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How to protect the proximal bronchial tree during stereotactic radiotherapy of ultracentral lung tumors: Lessons from MR-guided treatment

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ABSTRACT

Purpose: To use imaging data from stereotactic MR-guided online adaptive radiotherapy (SMART) of ultracentral lung tumors (ULT) for development of a safe non-adaptive approach towards stereotactic body radiotherapy (SBRT) of ULT.

Patients and Methods: Analysis is based on 19 patients with ULT who received SMART (10 × 5.0–5.5 Gy) on a 0.35 T MR-Linac (MRIdian®) in the prospective MAGELLAN trial. 4D-planning CT data of six patients served to quantify proximal bronchial tree (PBT) breathing motion. Daily fraction MRIs are used to calculate interfractional translations (mediolateral (ML), anterior-posterior (AP), superior-inferior (SI)) and their dosimetric consequences for the PBT. A planning risk volume (PRV) is calculated for an assumed non-adaptive SBRT in deep-inspiration breath hold (DIBH) with surface-guidance (AlignRT®). Finally, non-adaptive volumetric modulated arc (VMAT) SBRT is simulated with and without a PRV for N = 10 patients (10 × 5.5 Gy).

Results: The PBT shows relevant breathing motion, especially in superior-inferior direction (median ML: 2.5 mm, AP: 1.9 mm and SI: 9.2 mm). Furthermore, moderate interfractional translations are observed (mean absolute translation ML: 1.3 mm, AP: 1.3 mm, SI: 1.1 mm), with an estimated 2 mm PRV margin for interfractional changes alone. Simulated non-adaptive SBRT leads to PBT overdoses in 60 % of patients (median overdosed fractions VMAT: 2.5, predicted MR-linac plans 4). Both MR-guided online plan adaptation (SMART) and PRV-based non-adaptive VMAT prevent PBT overdoses, but SMART yields significantly higher planning target volume (PTV) coverage (SMART: median 96 % [IQR 95–96], VMAT: median 89 % [IQR 77–94], p = 0.014).

Conclusions: Both intrafractional breathing motion and interfractional translations may impact doses to the PBT during SBRT of ULT. SMART protects the PBT from overdoses while maintaining high PTV coverage. Non-adaptive SBRT appears safe with advanced breathing motion management and PRV, but yields inferior PTV coverage.

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Introduction

Whether stereotactic body radiotherapy (SBRT) of ultracentral lung tumors (ULT) should or should not be performed remains controversial [1]. Early on, SBRT of lung tumors close to the proximal bronchial tree (PBT) has raised concerns about dangerous late toxicity [2–4]. However, a growing body of mainly retrospective literature reports conflicting clinical outcomes after SBRT of ULT [5,6]. Accordingly, the HILUS trial has demonstrated high rates of severe bronchial bleedings [7], whereas the SUNSET trial has reported few severe toxicity [8]. These heterogeneous outcomes likely reflect differences in the definition of "ultracentral" location, SBRT delivery techniques, normal-tissue constraints and clinical risk factors such as bronchial tumor invasion [5,7,9,10]. ULT challenge us with a narrow therapeutic window that calls for modern motion management, reduction of treatment margins and perhaps a more homogeneous dose prescription [11].

Breathing motion is an essential challenge in pulmonary SBRT [12–14]. Additionally, image-guided radiotherapy (IGRT) techniques usually ensure the correct tumor position, but interfractional translations of neighboring organs-at-risk (OAR) remain [15,16]. Stereotactic magnetic resonance (MR)-guided online adaptive radiotherapy (SMART) compensates these uncertainties in an innovative way because it 1) correctly positions the patient with superior soft tissue contrast at the mediastinum, 2) maintains high target coverage while protecting mediastinal OAR via online plan adaptation and 3) minimizes breathing motion through gated dose delivery [15–18]. SMART of ULT has demonstrated encouraging first clinical results [19,20], so that we have launched the prospective MAGELLAN trial [21]. However, MR-guided SBRT remains highly sophisticated and requires increased treatment times and labor expenditure [15,22]. Currently, MR-linacs are only available at specialized centers. Therefore, we use imaging data from the prospective MAGELLAN trial to quantify the breathing motion and interfractional translations of the PBT, and simulated their dosimetric consequences. Thus, we aim to establish a reasonable non-adaptive SBRT technique to safely treat ULT.

Methods

Prospective patient data

Analysis was based on the first 19 patients with ULT who were included into the prospective MAGELLAN trial, which is currently ongoing at the University Hospitals in Heidelberg and Zurich [21]. Briefly, ultracentral location is defined as a planning target volume (PTV) overlap with the PBT or esophagus. The primary trial aim is to find the maximum tolerated dose of SMART to ULT. SBRT dose is escalated from 10 x 5.0 to maximum 10 x 6.5 Gy based on a time-to-event continuous reassessment method (TITE CRM). Patient characteristics are summarized in Table 1.

The trial is conducted according to the declaration of Helsinki and received IRB-approval.

Treatment planning and delivery

Our SMART approach has been described previously [15,21]. In short: patients are treated on an MRIdian® MR-linac (ViewRay) with 6 MV step-and-shoot IMRT. Planning computer tomography (CT) and MRI are performed on the same day, and the CT is deformably registered to the MRI. The gross tumor volume (GTV) is expanded by 2 mm to obtain the clinical target volume (CTV) and by another 3 mm to obtain the PTV. Treatment planning objectives are as follows:

- 95 % of the PTV is covered by the prescribed dose
- at most 2 % of the PTV exceed 125 % of the prescribed dose
- OAR constraints (Supplementary Table 1) are strictly prioritized over target coverage

Table 1
Patient characteristics (N = 19). KPI: Karnofsky Performance Index. FEV 1 s: Forced Expiratory Volume in 1 s. NSCLC: non-small cell lung cancer. ULT: ultracentral lung tumor.

	Median (Q1–Q3)
Age [yrs]	68.0 (61.0–76.0)
KPI [%]	90 (80–100)
FEV 1 s [%]	87.0 (69.0–97.5)
Maximum Tumor Diameter [cm]	2.4 (2.0–2.9)
	N (%)
Sex	
Female	8 (42 %)
Male	11 (58 %)
Treatment Indication	
Early-stage NSCLC	3 (16 %)
Oligometastases	16 (84 %)
Tumor Entity	
NSCLC	9 (47 %)
Sarcoma	3 (16 %)
Colorectal Carcinoma	2 (11 %)
Other	5 (26 %)
ULT type	
Type A	10 (53 %)
Type B	9 (47 %)
Direct bronchial contact	15 (79 %)
Radiation Dose	
10 × 5.0 Gy	9 (47 %)
10 × 5.5 Gy	10 (53 %)

During treatment, patients receive daily on-table MRI which is matched to the baseline MRI based on the GTV. Then, GTV and OAR are re-contoured inside the PTV_{expand} [23], and the plan is re-calculated (predicted) on the daily anatomy. If planning objectives are violated, the treating team creates an adapted plan. Finally, dose is delivered with cineMRI-based gating in repeated breath holds.

Analysis of intra- and interfractional changes

Imaging data was imported into RayStation® 11B (RaySearch, Stockholm, Sweden). In six patients, a 4D planning CT was available (8 breathing phases). We contoured the GTV and PBT on each breathing phase to create an internal gross tumor volume (IGTV) and internal risk volume (IRV), respectively. As the PBT is large and only the small high dose volumes matter (i.e. doses to 0.1–1 cm^3) [7,24], we focused on PBT branches with PTV overlap. Volumes of the IGTV, respective IPTV (total 5 mm margin), IRV and their overlap region were calculated. Moreover, breathing motion amplitudes of the PBT center of mass were quantified in three spatial directions (superior-inferior (SI), medio-lateral (ML), anterior-posterior (AP)). In all 19 patients, PBT contours were reviewed on baseline and daily MRIs, focusing on the overlap of the PBT and the PTV_{expand}. Interfractional translations were quantified for the PBT center of mass in the three spatial directions (SI, ML, AP) together with their mean and standard deviations (std) for each patient. The std of these individual errors were regarded as the systematic error $\Sigma_{interfractional}$ and random error $\sigma_{interfarctional}$.

Subsequently, we estimated planning risk volume (PRV) margins for the PBT in case of non-adaptive SBRT. To minimize breathing motion, we assumed SBRT in deep-inspiration-breath-hold (DIBH). At our department, SBRT in DIBH is performed via surface-guided radiotherapy (SGRT) with the AlignRT system® (Vision RT, London, United Kingdom) [25]. Therefore, we considered intrafractional errors of our SGRT system from the literature [26]: Σ 0.7 (AP), 1.5 (SI), 0.5 (ML) and σ 0.7 (AP), 0.9 (SI), 0.8 (ML). The required PRV margin is calculated according to [27]:

$$PRV(PBT) = 1.5^{*}\Sigma + 0.5^{*}\sigma$$

with

$$\Sigma = \sqrt{\Sigma^2_{interfractional} + \Sigma^2_{intrafractional}}$$

$$\sigma = \sqrt{\sigma^2_{interfractional} + \sigma^2_{intrafractional}}$$

Simulation of non-adaptive SBRT plans

For all patients who received SMART of 10 x 5.5 Gy (N = 10), we simulated a non-adaptive SBRT plan for our conventional linacs (6MV volumetric modulated arc therapy, VMAT) assuming DIBH as described elsewhere [25]. We generated one plan with a PRV and one plan without a PRV around the PBT for each patient. These baseline plans were calculated on the baseline MRI with deformably registered planning CT and then also re-calculated on the daily MRIs. We chose a 2 mm GTV-CTV margin and 5 mm CTV-PTV margin (in total 7 mm) according to our institutional standards. Since standards differ between institutions, we also used a 5 mm GTV-PTV margin to analyze how different margin strategies affect the PTV coverage and the extent of PBT overdoses in ULT. Moreover, we applied a 3 mm PRV margin around the PBT based on the results of our previous analysis. If a PRV was used, the PBT dose constraints were applied to this PRV. Other planning objectives remained unchanged.

Statistics

Intrafractional breathing motion and interfractional translations of the PBT as well as relevant dosimetric parameters of the different SBRT plans were described. The volumetric extent of PBT overdoses was compared between different SBRT plans by paired Wilcoxon signed rank tests. The significance level $\alpha = 0.05$ was chosen. All analyses were performed in Python version 3.10.9.

Results

Breathing motion

We analyzed intrafractional PBT breathing motion based on 4D planning CT in six patients (Fig. 1). The median [IQR] breathing amplitudes were 2.5 [1.9–3.7] mm ML, 1.9 [1.7–3.4] mm AP and 9.2 [5.7–12.3] mm SI (Table 2). Accordingly, the IRV was two times larger than its PBT branch (median [IQR] PBT: 7.4 [3.5–8.7] cm^3, IRV: 13.8 [7.3–19.5] cm^3). Similarly, the IGTV was two times larger than its GTV (GTV: 11.7 [7.8–22.7] cm^3, IGTV: 21.6 [10.3–34.8] cm^3), which led to a 1.5-fold PTV increase (PTV: 31.9 [23.7–55.2] cm^3, IPTV: 49.8 [29.2–73.0] cm^3). Consequently, the overlap between the PTV and the respective region-at-risk doubled (overlap PTV-PBT: 0.9 [0.6–1.2] cm^3, IPTV-IRV: 2.2 [1.8–4.7] cm^3).

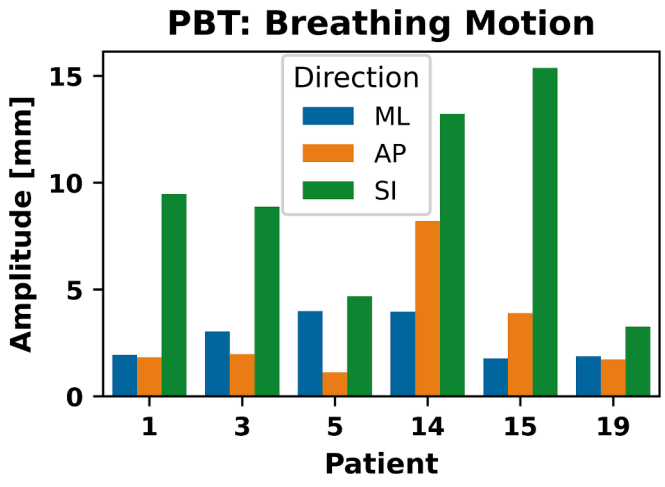

Fig. 1. Breathing motion of the proximal bronchial tree (PBT) for each patient (N = 6). ML: medio-lateral, AP: anterior-posterior, SI: superior-inferior.

Table 2
Analysis of proximal bronchial tree breathing motion and interfractional translations. The planning risk volume (PRV) is calculated according to the formula: PRV = 1.5* Σ + 0.5 * σ, where Σ denotes the systematic error and σ the random error [27]. Intrafraction errors are derived from [26]. ML: medio-lateral, AP: anterior-posterior, SI: superior-inferior, IQR: interquartile range.

	ML	AP	SI
Breathing Motion [mm]			
Median amplitude [IQR]	2.5 [1.9–3.7]	1.9 [1.7–3.4]	9.2 [5.7–12.3]
Interfractional Motion [mm]			
Mean absolute translation	1.3	1.3	1.1
Systematic error Σ	1.4	1.4	0.8
Random error σ	0.9	1.0	1.1
PRV (interfraction errors only)	2.3	2.3	1.6
PRV (inter- and intrafraction errors)	2.6	2.7	2.9

Interfractional PBT translations and PRV margins

We analyzed interfractional PBT translations in all 19 patients. Interfactional PBT translations in the range of −5 to + 5 mm were observed, but the mean absolute translation was only 1.3 mm ML, 1.3 mm AP and 1.1 mm SI (Fig. 2). Further descriptive analyses did not demonstrate an association of interfractional translations with ULT localization, tumor diameter or pulmonary function (Supplementary Figs. 1–3). Based on interfractional translations alone, a PRV margin of 2 mm would be required to avoid overdoses to the PBT in 90 % of non-adapted fractions [27] (Table 2). Further intrafractional uncertainties depend on the applied RT technique. We assumed non-adaptive SBRT in DIBH using SGRT with the AlignRT system® and derived the expected intrafractional translations from previous reports [25,26,28]. This resulted in a comprehensive PRV margin of 3 mm to account for intra- and interfractional translations.

Dosimetry of non-adaptive MR-guided SBRT

We chose all patients who received 10 x 5.5 Gy (N = 10) and compared the daily re-calculated baseline (predicted) plans with the adapted plans. We observed frequent violations of PBT dose constraints in the predicted plans (N = 29 / 100, 29 %). Ten out of 29 violations (35 %) were so enormous that the high dose region became more than three times larger than the volume of the dose constraint (0.33 cm^3) (Fig. 3). Violations occured in six (60 %) patients, with a median of four overdosed fractions per patient (range 1–10). Conversely, none of the adapted plans overdosed the PBT. Consequently, the predicted, non-adaptive, plans presented a statistically significantly higher PBT volume that receives ≥ 105 % of the prescribed dose (predicted: median 0.11 cm^3 [IQR 0.02–0.44 cm^3], adapted: 0.08 cm^3 [0.03–0.16 cm^3], $p < 0.0001$) and a statistically significantly higher PBT D_{max} (predicted: 59.7 Gy [57.9–62.0 Gy], adapted: median 58.7 Gy [58.1–59.7 Gy], $p < 0.0001$).

Dosimetry comparison of SMART and non-adaptive SBRT

For the same ten patients who received 10 x 5.5 Gy SMART, we calculated 6 MV VMAT plans with and without a PRV around the PBT to simulate non-adaptive SBRT in DIBH. According to our institutional standards, we applied a total 7 mm GTV-PTV margin. In two cases (20 %), the plan without PRV already complied with the dose constraints for the PRV and was used for both scenarios. Baseline MR-linac plans demonstrated a trend towards better PTV coverage with the prescribed dose when compared to VMAT plans without PRV (MR-linac: median 96 % [IQR 95–96], VMAT without PRV: 95 % [90–96], p = 0.13), and a significantly better PTV coverage when compared to VMAT plans with PRV (VMAT with PRV: 89 % [77–94], p = 0.014). Both VMAT plans

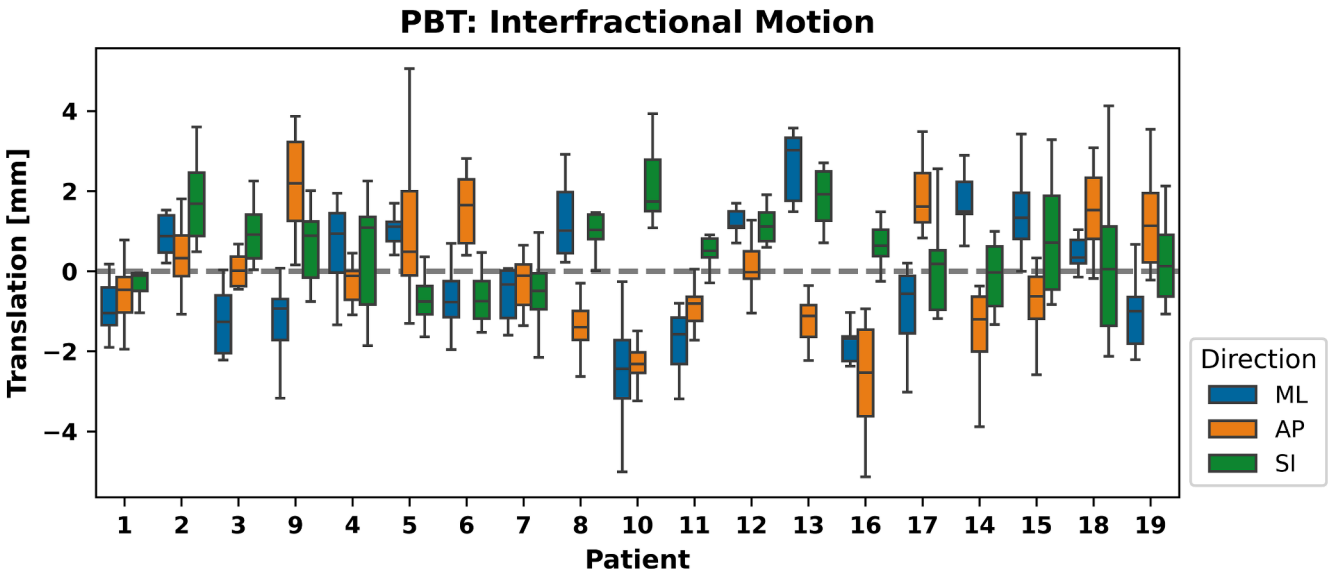

Fig. 2. Interfractional translations of the proximal bronchial tree (PBT) for each patient (N = 19). ML: medio-lateral, AP: anterior-posterior, SI: superior-inferior.

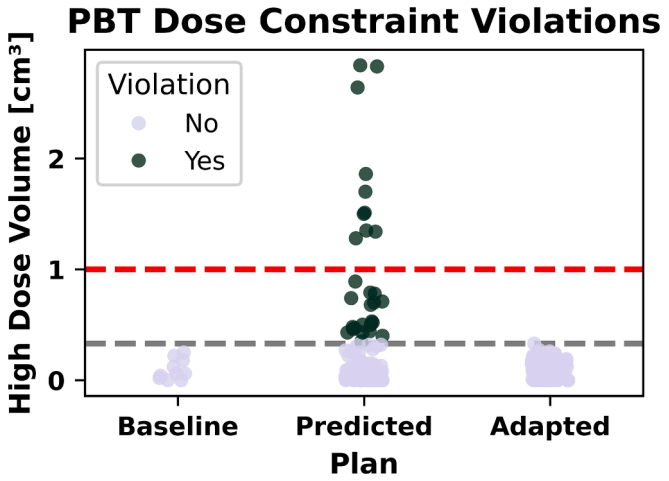

Fig. 3. High dose volume of the proximal bronchial tree (PBT) during MR-guided treatment. The PBT volume ≥ 105 % of the prescribed dose (= 57.75 Gy) is shown. Grey line: Dose constraint of 0.33 cm^3. Red line: 1 cm^3, three times the dose constraint. Black dots represent violations of the dose constraint. Left: Baseline plans, middle: predicted plans (baseline plan re-calculated on daily anatomy), right: adapted plans. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

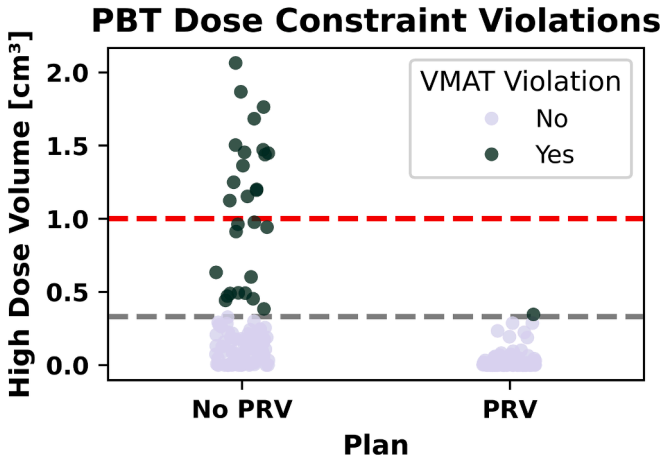

Fig. 4. High dose volume of the proximal bronchial tree (PBT) for VMAT plans with and without a planning risk volume (PRV). The PBT volume ≥ 105 % of the prescribed dose (= 57.75 Gy) is shown. Grey line: Dose constraint of 0.33 cm^3. Red line: 1 cm^3, three times the dose constraint. Black dots represent violations of the dose constraint. Left: Baseline plans, middle: predicted plans (baseline plan re-calculated on daily anatomy), right: adapted plans. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

yielded significantly lower mean lung doses, and VMAT plans with PRV also yielded significantly lower spinal cord maximum doses than baseline MR-linac plans. Otherwise, OAR doses were comparable (Supplementary Table 2).

VMAT plans without PRV demonstrated frequent daily violations of the PBT dose constraint (N = 28 / 100, 28 %). 15 out of 28 violations (54 %) were so enormous that the high dose region became more than three times larger than the initial volume of the dose constraint (0.33 cm^3) (Fig. 4). Violations occured in six (60 %) patients, with a median of 2.5 overdosed fractions per patient (range 1–10). Conversely, application of the PRV margin prevented PBT overdoses in all but one single fraction, where a mild overdose occurred. Accordingly, the VMAT plans without PRV presented a significantly higher PBT volume that receives ≥ 105 % of the prescribed dose (No PRV: median 0.17 cm^3 [IQR 0.05–0.46 cm^3], PRV: 0 cm^3 [0–0.02 cm^3], $p < 0.0001$) and a significantly higher PBT D_{max} (No PRV: 61.9 Gy [60.5–63.3 Gy], PRV: median 58.7 Gy [57.3–59.9 Gy], $p < 0.0001$) over all treatment fractions.

Finally, we repeated the analyses for VMAT plans with a 5 mm GTV-PTV margin, which increased PTV coverages and decreased OAR doses in general (Supplementary Table 3). MR-linac plans still showed better PTV coverage than VMAT plans with PRV, but a statistical significance was not reached (MR-linac: 96 % [95–96], VMAT with PRV: 93 % [87–97], $p = 0.13$). Similar to the scenario with larger PTV margins, violations of the PBT dose constraint occurred more frequently and to a greater extent in VMAT plans without PRV versus with PRV (without PRV: N = 28 / 100, 28 %; with PRV: N = 5 / 100, 5 %) (Supplementary Fig. 4). Hence, the VMAT plans without PRV presented a significantly higher PBT volume that receives ≥ 105 % of the prescribed dose (No PRV: 0.13 cm^3 [0.02–0.37 cm^3], PRV: 0 cm^3 [0–0.03 cm^3], $p < 0.0001$) and a significantly higher PBT D_{max} (No PRV: 61.5 Gy [60.3–63.5 Gy], PRV: median 58.2 Gy [57.1–60.4 Gy], $p < 0.0001$) over all treatment fractions.

Discussion

SBRT of ULT poses a clinical challenge, which might be addressed by SMART [15,16,29]. However, maintenance of an MR-linac is expensive, and many institutions do not have the opportunity to offer MR-guided treatment. Hence, our aim was to develop a safe non-adaptive approach to ultracentral SBRT.

First, we quantified the breathing motion of the PBT. As expected, the largest amplitude was observed in SI direction. Our findings align with Habermann et al. [13]. Furthermore, we observed the IRV to be twice as large as the original PBT branch. Habermann et al. [13] and Nardone et al. [14] found the IRV to be approximately 40–50 % larger than the whole PBT. Our focus on the PBT branch next to the PTV may explain the observed discrepancies and highlights the particular significance of PBT motion in ultracentral SBRT. Estimating the dosimetric impact of gross breathing motions is challenging because a 4D CT yields a short and artificial snapshot of the patient's breathing pattern [30]. Moreover, times spent in each reconstructed breathing phase varies. When calculating doses inside the IRV instead of the PBT contour on average CT, Nardone et al. found dose constraint violations in 42 % of centrally located lung tumors [14], while Habermann et al. estimated an NTCP increase of 3–23 % [13]. All in all, breathing motion should be minimized, and we suggest SBRT in DIBH as an alternative to MR-guided treatment.

Data from MR-guided treatment allows accurate quantification of interfractional changes. Even though interfactional PBT translations are moderate, they lead to frequent and sometimes extensive PBT overdoses. Both frequency and extent of overdoses was higher than we expected [15], which is likely due to our focus on ULT. Daily plan adaptation avoided all PBT overdoses, which underlines the utility of SMART for ULT. Additionally, our data supports the hypothesis that very inhomogeneous dose prescription, e.g. in the HILUS trial, carries a risk for severe overdoses [11] and should be avoided in ULT [5]. Previous reports corroborate our results. Henke et al. performed online plan adaptation in 28 % of fractions during ultracentral SBRT due to OAR constraint violations [29], while Finazzi et al. reported that they reduced OAR constraint violations by 20 % with SMART [16].

Without online-adaptive treatment techniques, PRVs might offer an alternative to protect OAR [27,31]. We estimated a 3 mm-PRV margin for the PBT to compensate for both inter- and intrafractional errors during SBRT in DIBH. Intrafractional errors of SGRT-based DIBH were derived from the literature [26] in agreement with our own experiences [25]. The accuracy of SGRT-based breath hold has been demonstrated elsewhere [28]. To validate our PRV concept, we simulated non-adaptive SBRT VMAT plans with and without a PRV. Moreover, we compared two different PTV margin strategies. At baseline, the VMAT plans reached significantly lower mean lung doses due to their higher conformality compared to step-and-shoot IMRT at the MR-linac. But daily re-calculations of the VMAT plans without PRV demonstrated frequent PBT overdoses, while VMAT plans with PRV prevented PBT overdoses. PBT overdoses occurred to a similar extent when comparing different PTV margin strategies. This dosimetric finding corroborates the theoretical estimations of the PRV margins. However, employment of a PRV margin came at the cost of reduced PTV coverage, which might in turn decrease local tumor control. PTV coverage was improved with smaller PTV margins in the VMAT plans, as would be expected. In this context, even further reductions of PTV margins may be possible for MR-guided SBRT because it detects the tumor motion via gating on cineMRI, whereas SGRT uses the thoracic wall as a surrogate. All in all, SMART offers a higher precision compared to non-adaptive SBRT techniques and/or SGRT approaches and combines superior target volume coverage with effective protection of OAR. Consequently, our first clinical experience with SMART of ULT has shown excellent local tumor control rates [32] in accordance with other reports [20].

We will increase the SBRT dose to ULT up to 10 x 6.5 Gy inside the MAGELLAN trial, so that the risk for PBT overdoses will likely increase. This is especially true for non-adaptive SBRT, which will likely show a more compromised PTV coverage, too. Hence, PRV margins and motion management increase the safety of non-adaptive SBRT, but MR-guided approaches and dose prescriptions may not be transferred uncritically to a non-adaptive approach.

Recently, the American Radium Society (ARS) has published guidelines for the treatment of medically inoperable stage I NSCLC in central or ultracentral locations. Among the recommendations are (1) contouring critical OARs on 4D-CT to consider breathing motion and (2) applying 3 mm PRV margins around critical OAR [33]. However, the experts disagreed on whether these two recommendations should be implemented based on low levels of evidence. Our data shed light on the benefits and limitations of motion management and PRVs when treating ULT with SBRT. Notably, our findings agree with the clinical suggestion of a 3 mm PRV margin around the PBT.

Limitations of our analyses include the small subset of patients with available 4D-CT. More sophisticated 4D −MRI techniques would be desirable. Furthermore, usage of PRV "margin recipes" has been criticized as overtly simple by Stroom et al. [31], although the authors concluded dependencies similar to McKenzie et al. [27] whose formula we used here. Recent advances in robust optimization might outperform margin formulas in the future [34]. Lastly, uncertainties in image registration and dose calculation using deformed CT images should be acknowledged as potential confounders.

Conclusion

Both intrafractional breathing motion and interfractional translations impact doses to the PBT during ultracentral SBRT. MR-guided online adaptive SBRT protects the PBT from overdoses while maintaining superior PTV coverage. Alternatively, techniques to minimize breathing motion, e.g. surface-guided SBRT in DIBH, together with PRV margins around the PBT can protect the PBT at the cost of decreased PTV coverage.

Patient consent statement

The data that underlies this manuscript has been collected within the prospective MAGELLAN trial (registered at ClinicalTrials.gov: NCT04925583 on 14th June 2021). The MAGELLAN trial has received local IRB approval at each trial site. Patient enrollment has not started before such local IRB approval. All patients have yielded written informed consent before trial enrollment, which is specified in the inclusion and exclusion criteria. The trial in general, and the analysis presented in this manuscript in specific, have been conducted according to the declaration of Helsinki and local IRB judgement.

CRediT authorship contribution statement

Sebastian Regnery: Conceptualization, Project administration, Methodology, Investigation, Data curation, Formal analysis, Visualization, Funding acquisition, Writing – original draft, Writing – review & editing. **Efthimios Katsigiannopulos:** Data curation, Investigation, Writing – review & editing. **Hin Lau:** Data curation, Writing – review & editing. **Philipp Hoegen-Saßmannshausen:** Investigation, Project administration, Writing – review & editing. **Fabian Weykamp:** Investigation, Writing – review & editing. **Claudia Katharina Renkamp:** Investigation, Writing – review & editing. **Carolin Rippke:** Investigation, Writing – review & editing. **Fabian Schlüter:** Investigation, Writing – review & editing. **Sophia Albert:** Investigation, Writing – review & editing. **Jan Meis:** Conceptualization, Methodology, Writing – review & editing. **Marietta Kirchner:** Methodology, Writing – review & editing. **Alexandra Balzer:** Methodology, Writing – review & editing. **Nicolaus Andratschke:** Project administration, Investigation, Writing – review & editing. **Matthias Guckenberger:** Project administration, Investigation, Writing – review & editing. **Jürgen Debus:** Supervision,

Conceptualization, Investigation, Writing – review & editing. **Sebastian Klüter:** Supervision, Investigation, Writing – review & editing. **Juliane Hörner-Rieber:** Supervision, Conceptualization, Methodology, Investigation, Funding acquisition, Writing – original draft, Writing – review & editing.

Declaration of Competing Interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: F. W. received speaker fees from AstraZeneca, Varian Medical Systems and Merck Sharp & Dohme and travel support for attending meetings from AstraZeneca, Varian Medical Systems, Novocure GmbH, Fraunhofer MEVIS and Micropos Medical as well as compensation for advisory boards from Novocure GmbH and Merck Sharp & Dohme. J.D. reports grants from Vision RT Limited, RaySearch Laboratories AB, Siemens Healthcare GmbH, Merck Serono GmbH, PTW-Freiburg Dr. Pychlau GmbH and Accuray Inc. JD reports receipt of an experimental accelerator by IntraOP. S. K. received speaker fees from Siemens Healthineers. J. H.-R. received speaker fees from ViewRay Inc. J. H.-R. received speaker fees from Pfizer Inc., travel reimbursement from ViewRay Inc., IntraOP Medical and Elekta Instrument AB as well as grants from IntraOP Medical and Varian Medical Systems.

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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.2024.100899.

References

[1] Roesch J, et al. SBRT for centrally localized NSCLC - what is too central? Radiat Oncol 2016;11(1):157.
[2] Song SY, et al. Fractionated stereotactic body radiation therapy for medically inoperable stage I lung cancer adjacent to central large bronchus. Lung Cancer 2009;66(1):89–93.
[3] Tekatli H, et al. Outcomes of hypofractionated high-dose radiotherapy in poor-risk patients with "Ultracentral" non-small cell lung cancer. J Thorac Oncol 2016;11(7):1081–9.
[4] Corradetti MN, Haas AR, Rengan R. Central-airway necrosis after stereotactic body-radiation therapy. N Engl J Med 2012;366(24):2327–9.
[5] Yan M, et al. Stereotactic body radiotherapy for ultra-central lung tumors: a systematic review and meta-analysis and international stereotactic radiosurgery society practice guidelines. Lung Cancer 2023;182:107281.
[6] Chen H, et al. Safety and effectiveness of stereotactic ablative radiotherapy for ultra-central lung lesions: a systematic review. J Thorac Oncol 2019;14(8):1332–42.
[7] Lindberg S, et al. Expanded HILUS trial: a pooled analysis of risk factors for toxicity from stereotactic body radiation therapy of central and ultracentral lung tumors. Int J Radiat Oncol Biol Phys 2023.
[8] Giuliani ME, et al. Stereotactic radiation for ultra-central non-small cell lung cancer: a safety and efficacy trial (SUNSET). Int J Radiat Oncol*Biol*Phys 2024;118(1):e2.
[9] Lau BC, et al. Pulmonary hemorrhage in patients treated with thoracic stereotactic ablative radiotherapy and antiangiogenic agents. J Thorac Oncol 2023.
[10] Ahmadsei M, et al. Dosimetric analysis of proximal bronchial tree subsegments to assess the risk of severe toxicity after stereotactic body radiation therapy of ultra-central lung tumors. Clin Transl Radiat Oncol 2024;45:100707.
[11] Rosenberg SA, et al. The nordic-HILUS trial: ultracentral lung stereotactic ablative radiotherapy and a narrow therapeutic window. J Thorac Oncol 2021;16(10):e79–80.
[12] Underberg RW, et al. Benefit of respiration-gated stereotactic radiotherapy for stage I lung cancer: an analysis of 4DCT datasets. Int J Radiat Oncol Biol Phys 2005;62(2):554–60.
[13] Habermann FOJ, et al. And yet it moves: clinical outcomes and motion management in stereotactic body radiation therapy (SBRT) of centrally located non-small cell lung cancer (NSCLC): shedding light on the internal organ at risk volume (IRV). Concept Cancers (basel) 2024;16(1).
[14] Nardone V, et al. 4D CT analysis of organs at risk (OARs) in stereotactic radiotherapy. Radiother Oncol 2020;151:10–4.
[15] Regnery S, et al. Adaptive MR-guided stereotactic radiotherapy is beneficial for ablative treatment of lung tumors in high-risk locations. Front Oncol 2021;11:757031.
[16] Finazzi T, et al. Role of on-table plan adaptation in MR-guided ablative radiation therapy for central lung tumors. Int J Radiat Oncol Biol Phys 2019;104(4):933–41.
[17] Henke L, et al. Simulated online adaptive magnetic resonance-guided stereotactic body radiation therapy for the treatment of oligometastatic disease of the abdomen and central thorax: characterization of potential advantages. Int J Radiat Oncol Biol Phys 2016;96(5):1078–86.
[18] Finazzi T, et al. Clinical outcomes of stereotactic MR-guided adaptive radiation therapy for high-risk lung tumors. Int J Radiat Oncol Biol Phys 2020;107(2):270–8.
[19] Regnery S, et al. To fly or not to fly: Stereotactic MR-guided adaptive radiotherapy effectively treats ultracentral lung tumors with favorable long-term outcomes. Lung Cancer 2023;179:107175.
[20] Sandoval ML, et al. MR-guided SBRT/hypofractionated RT for metastatic and primary central and ultracentral lung lesions. JTO Clin Res Rep 2023:100488.
[21] Regnery S, et al. Magnetic resonance guided adaptive stereotactic body radiotherapy for lung tumors in ultracentral location: the MAGELLAN trial (ARO 2021-3). Radiat Oncol 2022;17(1):102.
[22] Corradini S, et al. MR-guidance in clinical reality: current treatment challenges and future perspectives. Radiat Oncol 2019;14(1):92.
[23] Bohoudi O, et al. Fast and robust online adaptive planning in stereotactic MR-guided adaptive radiation therapy (SMART) for pancreatic cancer. Radiother Oncol 2017;125(3):439–44.
[24] Manyam BV, et al. Validation of RTOG 0813 proximal bronchial tree constraints for pulmonary toxicity with stereotactic body radiation therapy for central non-small cell lung cancer. Int J Radiat Oncol*Biol*Phys 2020.
[25] Naumann P, et al. Feasibility of optical surface-guidance for position verification and monitoring of stereotactic body radiotherapy in deep-inspiration breath-hold. Front Oncol 2020;10:573279.
[26] Guo HL, et al. SGRT-based stereotactic body radiotherapy for lung cancer setup accuracy and margin of the PTV. J Appl Clin Med Phys 2024;25(3):e14195.
[27] McKenzie A, van Herk M, Mijnheer B. Margins for geometric uncertainty around organs at risk in radiotherapy. Radiother Oncol 2002;62(3):299–307.
[28] Nguyen D, et al. Reproducibility of surface-based deep inspiration breath-hold technique for lung stereotactic body radiotherapy on a closed-bore gantry linac. Phys Imaging Radiat Oncol 2023;26:100448.
[29] Henke LE, et al. Stereotactic MR-guided online adaptive radiation therapy (SMART) for ultracentral thorax malignancies: results of a phase 1 trial. Adv Radiat Oncol 2019;4(1):201–9.
[30] Cusumano D, et al. Predicting tumour motion during the whole radiotherapy treatment: a systematic approach for thoracic and abdominal lesions based on real time MR. Radiother Oncol 2018;129(3):456–62.
[31] Stroom JC, Heijmen BJM. Limitations of the planning organ at risk volume (PRV) concept. Int J Radiat Oncol Biol Phys 2006;66(1):279–86.
[32] Regnery S, et al. Comparison of different dose accumulation strategies to estimate organ doses after stereotactic magnetic resonance-guided adaptive radiotherapy. Radiat Oncol 2023;18(1):92.
[33] Park HS, et al. Executive summary of the American Radium Society® (ARS) Appropriate Use Criteria (AUC) for non-small cell lung cancer in a central/ultra-central location: systematic review and guidelines. J Thorac Oncol 2024.
[34] Unkelbach J, et al. Robust radiotherapy planning. Phys Med Biol 2018;63(22):22tr02.