cc} < 12 Gy skin constraint was only feasible in 2 patients, one treated in the prone and one treated in the supine position. The D_{1cc} of the skin was below 16 Gy in all patients. In the total group of patients, the mean ipsi-

Table 1
Baseline and target volume characteristics.

	Prone position Median (IQR) (n = 10)	Supine position Median (IQR) (n = 10)
Tumor lateralisation (%)		
- Left	40%	50%
- Right	60%	50%
Tumor location (%)		
- Central	50%	20%
- Medial quadrant	20%	30%
- Lateral quadrant	30%	50%
Gross tumor volume (cc)	0.6 (0.3–1.3)	1.1 (0.7–2.0)
Clinical target volume (cc)	74.0 (58.7–85.6)	72.9 (67.5–86.3)
Planning target volume [*] (PTV) (cc)	100.1 (78.4–113.1)	104.9 (95.5–121.9)
Ipsilateral breast volume (cc)	1119.8 (824.3–1480.1)	1116.5 (1000.2–1269.7)
Ratio PTV/ipsilateral breast (%)	8.9% (7.2–9.8)	11.6% (7.6–13.8)

* Median and interquartile range unless otherwise specified.

** Clinical target volume with an additional 3 mm margin.

lateral breast volume receiving half of the prescription dose to the GTV (i.e. 10 Gy) was 20% (IQR 15.6–22.8%).

3.3. Prone versus supine MRI-linac plan

Coverage, inhomogeneity (i.e. overdosage) and OAR dosimetry across the two treatment approaches are illustrated in Table 2. Representative dose distributions are illustrated in Fig. 1. In the MRI-linac plans, the differences in median D_{20cc} chest wall and mean lung dose were Δ8.1 Gy and Δ0.5 Gy, respectively, in favor of the prone position (Table 2, Fig. 2). Differences in heart and skin dosimetry between the two approaches fluctuated across various parameters (Table 2, Fig. 3) and therefore no treatment position was clearly more beneficial. The dose to the ipsilateral or contralateral breast appeared not to be associated with a specific treatment position (Table 2).

3.4. Clinical versus MRI-linac plan in the supine treatment position

In the actual delivered plans in the supine group, the median values of the mean ipsilateral breast, ipsilateral lung, and heart dose were 4.5 Gy (IQR 3.9–5.3 Gy), 1.4 Gy (IQR 0.8–1.6 Gy), and 0.7 Gy (IQR 0.5–0.9 Gy), respectively (data not shown). In the

Table 2

Dosimetry of single dose MR-linac based treatment in the prone and supine position with a 20 Gy and 15 Gy prescribed dose to the gross tumor volume (GTV) and clinical target volume (CTV), respectively.

	Prone position Median (IQR) (n = 10)	Supine position Median (IQR) (n = 10)
Coverage		
• V _{95%} PTV _{GTV} (%) [*]	99.7 (99.1–100)	99.3 (98.7–99.9)
• mean dose PTV _{GTV} (Gy)	20.1 (20.0–20.1)	20.1 Gy (20.0–20.1)
• V _{95%} PTV _{CTV} (%) [*]	99.6 (99.2–99.8)	99.0 (99.0–99.3)
• mean dose PTV _{CTV} (Gy)	15.7 (15.7–15.9)	16.1 (15.9–16.3)
Overdosage (%)		
• V _{19Gy} PTV _{CTV}	5.1 (4.1–6.5)	8.8 (6.1–10.5)
• V _{21Gy} PTV _{CTV}	0 (0–0)	0 (0–0)
Dose to organs at risk		
Ipsilateral breast		
• V _{100%} PD _{CTV} (%)	7.2 (5.7–8.1)	7.8 (6.9–10.8)
• V _{50%} PD _{CTV} (%)	25.6 (20.8–28.9)	26.3 (20.3–29.6)
• V _{100%} PD _{GTV} (%)	0.2 (0.1–0.3)	0.4 (0.2–0.6)
• V _{50%} PD _{GTV} (%)	20.0 (16.6–22.9)	19.9 (14.8–23.2)
• mean dose (Gy)	4.6 (3.9–5.0)	4.6 (3.8–5.4)
Skin		
• D _{1cc}	15.0 (14.7–15.3)	14.7 (14.0–15.4)
• D _{10cc}	13.4 (12.4–13.9)	11.8 (10.6–12.9)
• V _{12Gy}	17.3 (11.7–22.8)	9.6 (5.9–13.9)
Heart		
• mean dose (Gy)	0.8 (0.5–1.0)	0.8 (0.5–1.1)
• V _{2.8Gy} (%)	0 (0–0.7)	3.2 (0–4.6)
Chest wall		
• D _{20cc} (Gy)	4.3 (2.2–5.2)	12.4 (9.9–13.5)
Ipsilateral lung		
• mean dose (Gy)	0.4 (0.3–0.6)	0.9 (0.6–1.1)
Contralateral breast		
• D _{max} (Gy)	2.7 (2.4–3.1)	2.0 (1.6–3.1)
Treatment delivery		
• No. segments	95.5 (93.0–96.3)	82.4 (79.0–90.3)
• No. monitor units	4765.9 (4450.0–5047.9)	5442.6 (5014.6–6024.7)
• Delivery time (s)	852.5 (766.7–870.1)	892.3 (839.6–984.3)

* V_{xx%} = volume receiving xx% of the prescribed dose to the CTV (15 Gy), GTV (20 Gy) or a certain no. of Gy.

** Prescribed dose; IQR = interquartile range;

PTV_{GTV/CTV} – planning target volume of the CTV/GTV.

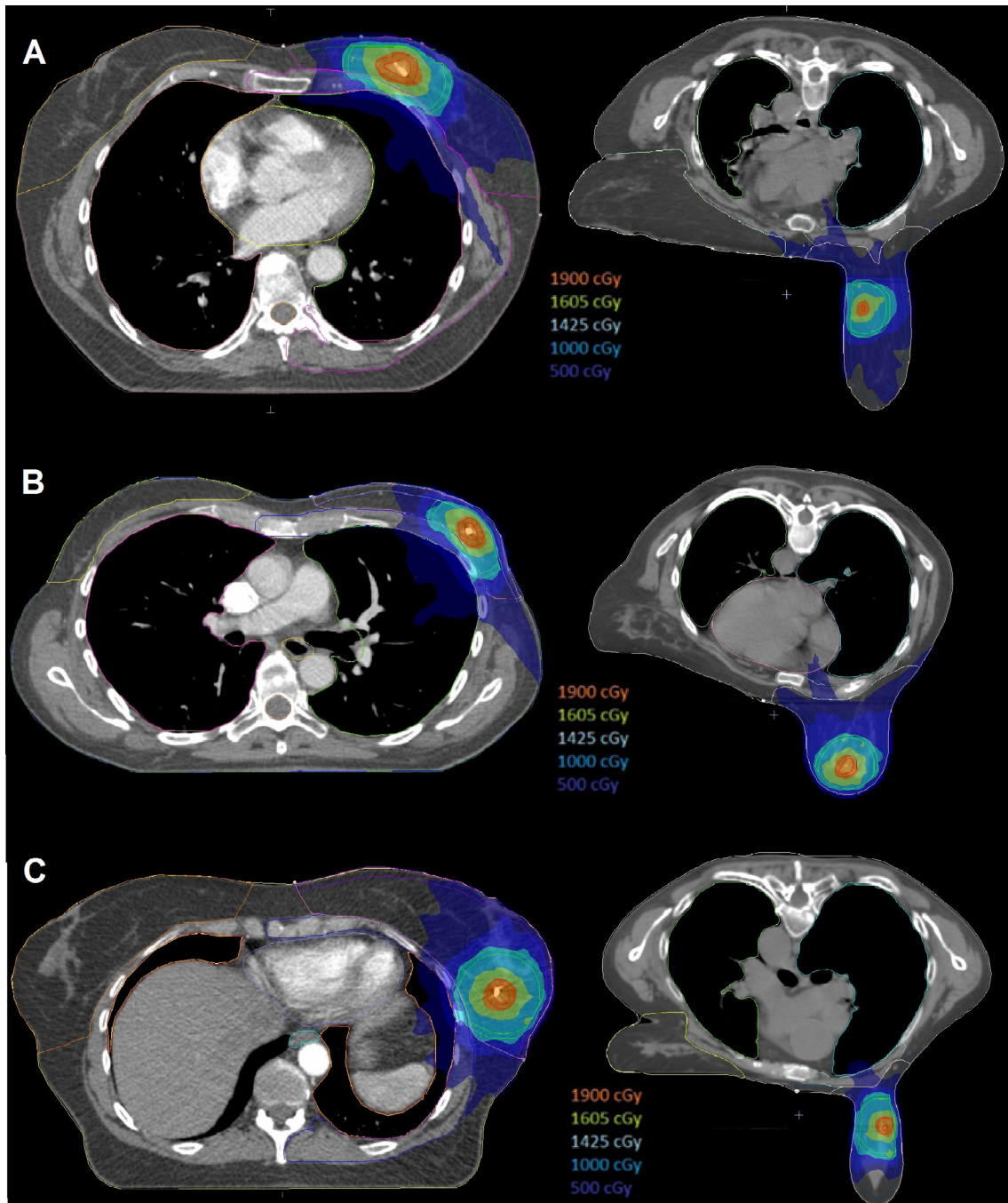


Fig. 1. Representative dose distributions for a medial (A), central (B) and lateral (C) tumor illustrating heart, ipsilateral lung and chest wall volumes receiving less dose in the prone versus supine treatment position.

MRI-linac plans, the median differences in mean ipsilateral breast, ipsilateral lung, and heart dose were below 1 Gy (i.e. $+\Delta 0.1$ Gy, $-\Delta 0.5$ Gy and $+\Delta 0.1$ Gy, respectively (Table 2)), compared to the clinical plans.

3.5. Clinical versus MRI-linac plan in the prone treatment position

In the actual delivered plans in the prone group, the median values of the mean ipsilateral breast, ipsilateral lung, and heart dose were 3.8 Gy (IQR 3.1–4.4 Gy), 0.3 Gy (IQR 0.2–0.4 Gy) and 0.1 Gy (IQR 0.0–0.3 Gy), respectively (data not shown). In the current prone MRI-linac plans, the median differences in mean ipsilateral breast, ipsilateral lung, and heart dose were again below 1 Gy

(i.e. $+\Delta 0.8$, $+\Delta 0.1$ and $+\Delta 0.7$), despite a larger target volume compared to the actual delivered plans.

Differences in various skin parameters between the MRI-linac and clinical delivered plans are illustrated in Table 3.

3.6. Technical feasibility

In all patients treated in the supine position, the isocenter was located within the body contour, mostly at mid-mediastinal position. In patients treated in the prone position, the fixed isocenter was located outside the body contour, in the midline, due to the position of the breast board. All patients treated in the prone position, would have fit the 70 cm MRI-linac bore, given that the

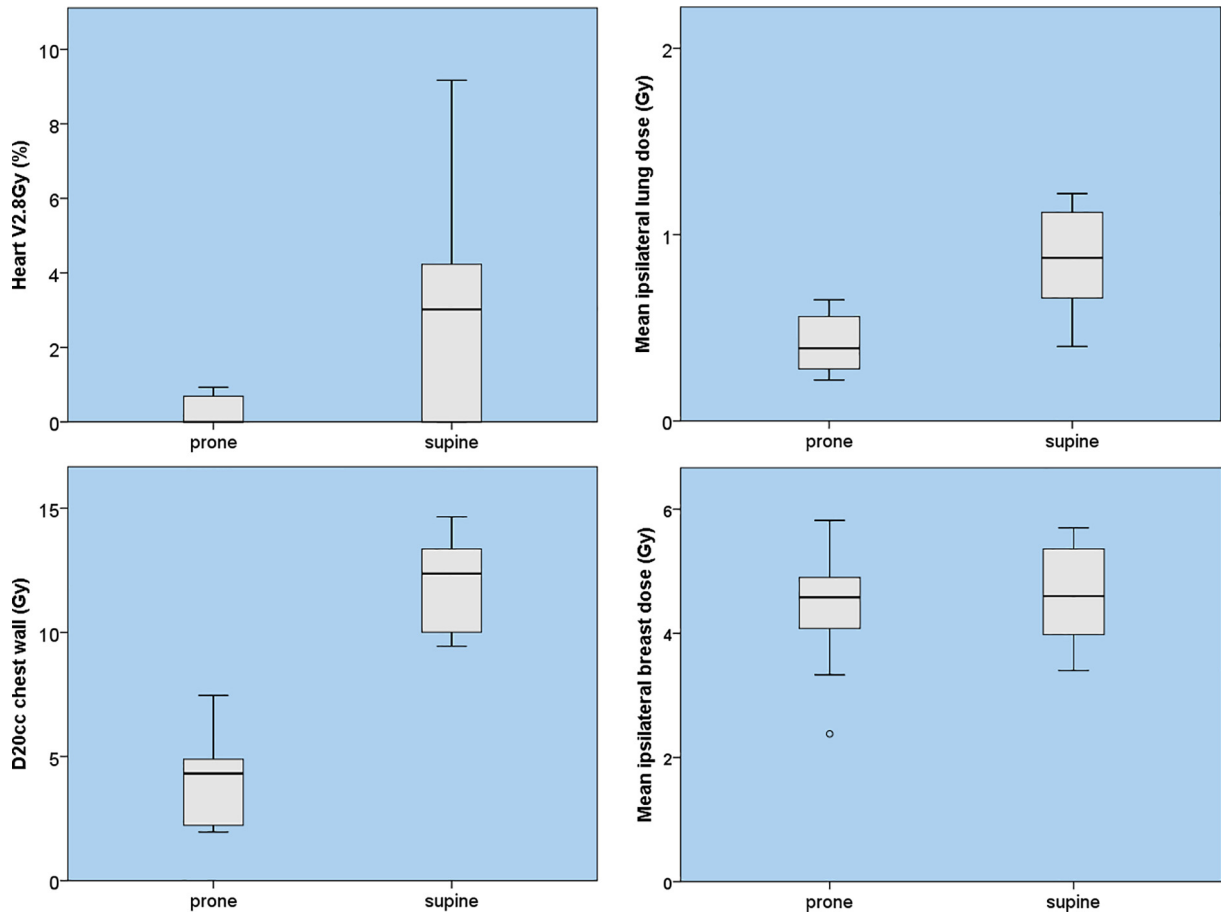


Fig. 2. Boxplot illustrating the V_{2.8Gy} dose to the heart, mean ipsilateral lung dose, D_{20cc} dose to the chest wall and mean ipsilateral breast dose with the prone versus supine treatment position.

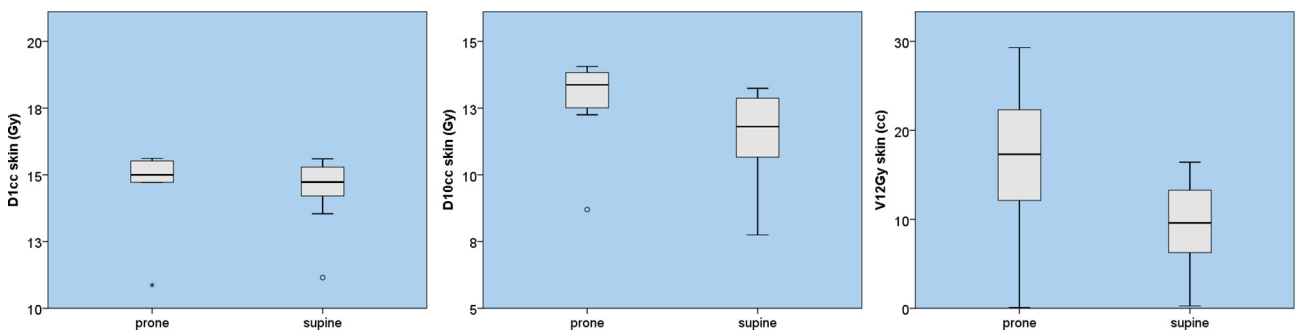


Fig. 3. Boxplot illustrating the variation in dosimetric skin parameters between the prone and supine treatment position.

Table 3

Comparison of skin parameters between the clinical and MRI-linac treatment plans in the prone and supine treatment position.

	Supine position		Prone position [*]	
	Median (IQR) (n = 10)		Median (IQR) (n = 10)	
	MRI-linac plan	Clinical plan	MRI-linac plan	Clinical plan
D _{1cc} skin (Gy)	14.7 (14.0–15.4)	14.7 (13.6–15.7)	15.0 (14.7–15.3)	16.8 (14.2–18.3)
D _{10cc} skin (Gy)	11.8 (10.6–12.9)	12.2 (10.1–12.7)	13.4 (12.4–13.9)	11.9 (10.4–14.6)
V _{12Gy} skin (cc)	9.6 (5.9–13.9)	10.8 (4.5–13.4)	17.3 (11.7–22.8)	9.8 (4.7–18.0)

^{*} In the clinical plans, a uniform 21 Gy dose was prescribed to the clinical target volume (CTV) including the gross tumor volume (GTV) whereas in the MRI-linac plans an integrated boost of 15/20 Gy was prescribed to the CTV/GTV, respectively.

largest measured distance from the table to the most posterior extent of the patient was 44 cm. No virtual collision issues were encountered in patients treated in either position.

4. Discussion

To our knowledge, the current study is the first to address the dosimetric feasibility of a prone and supine treatment approach using an MRI-linac for single dose preoperative APBI. When setting up the current study, we presumed that certain technical specifications of the MRI-linac and treatment position might negatively alter treatment planning and therefore dosimetric feasibility of the predefined OAR constraints, compared to conventional CT-linac based treatment. Nonetheless, our results showed that single dose APBI on the MRI-linac is feasible with respect to adequate target volume coverage and acceptable normal tissue doses, in both the prone and supine treatment position. Preliminary OAR dosimetry favored a prone approach.

Two previous studies have focused on magnetic field dose effects for postoperative RT in the supine position [26,27]. Van Heijst *et al* investigated the magnetic-field impact on skin dose with WBI (42.56 Gy in 16 fractions, 2-field forward IMRT) and APBI (38.5 Gy in 10 fractions, 7-field IMRT) at 0T, 0.35T and 1.5T [26]. A negative impact of the magnetic field was more prominent in WBI, whereas with APBI, its effect on the skin was perceived as negligible. Other OARs were not adversely influenced by the magnetic field. Kim *et al* analyzed the 1.5T magnetic field dose effects using a tangential beam arrangement, 5-beam IMRT, and VMAT for APBI delivered in 8 fractions of 5 Gy [27]. Heart and lung doses were minimally impacted by the magnetic field. Depending on the skin parameter and definition (i.e. first 3 mm versus 5 mm subcutaneous tissue), some negative impact on dosimetry could be observed. Nonetheless, for some skin parameters (e.g. D_{1cc}) this could be mitigated by increasing the number of beams (i.e. 5-beam IMRT versus tangential field). At first glance, these two studies might appear conflicting with respect to the evaluated impact of the magnetic field in APBI, probably due to variations in skin definition and parameters (e.g. mean dose, D_{1cc} , D_{2cc}), and significance level of observed differences (i.e. α 0.05 versus 0.10). Nonetheless, both studies conclude that additional beams reduce the skin dose and the magnetic field does not compromise other OAR dosimetry. In our study, we observed that for both positions the OARs were not compromised. This is further strengthened by the comparison of the clinical and MRI-linac plans in supine position with the same prescribed dose, and similar constraints during treatment plan optimization, with minor absolute dosimetric differences, including skin parameters (Table 3). Therefore, limited clinical impact is anticipated, nonetheless these findings will need to be confirmed in future MRI-linac clinical trials to establish safety and tolerability. For the prone MRI-linac plans, a direct comparison of the MRI-linac to the actual delivered plans is partially impeded by differences in CTV margin, prescription dose (i.e. 21 Gy versus 15/20 Gy) and OARs constraints for plan optimization. Still, one observation is interesting for description: despite the lower 15/20 Gy prescribed dose with the MRI-linac plans, the median V_{12Gy} was higher, 17.3 cc versus 9.8 cc compared to the prone clinical plans with a 21 Gy prescribed dose (Table 3). This is likely attributable to the increase in CTV margin from 1.5 cm utilized in the clinical plans to a 2.0 cm extension from GTV in the MRI-linac plans.

Our institutions have focused on the concept of single dose preoperative APBI to enable a radiosurgical approach in low-risk breast cancer. Since CT-based target delineation may be suboptimal due to the reduced soft tissue contrast differentiation, MRI-guided targeting may be uniquely suited to this approach [11,12]. The MRI-linac could have the potential to minimize the

PTV margin. Moreover, since the set-up error might increase in prone compared to supine treatment position, on-line imaging could also account for position verification issues. This might result in decreased irradiated volumes and a further decrease of RT-induced toxicity. In the context of post-operative APBI, due to the elongation of the tumor bed in the prone position, the mean CTV and PTV volumes are significantly higher for patients treated prone versus supine [28]. At the same time, prone positioning appears to be more beneficial with respect to non-target tissue dosimetry, especially in patients with right-breast cancers or left-breast cancers in women with large breasts [29]. This is in line with our observation given the mean dose to the ipsilateral lung, $V_{2.8Gy}$ heart and especially D_{20cc} chest wall which appear to be smaller in the prone treatment position (Table 2, Fig. 2). A prerequisite for a radiosurgical approach in early-stage breast cancer concerns adequate dose prescription and the importance of high biological effective doses (BED) for local tumor control, as illustrated in the case of stereotactic RT in early-stage lung cancer [30]. Compared to an offline, MRI-guided approach to the intact tumor, real-time tumor imaging with the MRI-linac allows potentially for plan adaptation strategies, and thus BED escalation for high-risk tissue, possibly further enhancing the local tumor control probability. Furthermore, from a patient's perspective, an MRI-linac based single dose APBI might provide less burdening invasive procedures, e.g. no additional fiducial marker is required for position verification. Moreover, a pseudo-CT-scan based on the online MR-images, instead of a separate RT planning-CT, might be sufficient for treatment planning.

Still, certain limitations of the current study have to be addressed. First, the practical feasibility of the single dose MRI-linac treatment approach for breast cancer patients is still under investigation. Also, similar PTV margins to the clinical plans were used for the MRI-linac, since at this stage of research it is yet unknown what the extent of this PTV margin should be, whereas smaller MRI-linac margins would more easily result in feasible coverage and OAR dosimetry. At our department, a clinical study is currently ongoing towards the development of an adaptive MRI-linac workflow in the supine and the prone position, thereby also including the practical feasibility of various breast boards, treatment time delivery considerations, comfort evaluation for breast cancer patients and evaluation of the most adequate PTV-margin. Second, evaluation of the prone and supine treatment approach has been done with distinct patients (e.g. variation in Body Mass Index, tumor localization in breast quadrant, more left-sided breast cancer in patients treated in the supine position) rather than in a pairwise fashion and thus may not fully capture dosimetric differences between the supine and prone position when using an MRI-linac. We therefore cannot elaborate on specific treatment positions being more favorable for specific patients. Furthermore, it has to be noted that the clinical and MRI-linac plans in the prone position have been performed with a different prescribed dose, CTV and PTV definitions and therefore a direct dosimetric comparison was not possible. Nonetheless, our main study goal was to investigate the dosimetric feasibility according to actually utilized clinical predefined constraints, which we could evaluate based on our data. Our results thus far are encouraging in both treatment positions, nonetheless MRI-linac based single dose ablative APBI as radiosurgical alternative to current breast conserving therapy in early-stage breast cancer will of course need to be confirmed in the clinical setting.

5. Conclusion

Single dose APBI on the MRI-linac to the intact tumor is dosimetrically feasible in both the supine and prone position for early-stage low-risk breast cancer. Although dose constraints were

met for both treatment positions, OAR dosimetry might favor a prone treatment position.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.ctro.2018.09.001>.

References

- [1] Vaidya JS, Wenz F, Bulsara M, et al. Risk-adapted targeted intraoperative radiotherapy versus whole-breast radiotherapy for breast cancer: 5-year results for local control and overall survival from the TARGIT-A randomised trial. *Lancet* 2013.
- [2] Polgar C, Fodor J, Major T, et al. Breast-conserving therapy with partial or whole breast irradiation: ten-year results of the Budapest randomized trial. *Radiother Oncol* 2013;108(2):197–202.
- [3] Coles CE, Griffin CL, Kirby AM, et al. Partial-breast radiotherapy after breast conservation surgery for patients with early breast cancer (UK IMPORT LOW trial): 5-year results from a multicentre, randomised, controlled, phase 3, non-inferiority trial. *Lancet* 2017;390(10099):1048–60.
- [4] Polgár C, Ott OJ, Hildebrandt G, et al. Late side-effects and cosmetic results of accelerated partial breast irradiation with interstitial brachytherapy versus whole-breast irradiation after breast-conserving surgery for low-risk invasive and in-situ carcinoma of the female breast: 5-year results of a randomised, controlled, phase 3 trial. *Lancet Oncol* 2017;18(2):259–68.
- [5] Livi L, Meattini I, Marrazzo L, et al. Accelerated partial-breast irradiation using intensity-modulated radiotherapy versus wholebreast irradiation: 5-year survival analysis of a phase 3 randomised controlled trial. *Eur J Cancer* 2015;51:451–63.
- [6] Rodriguez N, Sanz X, Dengra J, et al. Five-year outcomes, cosmesis, and toxicity with 3-dimensional conformal external beam radiation therapy to deliver accelerated partial breast irradiation. *Int J Radiat Oncol Biol Phys* 2013;87(5):1051–7.
- [7] van Mourik AM, Elkhuizen PH, Minkema D, et al. Multiinstitutional study on target volume delineation variation in breast radiotherapy in the presence of guidelines. *Radiother Oncol* 2010;94(3):286–91.
- [8] Van der Leij F, Elkhuizen PH, Janssen TM, et al. Target volume delineation in external beam partial breast irradiation: less inter-observer variation with preoperative – compared to postoperative delineation. *Radiother Oncol* 2014;110(3):467–70.
- [9] Nichols EM, Dhople AA, Mohiuddin MM, et al. Comparative analysis of the post-lumpectomy target volume versus the use of pre-lumpectomy tumor volume for early-stage breast cancer: implications for the future. *Int J Radiat Oncol Biol Phys* 2010;77(1):197–202.
- [10] Di Leo G, Trimboli RM, Benedek A, et al. MR imaging for selection of patients for partial breast irradiation: a systematic review and meta-analysis. *Radiology* 2015;277(3):716–26.
- [11] Schmitz AC, van den Bosch MA, Loo CE, et al. Precise correlation between MRI and histopathology – exploring treatment margins for MRI-guided localized breast cancer therapy. *Radiother Oncol* 2010;97(2):225–32.
- [12] den Hartogh MD, Philippens MEP, van Dam IE, et al. MRI and CT imaging for preoperative target volume delineation in breast-conserving therapy. *Radiat Oncol* 2014;26(9).
- [13] Horton JK, Blitzblau JC, Yoo S, et al. Preoperative single-fraction partial breast radiation therapy: a novel phase 1 Dose escalation protocol with radiation response biomarkers. *Int J Radiat Oncol Biol Phys* 2015;92:846–55.
- [14] Charaghvandi RK, den Hartogh MD, van Ommen AM, et al. MRI-guided single fraction ablative radiotherapy for early-stage breast cancer: a brachytherapy versus volumetric modulated arc therapy dosimetry study. *Radiother Oncol* 2015;117(3):477–82.
- [15] Charaghvandi RK, van Asselen B, Philippens MEP, et al. Redefining radiotherapy for early-stage breast cancer with single dose ablative treatment: a study protocol. *BMC Cancer* 2017;17:181.
- [16] Charaghvandi KR, Yoo S, van Asselen B, et al. Treatment constraints for single dose external beam preoperative partial breast irradiation in early-stage breast cancer. *Clin Transl Radiat Oncol* 2017;6:7–14.
- [17] Horton JK, Siamakpour-Reihani S, Lee CT, et al. FAS death receptor: a breast cancer subtype-specific radiation response biomarker and potential therapeutic target. *Radiat Res* 2015;184(5):456–69.
- [18] Raaymakers BW, Lagendijk JJ, Overweg J, et al. Integrating a 1.5 T MRI scanner with a 6 MV accelerator: proof of concept. *Phys Med Biol* 2009;54(12):N229–37.
- [19] Crijns SP, Raaymakers BW, Lagendijk JJ. Proof of concept of MRI-guided tracked radiation delivery: tracking one-dimensional motion. *Phys Med Biol* 2012;57(23):7863–72.
- [20] Kerkmeijer LG, Fuller CD, Verkooijen HM, et al. The MRI-linear accelerator consortium: evidence-based clinical introduction of an innovation in radiation oncology connecting researchers, methodology, data collection, quality assurance, and technical development. *Front Oncol* 2016;13(6):215.
- [21] Raaijmakers AJE, Raaymakers BW, Lagendijk JJ. Integrating a MRI scanner with a 6 MV radiotherapy accelerator: dose increase at tissue-air interfaces in a lateral magnetic field due to returning electrons. *Phys Med Biol* 2005;50:1363–76.
- [22] Raaijmakers AJE, Raaymakers BW, van der Meer S, et al. Integrating a MRI scanner with a 6 MV radiotherapy accelerator: impact of the surface orientation on the entrance and exit dose due to the transverse magnetic field. *Phys Med Biol* 2007;52:929–39.
- [23] Verkooijen HM, Kerkmeijer LGW, Fuller CD, et al. R-IDEAL: a framework for systematic clinical evaluation of technical innovations in radiation oncology. *Front Oncol* 2017;3(7):59.
- [24] Blitzblau RC, Arya R, Yoo S, Baker JA, Chang Z, Palta M, Duffy E, Horton JK. A phase 1 trial of preoperative partial breast radiation therapy: Patient selection, target delineation, and dose delivery. *Pract Radiat Oncol* 2015;5(5):e513–20. <https://doi.org/10.1016/j.proro.2015.02.002>.
- [25] Raaymakers BW, Jürgenliemk-Schulz IM, Bol GH, et al. First patients treated with a 1.5 T MRI-Linac: clinical proof of concept of a high-precision, high-field MRI guided radiotherapy treatment. *Phys Med Biol* 2017;62(23):L41–50.
- [26] van Heijst TC, den Hartogh MD, Lagendijk JJ, et al. MR-guided breast radiotherapy: feasibility and magnetic-field impact on skin dose. *Phys Med Biol* 2013;58(17):5917–30.
- [27] Kim A, Lim-Reinders S, McCann C, et al. Magnetic field dose effects on different radiation beam geometries for hypofractionated partial breast irradiation. *J Appl Clin Med Phys* 2017;13.
- [28] Lakosi F, Gulyban A, Simoni SB, et al. The influence of treatment position (Prone vs. Supine) on clip displacement, seroma, tumor bed and partial breast target volumes: comparative study. *Pathol Oncol Res* 2016;22(3):493–500.
- [29] Kirby AM, Evans PM, Donovan EM, et al. Prone versus supine positioning for whole and partial-breast radiotherapy: a comparison of non-target tissue dosimetry. *Radiother Oncol* 2010;96(2):178–84.
- [30] Zhang J, Yang F, Li B, et al. Which is the optimal biologically effective dose of stereotactic body radiotherapy for Stage I non-small-cell lung cancer? a meta-analysis. *Int J Radiat Oncol Biol Phys* 2011;81(4):e305–16.