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Original Research Article

# The role of online MR-guided multi-fraction stereotactic ablative radiotherapy in lung tumours

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ABSTRACT

*Background:* The aim of this prospective observational study was to evaluate the dosimetry benefits, changes in pulmonary function, and clinical outcome of online adaptive MR-guided SBRT.

*Methods:* From 11/2020–07/2022, 45 consecutive patients with 59 lesions underwent multi-fraction SBRT (3–8 fractions) at our institution. Patients were eligible if they had biopsy-proven NSCLC or lung cancer/metastases diagnosed via clinical imaging. Endpoints were local control (LC) and overall survival (OS). We evaluated PTV/GTV dose coverage, organs at risk exposure, and changes in pulmonary function (PF). Acute toxicity was classified per the National Cancer Institute-Common Terminology Criteria for Adverse Events version 5.0.

*Results:* The median PTV was 14.4 $cm^3$ (range: 3.4 – 96.5 $cm^3$). In total 195/215 (91%) plans were reoptimised. In the reoptimised vs. predicted plans, PTV coverage by the prescribed dose increased in 94.6% of all fractions with a median increase in PTV $V_{PD}$ of 5.6% (range: −1.8 – 44.6%, $p < 0.001$), increasing the number of fractions with PTV $V_{PD} \geq 95\%$ from 33% to 98%. The PTV $D_{95\%}$ and $D_{98\%}$ ($BED_{10}$) increased in 93% and 95% of all fractions with a median increase of 7.7% ($p < 0.001$) and 10.6% ($p < 0.001$). The PTV $D_{95\%}$ ($BED_{10}$) increased by a mean of 9.6 Gy (SD: 10.3 Gy, $p < 0.001$). At a median follow-up of 21.4 months (95% CI: 12.3–27.0 months), 1- and 2-year LC rates were 94.8% (95% CI: 87.6 – 100.0%) and 91.1% (95% CI: 81.3 – 100%); 1- and 2-year OS rates were 85.6% (95% CI: 75.0 – 96.3%) and 67.1 % (95% CI: 50.3 – 83.8%). One grade ≥ 3 toxicity and no significant reduction in short-term PF parameters were recorded.

*Conclusions:* Online adaptive MR-guided SBRT is an effective, safe and generally well tolerated treatment option for lung tumours achieving encouraging local control rates with significantly improved target volume coverage.

*Abbreviations:* AJCC, American Joint Committee on Cancer; $BED_{10}$, Biologically effective dose assuming an α/β ratio of 10 Gy; CCI, Charlson comorbidity index; CI, Confidence interval; CIF, Cumulative incidence function; CT, Computed tomography; DLCOcSB, Diffusing capacity of lung for carbon monoxide corrected for hemoglobin; $D_{x\%}$, The dose covering x% of the target volume; $D_{mean}$, Mean dose covering the target volume; ECOG-PS, Eastern Cooperative Oncology Group Performance Status; EQD2/2, Equivalent dose in 2 Gy fractions assuming an α/β ratio of 2 Gy; EQD2/3, Equivalent dose in 2 Gy fractions assuming an α/β ratio of 3 Gy; FEV1, Forced expiratory volume in one second; FVC, Forced vital capacity; GTV, Gross tumour volume; IDL, Isodose line; IASLC, International Association for the Study of Lung Cancer; IQR, Interquartile range; KM estimate, Kaplan-Meier estimate; LCI, Lower confidence interval; MR-LINAC, MRI-guided linear accelerator; MR/MRI, Magnetic resonance imaging; MTD, Maximum tolerated dose; N, Absolute number; NCI-CTCAE, National Cancer Institute Common Terminology Criteria for Adverse Events; NSCLC, Non-small cell lung cancer; OAR, Organ at risk; oMRgRT, Online adaptive MR-guided radiotherapy; OS, Overall survival; p, p-value; PBT, Proximal bronchial tree; PET-CT, Positron emission tomography-computed tomography; PFS, Progression-free survival; PFT, Pulmonary function test; PS, Performance status; PTV, Planning target volume; SABR, Stereotactic ablative radiotherapy; SBRT, Stereotactic body radiation therapy; SCLC, Small cell lung cancer; SD, Standard deviation; SPLC, Second primary lung cancer; TCD90, Dose to achieve 90% tumour control probability; TCP, Tumour control probability; TPS, Treatment planning system; UICC, Union for International Cancer Control; UCI, Upper confidence interval; UCT, Ultracentral lung tumours; V20, Volume of the lung receiving ≥ 20 Gy; $V_{PD}$, % of the target volume covered by the prescribed dose.

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## Introduction

Lung cancer is the leading cause of cancer mortality worldwide [1]. The majority of lung cancer patients are diagnosed as non-small cell lung cancers (NSCLC) [2]. Furthermore, the lung is the second most frequent location of metastases [3]. Stereotactic body radiation therapy (SBRT) is the standard of care in inoperable early-stage NSCLC and is increasingly utilised for the management of lung metastases [4,5]. Local consolidative therapy including SBRT has been shown to prolong progression-free survival (PFS) in oligometastatic/oligoprogressive NSCLC patients in three recently published randomized phase II trials with one trial also showing prolonged overall survival (OS) [6–9]. In addition, it has been postulated that local control of all visible disease sites can result in less disease progression at new sites in these patients [7,10].

Accurate delivery of SBRT to lung tumours faces distinct challenges: inter- and intrafractional anatomical changes due to cardiac and respiratory motion and proximity to organs at risk (OAR), potentially leading to under-dosing of the target volume and insufficient OAR sparing [11–13]. OAR sparing is especially pertinent in inoperable NSCLC patients, who are often frail and present with cardiopulmonary comorbidities and are at higher risk for lung toxicities as well as for metastatic patients likely facing multiple or repeated local ablative treatments during the course of their disease.

In this context, the advancement of online adaptive MR-guided radiotherapy (oMRgRT) is of relevance for the treatment of lung cancers, allowing for daily anatomical plan adaptation and continuous, non-invasive tumour-tracking and -gating [14–17]. Initial studies have demonstrated the feasibility and safety of adaptive stereotactic oMRgRT for lung cancers and have reported dosimetric and clinical benefits including improved target coverage, OAR sparing, low toxicity, and promising local control (LC) and progression-free survival (PFS) [18–28]. However, previous studies often comprise relatively small and inhomogeneous cohorts [13,29].

Previously, we reported our experience with online adaptive MRgRT, reporting dosimetry benefits for lung tumours, and various anatomical sites [28]. The aim of this monocentric prospective study was to evaluate the dosimetry benefits, changes in pulmonary function, and clinical outcomes of online adaptive MR-guided SBRT in the treatment of lung tumours in a single-centre patient cohort and supplement the existing literature.

## Patients and methods

### *Patient and treatment characteristics*

From November 2020 through July 2022, 45 consecutive patients with 59 lung tumours underwent online adaptive stereotactic MRgRT (abbreviated oMRgRT in the following) on the MRIdian system (ViewRay Inc, Oakwood Village, USA) at our institution. This prospective observational single-centre study was approved by the Ludwig Maximilian University of Munich ethics committee (reference number: 20–0291). All patients underwent online adaptive stereotactic MRgRT to the lung in 3–8 fractions.

### *Stereotactic oMRgRT workflow/delivery of online MR-guided SBRT*

The technical design of the MRIdian [17,30] and our workflow have been previously described [31]. Patients underwent MRI simulation in inspiration breath-hold (BH) and supine position with arms above the head using a dedicated positioning device (WingSTEP, IT-V, Innsbruck, Austria). Thereafter, a standard planning computed tomography (CT) scan using the same patient positioning and BH level was conducted to obtain tissue density information. Image datasets were then co-registered using the deformable registration algorithm of the integrated MRIdian treatment planning system (TPS). The target volume and OARs were contoured on the 3D MR simulation scan. An isotropic gross tumour volume (GTV) expansion of 5 mm was used to generate the planning target volume (PTV). The treatment planning objectives were a PTV coverage by the prescribed dose (PD) PTV $V_{PD} \geq 98\%$ with a peripheral $BED_{10} \geq 95$ Gy.

To generate the predicted treatment plans for each treatment fraction, a 3D setup MRI scan was acquired for a translational patient setup correction (couch shift) on the day of each treatment fraction. The MRI of the baseline plan was then registered via deformable image registration to 3D setup MRI of the day with all target structures, OARs and the electron density of the planning CT propagated onto the setup MRI. All contours were edited (if necessary) and a tracking contour was defined and the baseline plan was calculated on the MRI (i.e. the synthetic CT) of the day, resulting in the predicted dose (baseline plan calculated on the anatomy of the day with updated structures). In case of a subsequent plan adaptation, a partial re-contouring approach was used for most OARs, editing only structures within 3 cm of the PTV. Reasons for treatment plan adaptation were either insufficient target coverage and/or violations of OAR constraints. Online plan adaptation was performed either as reoptimisation with the objectives of the baseline plan or as full reoptimisation with adapted objectives and/or plan parameters. The dose distribution of the online adapted plan is referred to as reoptimised treatment plan and calculated on the current synthetic CT (based on the MR of the day) with updated structures. All dose calculation settings for the reoptimised dose and the predicted dose were identical as defined in the baseline plan. Before treatment, the reoptimised dose distribution plans were verified for quality assurance, using a secondary Monte Carlo code.

For intrafractional tumour tracking via a 2D balanced steady-state free progression (bSSFP) cine MRI sequence, the tracking structure was propagated onto a 2D cine MRI slice, and a gating region of interest (ROI) was created by expansion of the tracking structure. These structures were subsequently used for online beam gating. All patients in which the target volume showed a breathing-related motion were treated using a breath-hold technique.

All baseline plans were validated dosimetrically with an ionisation chamber and/or diode detector array (ArcCheck-MR; Sun Nuclear Corporation, Melbourne, FL, USA) prior to the first fraction.

### *Dosimetric outcome analysis of oMRgRT*

We analysed dosimetric changes in PTV/GTV $D_{95\%}$ and $D_{98\%}$, GTV $D_{mean}$ and OAR exposure. Extraction and comparison of dose volume histogram (DVH) parameters and statistical outcome analysis thereof have been described in our previous work [28]. Briefly, DVH parameters were extracted from the MRIdian TPS for the baseline, predicted (non-adapted) and reoptimised scenarios for all fractions: the dose to 98%, 95%, 50% and 2% of the volume of the PTV (PTV $D_{98\%}$ = near minimum dose, PTV $D_{95\%}$, PTV $D_{50\%}$ = median dose, PTV $D_{2\%}$ = near maximum dose) and the mean PTV dose (PTV $D_{mean}$). All parameters were also reported for the GTV. In order to evaluate the PTV coverage, the percentage of PTV receiving the PD (PTV $V_{PD}$) was also extracted.

To assess organs at risk (OAR) sparing, conventionally accepted OAR constraint parameters according to Gerhard et al. for 3- and 5-fraction schemes and according to Timmerman et al. for the 8-fraction scheme were chosen [32,33]. In addition, technical parameters like the gantry and multileaf collimator (MLC) time, beam-on time (BOT) for the baseline plans were also extracted from the TPS. Total treatment time was noted after each treatment and separately analysed.

### *Statistical analysis*

Changes in dosimetric parameters were statistically evaluated using the Wilcoxon signed rank test. Survival data were estimated using the Kaplan-Meier method and variables compared using the log-rank test. Comparisons between subgroups were tested using the Mann-Whitney *U*

test for continuous variables and Fisher's exact test for categorical variables. Local control was defined as no local progression at the irradiation site assessed by positron emission tomography (PET-)CT or CT imaging at follow-up as per Response Evaluation Criteria in Solid Tumours guideline (version 1.1). PFS was defined as the time from the first SBRT to disease recurrence at any site, including second primary lung cancer (SPLC). OS was defined as the time to death from any cause or last follow-up. Further, median follow-up was calculated as the time from SBRT to last/loss of follow-up using the reverse Kaplan-Meier method. All tests were evaluated such that a p-value of $< 0.05$ was considered significant.

Pulmonary function test (PFT) parameters assessed included forced vital capacity (FVC), forced expiratory volume in 1 s (FEV1s), and single-breath diffusing capacity of the lung for carbon monoxide corrected for haemoglobin (DLCOcSB). Changes in PFT were calculated by subtracting the baseline value from the follow-up and were evaluated using the paired Wilcoxon signed rank test. A p-value of less than 0.05 was considered statistically significant.

Acute toxicity was classified per the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) version 5.0 up to three months post-treatment (six months post-treatment for pneumonitis where applicable). Late toxicities were defined as 3 months or longer from the end of treatment. Two patients were treated twice within a week (each with separate treatment plans). In these cases, pulmonary function tests and adverse events were not evaluated separately, resulting in a total number of 51 follow-up evaluations except for radiation pneumonitis, in which case a patient treated twice within 4 months was evaluated only once, resulting in 50 follow-up evaluations for radiation pneumonitis. All calculations and statistics were performed using Excel v. 16.0 (Microsoft Corporation, Redmond, WA, USA), OriginPro, Version 2021b (OriginLab Corporation, Northampton, MA, USA) and the tidycmprsk package (version 0.2.0) in R (version 4.2.1) using Rstudio (Boston, MA).

### *Clinical outcome analysis of oMRgRT*

Patients were assessed prior to treatment and followed 6 weeks after SBRT. Generally, a whole-body PET-CT or CT thorax/upper abdomen scan was performed every 3 months for the first 2 years, every 6 months for the following 2 years, and annually thereafter for primary NSCLC patients and every 3 months for metastatic patients. Prior to SBRT, pulmonary function tests were performed at baseline and routinely following SBRT.

In a post-hoc analysis of a prospectively maintained database, we assessed local control (LC), progression-free survival (PFS), and overall survival (OS). We further evaluated toxicity, acute changes in pulmonary function, and adverse pulmonary events such as exacerbation of chronic obstructive pulmonary disease (COPD), and lung fibrosis.

## Results

### *Patient and treatment characteristics*

In total, 6 patients had biopsy-proven inoperable early-stage NSCLC (American Joint Committee on Cancer/Union for International Cancer Control Stages I-II), 16 had metastatic NSCLC, 2 had clinically diagnosed lung tumours, 1 patient had combined SCLC, and 20 patients had lung metastases. Table 1 summarises patient and tumour characteristics. The median patient age was 69 years (range, 38–88), most patients were male (64%), and 56% were former or current smokers (84% of primary lung cancer patients vs. 20% of patients treated for lung metastases, $p < 0.001$). The median ECOG score was 1 and the median Charlson Comorbidity Index (CCI) calculated without oncological diagnoses was 4 (range, 0–8).

Overall, patients with primary lung cancers (n = 25) were older than patients treated for lung metastases (median age 72 years vs. 64 years [$p < 0.05$]). Patients treated for primary lung cancers also had a higher median CCI score (4 vs. 3, $p < 0.05$) and a higher proportion of lung comorbidities (n = 13/25 vs. n = 2/20, $p < 0.05$) while other risk factors such as prior lung radiotherapy and/or lung resection were similar in both groups. Among primary lung cancer patients, two patients received 3 courses of SBRT. In the lung metastases group, 3 patients received repeat SBRT, with 2 patients receiving 2 courses and 1 patient receiving 3 courses. In total, 6 patients were simultaneously treated for two lesions with one treatment plan. Patients were prescribed different fractionation schemes contingent upon risk factors e.g., central tumours (n = 7) and prior pneumonectomy (n = 3): either 40.5 Gy in 3 fractions (n = 41), 45.0 Gy in 3 fractions (n = 2) prescribed to the 65% isodose line (IDL), and 50.0 Gy in 5 fractions (n = 8), or 60.0 Gy in 8 fractions (n = 8) prescribed to the 80% IDL with plans prescribed such that at least 98% of target volume received the prescription dose (PD), delivering a $BED_{10} \geq 100$ Gy to the central region of the target (GTV). In total, 53 treatment plans for 59 lesions and a total of 215 fractions were analysed.

**Table 1**
Patient and treatment characteristics. Data is shown as median (range) or number (percentage) as indicated.

| All patients (n = 45) | n (%) |
|---|---|
| **Sex** | |
| Male | 29 (64) |
| Female | 16 (36) |
| **Age at time of SBRT, median (range) [yrs]** | 69 (38–88) |
| **Treatment indication** | |
| **Primary lung cancer** | **25 (56)** |
| Early-stage NSCLC (histologically confirmed) | 6 (13) |
| Early-stage lung cancer (not histologically confirmed) | 2 (4) |
| Combined SCLC | 1 (2) |
| Metastasised NSCLC | 16 (36) |
| **Lung metastases (initial histology)** | **20 (44)** |
| Colorectal cancer | 7 (16) |
| Sarcoma | 4 9) |
| Head and neck cancer | 2 (4) |
| Melanoma | 1 (2) |
| Prostate cancer | 1 (2) |
| Pancreatic cancer | 1 (2) |
| Gastrointestinal cancer | 1 (2) |
| Cholangiocellular cancer | 1 (2) |
| Germ cell tumour | 1 (2) |
| Cancer of unknown primary (CUP) | 1 (2) |
| **Previous lung radiation therapy** | 14 (31) |
| **Previous lung resection** | 15 (33) |
| **Pulmonary comorbidity (i.e., COPD, lung emphysema, or lung fibrosis)** | 15 (33) |
| **All treatments (n = 53)** | **n (%)** |
| **ECOG performance status** | |
| 0 | 22 (42) |
| 1 | 25 (47) |
| 2 | 2 (4) |
| not documented | 4 (8) |
| **Pulmonary function** | |
| $FEV_{1s}$ [% predicted] | 74 (38–129) |
| FVC [% predicted] | 85 (35–122) |
| $DLCO_{cSB}$ [% predicted] | 54 (22–104) |
| CCI, median (range) | 4 (0–8) |
| **All tumours (n = 59)** | **n (%)** |
| **Tumour location** | |
| Right upper lobe | 11 (18) |
| Right middle lobe | 2 (3) |
| Right lower lobe | 13 (22) |
| Left upper lobe | 13 (22) |
| Left lower lobe | 14 (23) |
| **Central tumors (IASLC)** | 7 (12) |
| **PTV, median (range), $cm^3$** | 14.4 (3.4 – 96.5) |
| **Fractionation** | |
| 3 × 13.5 Gy (prescribed to the 65 % IDL) | 41 (69) |
| 3 × 15.0 Gy (prescribed to the 65 % IDL) | 2 (3) |
| 5 × 10.0 Gy (prescribed to the 80 % IDL) | 8 (14) |
| 8 × 7.5 Gy (prescribed to the 80 % IDL) | 8 (14) |

The median breath-hold PTV was 14.4 $cm^3$ (range, 3.4–96.5 $cm^3$). The median beam-on-time (BOT) for the baseline plans was 6.2 min (range, 2.7–15.2 min). The median total duration of a treatment session, including reoptimisation and dose delivery in gated breath-holds was 48 min (range, 28–110 min).

The median PTV $V_{PD}$ in the baseline plans was 98.0% (range, 83.8–100.0%) with 83.8% in a lesion treated simultaneously. The median PTV $D_{95\%}$, $D_{50\%}$, and $D_{2\%}$ as a function of the prescribed dose were 103.1% (range, 95.0–107.4%), 121.0% (range, 109.4–129.0%), and 147.3% (range, 116.7–152.3%), respectively.

### *Online plan adaption*

In total, 195/215 (91%) of all treatment plans were reoptimised during the online adaptive workflow. Full planning data was available for 185 plans. Table 2 summarises the changes in target volume parameters. PTV $V_{PD}$ increased in 94.6% of all fractions with a median change in PTV $V_{PD}$ of 5.6% (range, −1.8–44.6%) ($p < 0.001$), increasing the number of fractions with PTV $V_{PD} \geq 95\%$ from 33% to 98% (Table 2 and Figs. 1–3). Moreover, the PTV $D_{95\%}$ und $D_{98\%}$ ($BED_{10}$) increased in 93% and 95% of all fractions while PTV $D_{50\%}$ ($BED_{10}$) increased in 65% of all plans.

Acceptable minor OAR deviations (in patients with central tumours/tumours in close proximity to the chest wall) were observed in a few cases where target coverage was prioritised over OAR exposure, most commonly regarding the ipsilateral lung $V_{20}$ and chest wall $D_{0.03cc}/D_{30cc}$ which increased by a median of 4.4% ($p < 0.001$) and 1.7% ($p > 0.05$)/6.0% ($p < 0.001$), respectively (Supplementary Table 1). In contrast, $D_{0.03cc}$ decreased slightly for the spinal cord (median change −1.8%, $p < 0.05$), while none of the other OAR maximum doses ($D_{0.03cc}$) changed significantly.

### *Clinical outcomes*

The median follow-up from the end of SBRT was 21.4 months (95 % CI: 12.3–27.0 months) with 33/45 (73%) patients alive at the time of analysis. 1 and 2-year overall survival were 85.6% (95% CI: 75.0–96.3%) und 67.1% (95% CI: 50.3–83.8%) (Fig. 4). The median OS was not reached. 1- and 2-year local control rates were 94.8% (95% CI: 87.6–100.0%) and 91.1% (95% CI: 81.3–100%), respectively (Fig. 5). A competing risks analysis with local failure (defined as first event per patient) vs. death before local failure was performed to correctly estimate local control rates in the presence of competing events (Fig. 6). The cumulative incidence rates for death without local failure at 12 and 24 months, respectively, were 7 and 14, while the cumulative incidence of local failure at 12 and 24 months was 2, respectively.

A total of 5 local failures were observed, two of which occurred in a male patient with combined SCLC histology. One patient with a germ cell tumour another with metastatic NSCLC and a patient with only a clinical diagnosis also experienced local recurrence. Further, 1- and 2-year estimated PFS rates were 35.4 % (95 % CI: 21.5–49.2 %) und 20.3 % (95 % CI: 7.5–33.2 %), respectively (Fig. 7).

The most common all-grade treatment-related toxicity was radiation pneumonitis (30%), dyspnoea (12%), and cough (6%). There was one case of $\geq 3$ CTCAE toxicity where a patient with underlying pulmonary fibrosis developed radiation pneumonitis and died 5.8 months after treatment from complications of pneumonia (Table 3).

At a median time of 1.5 months (range, 0.3–13.0 months) post-SBRT, PFTs revealed a slight decrease in FVC (both absolute and % predicted values) with a median decrease of FVC [L] of −5% (range, −37–30%) ($p < 0.05$) and a median decrease of FVC [% predicted] of −3% (range, −39 – 14%) ($p < 0.05$). No significant changes were observed regarding FEV1s and DLCOcSB: FEV1s [L] and FEV1s [% predicted] decreased by a median of −3% (range, −33 – 54%) ($p > 0.05$) and −3% (range, −32 – 36%) ($p > 0.05$), respectively. DLCOcSB [mmol/min/kPa] and DLCOcSB [% predicted] decreased by a median of −1% (range, −37 – 35%) ($p > 0.05$) and −1% (range, −37 – 39%) ($p > 0.05$), respectively.

### *Clinical outcome based on subgroups*

There was no significant difference in local control probability based on tumour location (central vs. peripheral tumours as per the International Association for the Study of Lung Cancer–IASLC definition) ($p > 0.05$, log-rank test). Further analysis was performed to evaluate local control probability in the primary NSCLC/no histology vs. non-NSCLC subgroups: there was no significant difference in local control probability between both subgroups ($p > 0.05$, log-rank test) (Supplementary Figs. 1 and 2).

**Table 2**
PTV/GTV changes in reoptimised vs. predicted plans, indicating the benefits of online plan adaption. Data is presented as median change (range) [%] and mean absolute change [Gy] of the biologically effective dose assuming an α/β ratio of 10 Gy ($BED_{10}$). PTV coverage by the prescribed dose ($V_{PD}$) increased in 94.6% of all fractions while PTV $D_{95\%}$ und $D_{98\%}$ ($BED_{10}$) increased in 93% and 95% of all fractions.

| Target volume | Parameter | Median change, (range) [%] | Mean change (SD) [Gy] | *p* |
|---|---|---|---|---|
| PTV | $V_{PD}$ | 5.6 (−1.8 – 44.6) | | <0.001 |
| | $D_{95\%}$ ($BED_{10}$) | 7.7 (−3.7 – 120.0) | 9.6 (10.3) | <0.001 |
| | $D_{98\%}$ ($BED_{10}$) | 10.6 (−2.9 – 117.6) | 11.9 (9.6) | <0.001 |
| | $D_{50\%}$ ($BED_{10}$) | 1.8 (−5.8 – 14.5) | 2.3 (4.6) | <0.001 |
| | $D_{mean}$ ($BED_{10}$) | 2.2 (−27.3 – 16.6) | 3.0 (5.7) | <0.001 |
| | $D_{2\%}$ ($BED_{10}$) | 1.8 (−5.8 – 14.5) | 2.3 (4.6) | <0.001 |
| GTV | $V_{PD}$ | 0.0 (0.0 – 23.1) | | <0.001 |
| | $D_{95\%}$ ($BED_{10}$) | 3.4 (−6.9 – 38.6) | 5.7 (7.7) | <0.001 |
| | $D_{98\%}$ ($BED_{10}$) | 4.2 (−10.0 – 58.1) | 7.6 (10.1) | <0.001 |
| | $D_{50\%}$ ($BED_{10}$) | 0.7 (−7.1 – 10.9) | 0.9 (4.8) | <0.05 |
| | $D_{mean}$ ($BED_{10}$) | 0.9 (−22.2 – 15.5) | 1.3 (5.8) | <0.001 |
| | $D_{2\%}$ ($BED_{10}$) | −1.2 (−12.5 – 13.1) | −1.9 (7.3) | <0.01 |

## Discussion

We report our two-year clinical experience with stereotactic online adaptive MR-guided radiation therapy in the treatment of lung tumours. Clinical outcomes at the time of analysis were encouraging with 1- and 2-year LC rates of 94.8% (95 % CI: 87.6–100.0%) und 91.1 % (95% CI: 81.3–100%) and one CTCAE grade $\geq 3$ treatment-related toxicity.

oMRgRT can offer meaningful benefits to lung tumour patients with initial studies indicating dosimetric and clinical benefits such as improved target coverage, OAR sparing, low toxicity, and promising local control and local progression-free survival [18–20,22,24–28,34]. However, existing studies often report on relatively small cohorts, varying fractionation schemes, and treatments partly or wholly delivered on an earlier MR-guided treatment platform (ViewRay Co-60).

In a phase I trial, Henke et al. treated 5 patients with ultra-central lung tumours (4 oligometastatic and one inoperable NSCLC) with oMRgRT (5 × 10 Gy) with planning objectives of PTV $V_{95\%} \geq 95\%$ and strict OAR constraint adherence. Online plan adaptation was performed in 40% of delivered fractions with 4/5 of patients receiving ≥1 adapted fraction. They further reported a 6-month LC rate of 100% and no grade $\geq 3$ treatment-related toxicity within this period [20].

The largest to date clinical experience of multi-fraction MR-guided SBRT for lung tumours reported on 50 patients with 54 tumours, with most of these treatments (63%) delivered exclusively on the MRIdian

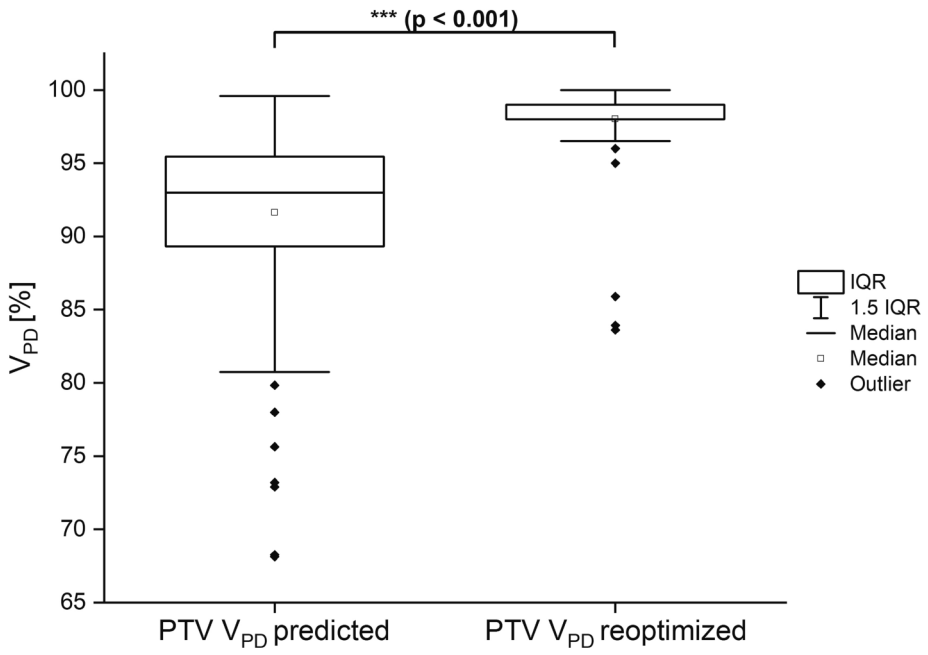


**Fig. 1.** Boxplot highlighting the benefit of plan reoptimisation regarding PTV coverage by the prescribed dose (PTV $V_{PD}$) [%]: PTV $V_{PD}$ increased by a median change of 5.6% ($p < 0.001$, range: −1.8 – 44.6%) in reoptimised vs. predicted plans, increasing the number of fractions with PTV $V_{PD} \geq 95\%$ from 33% to 98%.

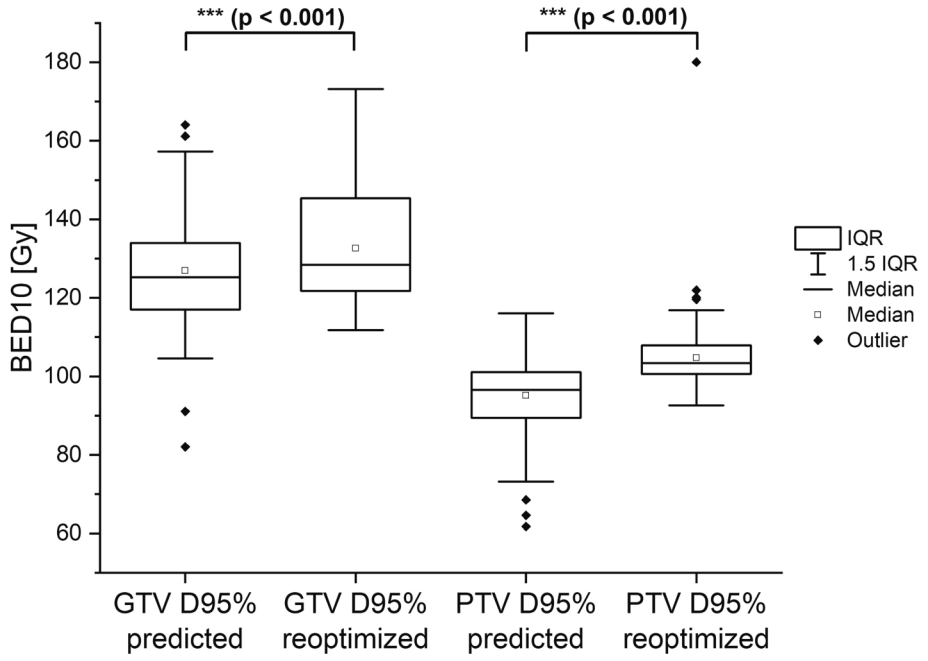


**Fig. 2.** Boxplot showing the changes in GTV and PTV $D_{95\%}$ ($BED_{10}$) in reoptimised vs. predicted plans. Plan reoptimisation increased PTV $D_{95\%}$ ($BED_{10}$) in 93% of fractions with a median change of 7.7% (range: −3.7 – 120.0, $p < 0.001$) and a mean increase of 9.6 Gy (SD:10.3 Gy, $p < 0.001$) ($BED_{10}$). GTV $D_{95\%}$ ($BED_{10}$) increased by a mean of 5.7 Gy (SD: 7.7, $p < 0.001$).

Cobalt-60 system [26]. The present report, to the best of our knowledge, comprises the largest clinical experience to date of MR-guided SBRT for lung tumours delivered on the MRIdian MR-Linac system. A distinct feature of our analysis is the inclusion of pulmonary function changes which have not been reported previously in this context.

In the above-mentioned report, Finazzi et al. treated patients with high-risk lung tumours and reported 12-month LC, OS, and DFS rates of 95.6%, 88.0%, and 63.6% and no grade > 3 toxicity [26]. We found similarly encouraging clinical outcomes. However, it must be noted, that our cohort differs substantially from the former (early-stage NSCLC: 58% vs. 19% and stage IV NSCLC: 4% vs. 36% in the UMC Amsterdam vs. the current cohort). Furthermore, the authors reported delivery of reoptimised plans in 91% of fractions, which is in complete agreement with our results. The average increase in PTV $V_{PD}$ was 4.4% per fraction [26]. Our results differ slightly from these findings with a median (mean) increase of 5.6% (7.4%). In an earlier study, the authors investigated the role of on-table plan adaption for central lung tumours by comparing 168 predicted/reoptimised plans [24]. Plan adaptation improved PTV coverage in 61% of fractions with a mean increase in PTV $V_{PD}$ of 4.6% and a median of 91.2% and 95.0% in predicted and

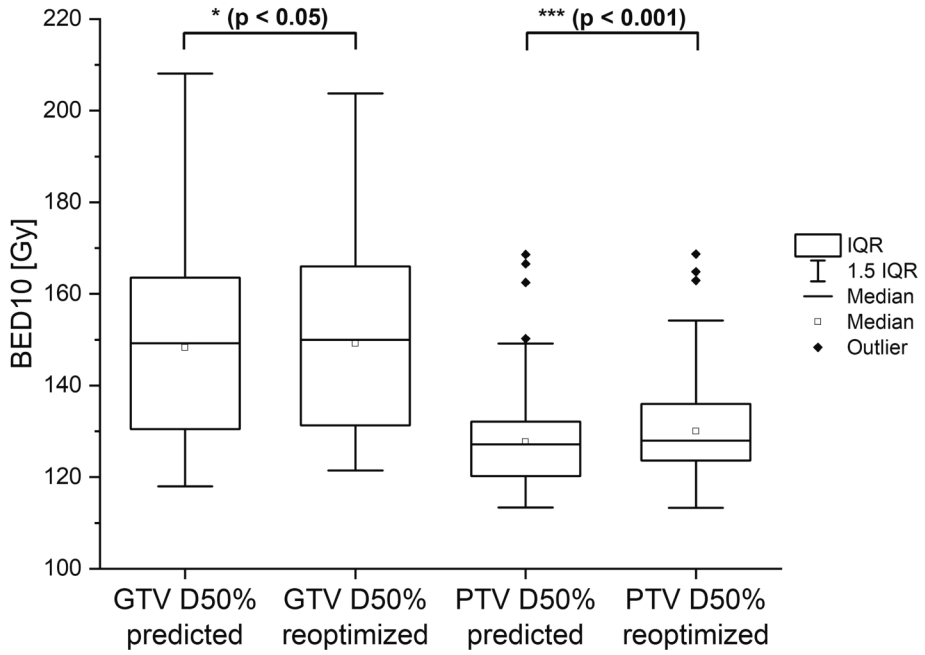


**Fig. 3.** Boxplot indicating minor increases in median doses ($BED_{10}$) to the GTV and PTV ($GTV/PTV_{D50\%}$) in reoptimised vs. predicted plans: GTV $D_{50\%}$ ($BED_{10}$) increased by a mean of 0.9 Gy (SD: 4.8 Gy, $p < 0.05$) PTV $D_{50\%}$ ($BED_{10}$) increased by a mean of 2.3 Gy (SD: 4.6 Gy, $p < 0.001$).

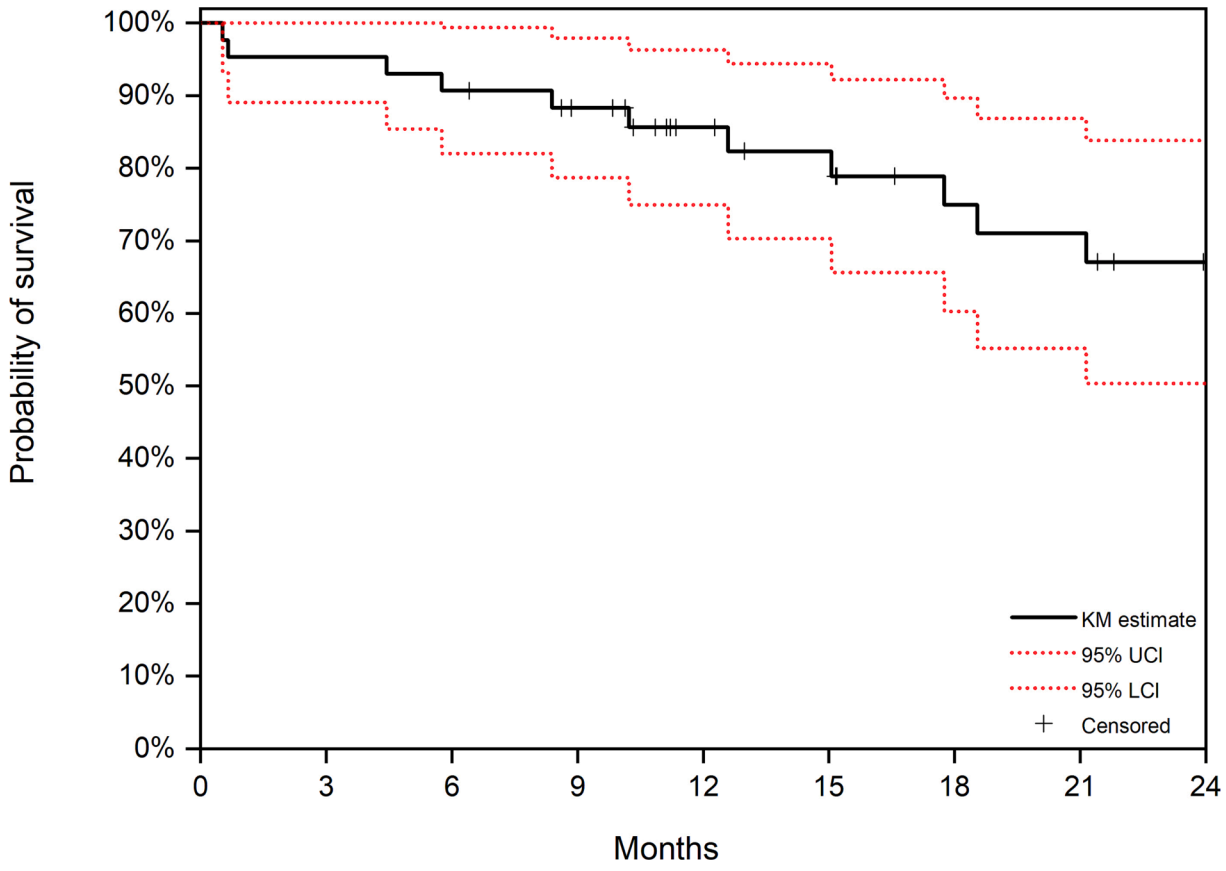


**Fig. 4.** Kaplan-Meier estimate of overall survival OS) probability. Median follow-up from the end of SBRT was 21.4 months (95% CI: 12.3 - 27.0 months) with 33/45 (73%) of patients alive at analysis. 1 and 2-year OS probability were 85.6% (95% CI: 75.0 – 96.3 %) und 67.1% (95% CI: 50.3 – 83.8%). The median OS was not reached.

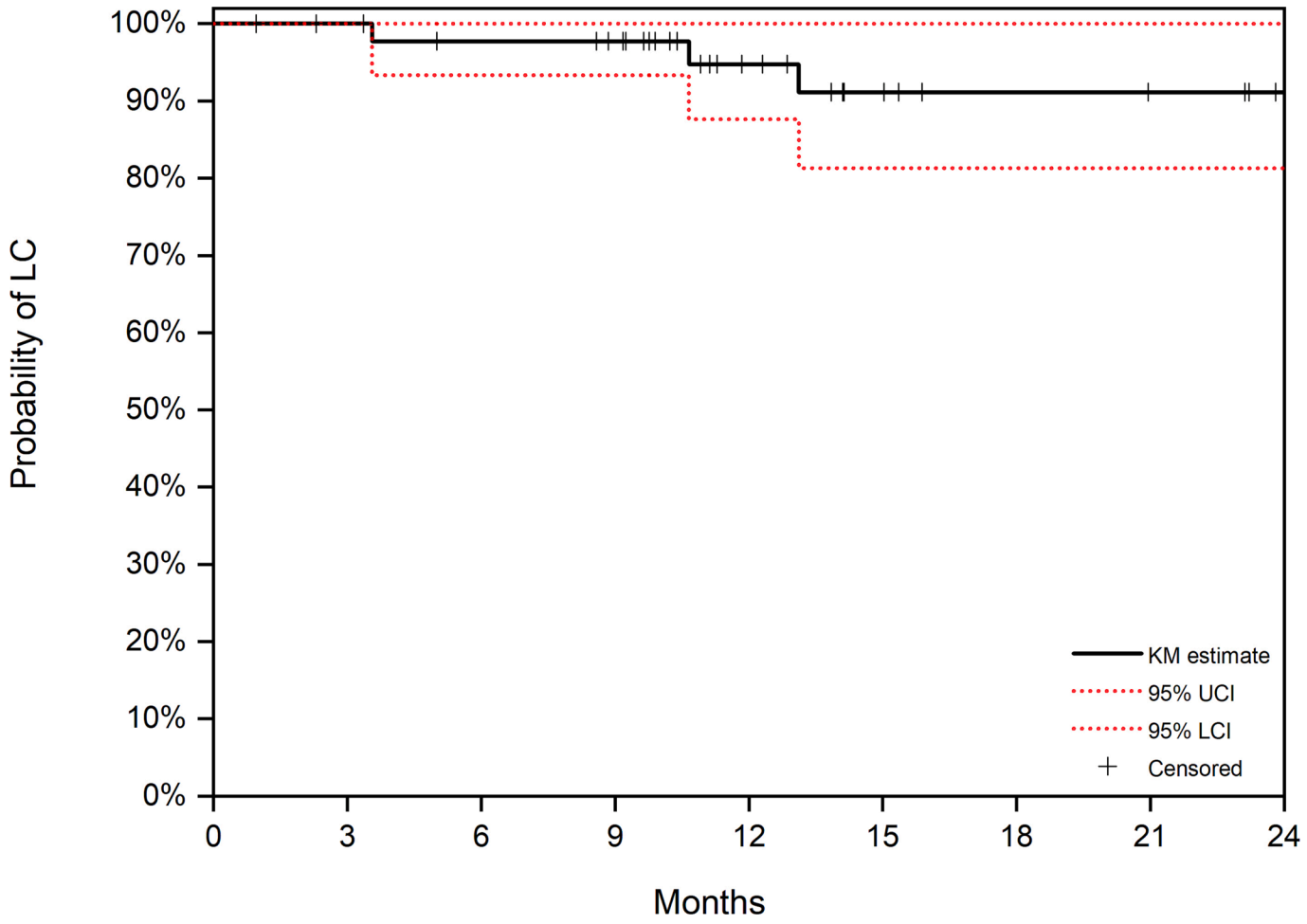


**Fig. 5.** Kaplan-Meier estimate of local control (LC) probability. 1- and 2-year local control rates were 94.8% (95% CI: 87.6 – 100.0%) and 91.1% (95% CI: 81.3 – 100%), respectively.

reoptimised plans, respectively [24]. In another study by the same group, SBRT in 25 peripheral lung tumours were analysed. The authors reported an improved PTV $V_{PD}$ from a median of 92.1% in predicted vs. 95.0% in reoptimised plans [25].

Regnery et al. recently analysed dose characteristics between predicted and adapted plans in a prospective cohort of 21 patients with lung tumours located peripherally (n = 10/21) centrally (n = 2), or ultra-centrally (n = 11) [27]. Plan adaptation was performed in 93.3% of fractions and fewer plans with violated planning objectives (94% vs. 17%) were observed. Similarly, to our results, Regnery et al. found a moderate increase in PTV coverage of 6.3% while GTV coverage remained similarly high before and after plan adaptation. Furthermore, while PTV and GTV mean BED were found to increase only slightly, the authors noted a large increase in PTV minimum $BED_{10}$ and a moderate increase in minimum GTV $BED_{10}$ [27]. This in good agreement with our findings of improved PTV and GTV $D_{95\%}$ and $D_{98\%}$ and slight changes in PTV and GTV $D_{mean}$.

Finally, our results confirm a prior investigation by our institution in which the dosimetry benefits of stereotactic MR-guided adaptive radiation therapy in 50 patients, including 10 lung cancer cases (treated with 40.5 Gy in 3 fractions prescribed to the 65% IDL) demonstrated significant improvements in GTV and PTV $D_{95\%}$ and $D_{98\%}$ [28]. The slightly lower adaptation rate of 84.4% in our previous study can be attributed to the lower rate of higher-risk lung tumours in this cohort [28].

It is currently unknown, what clinical effects moderate dosimetric increases, as shown in our results, could have. Clinical data suggests that SBRT delivery can be further optimised with 5-year LF rates of >10% for early-stage NSCLC [35,36] and 25% in the context of lung metastases – and in this context fatal toxicity of 4.5% [5]. Higher biologically effective doses have further been shown to be associated with significantly improved LC for oligometastatic NSCLC, stipulating for more individualised strategies such as isotoxic dose escalation for higher-risk patients [10]. Also, 2 recent models have demonstrated assuming an α/β ratio of approx. 20 Gy for early-stage NSCLC, a steep dose–response relationship with high rates of durable LC when physical doses of 43–50 Gy are delivered in 3 to 5 fractions [37]. In the current analysis we delivered similar physical doses in 3/5 fractions. However, an α/β ratio of 10 was assumed. Another systematic analysis of a large set of published clinical data using different radiobiological models showed that local tumour control probability (TCP) for SBRT of early-stage NSCLC has strong dependence on $BED_{20}$. The six models predicted that a $BED_{20}$ of 90 Gy suffices to achieve TCP ≥ 95% [38]. Vis-à-vis the TCP of lung metastases, a strong dose–response relationship has also been observed with the dose to achieve 90% TCP (TCD90; $BED_{10}$ of maximum PTV dose) estimated at 160 Gy–not significantly different from the TCD90 for primary NSCLC (176 Gy) [39]. Further, primary cancer site within the metastatic cohort was not found to influence the dose–response-relationship. A comparison of TCP models applied to 770 lung metastases found a TCD90 after 15.5 months of 146 Gy and 133 Gy for 2 fundamental Bayesian cure rate models and found the $BED_{10}$ at the isocenter to be the strongest predictor of TCP in all models [40]. Thus, in our analysis by increasing the BED (notably assuming an α/β ratio of about 10 Gy) in reoptimised plans, increase in local TCP was potentially achieved.

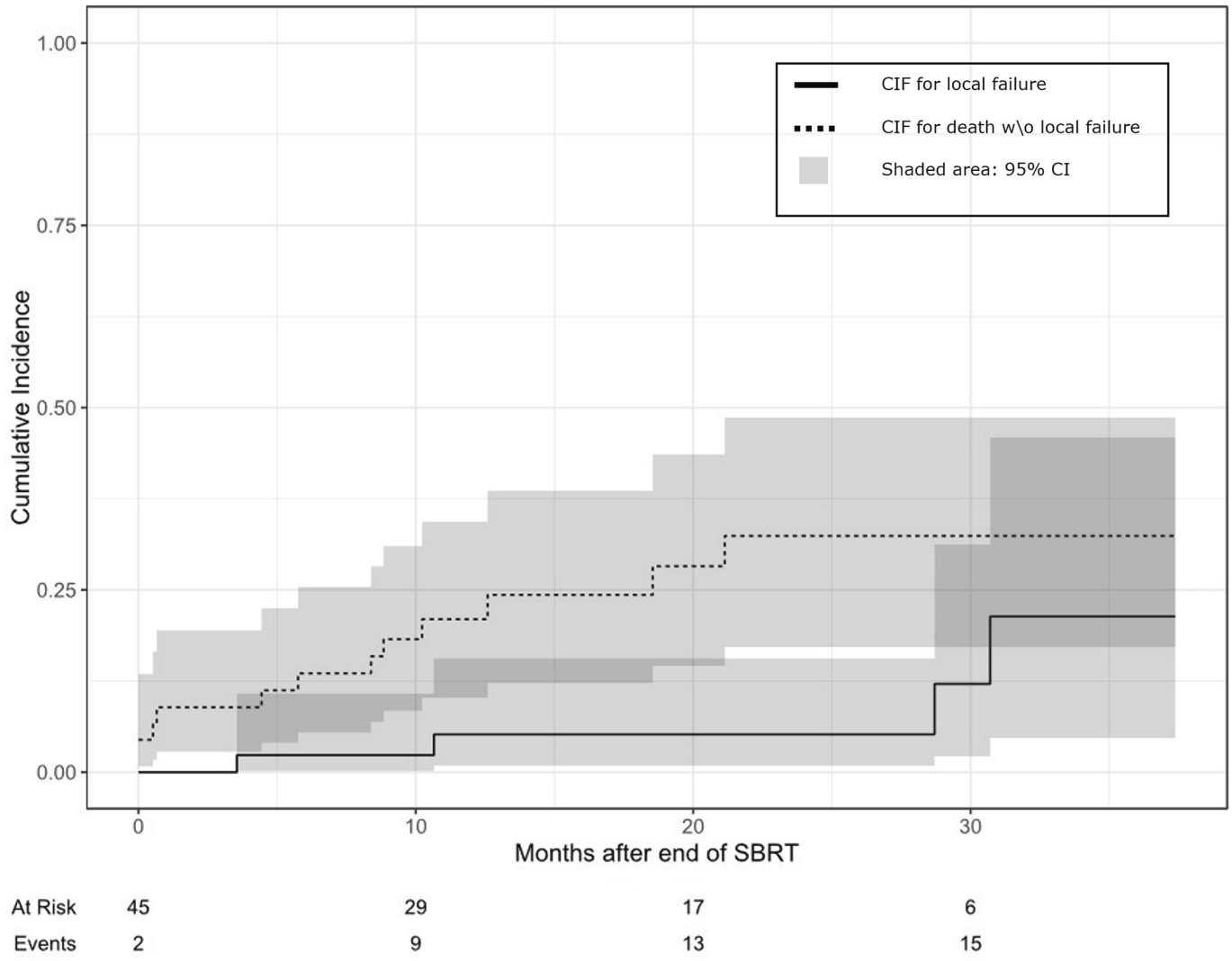


**Fig. 6.** Competing risks analysis with local failure (defined as first event per patient) vs. death before local failure. The cumulative incidence rates for death without local failure at 12 and 24 months, respectively, were 7 and 14, while the cumulative incidence of local failure at 12 and 24 months was 2, respectively.

Conversely, a recently published analysis using a Probit model determined not only $BED_{10}$ at the isocenter but also mean $BED_{10}$ to be the strongest predictors of 3-year TCD90 for NSCLC treated with SBRT [41]. In our analysis, the mean dose barely changes with plan adaptation.

In a recently published phase 2 study by Chang et al, immunotherapy with SBRT compared with SBRT alone improved event-free survival in patients with early-stage treatment-naive or recurrent node-negative NSCLC, with tolerable toxicity [42]. While phase 3 studies are pertinent to confirm these findings, this could be a potential strategy going forward for early-stage NSCLC as a large portion of our patients showed early progression or died shortly after treatment. Thus, meticulous selection of patients with oligometastatic/oligorecurrent/oligopersistent/oligoprogressive disease who could potentially benefit from local ablative treatments is pertinent.

Nevertheless, our findings further support the notion that the daily adaptive capability of oMRgRT could widen the therapeutic window for lung tumours patients, permitting isotoxic treatment intensification and increasing the therapeutic ratio of radiotherapy.

There are several clinical trials currently investigating the potential of oMRgRT in the context of lung cancer [34]. PUMA (NCT05237453) is an early clinical trial, aiming to demonstrate the feasibility of oMRgRT in locally advanced NSCLC and in a second phase aiming to compare the benefits of MR-guided vs. CT-based online adaptive radiotherapy approaches [43]. The results of such studies could improve future clinical decision-making regarding the optimal use of MR-guided radiotherapeutic treatments for lung cancer patients.

Pulmonary function tests (PFT) are a more objective measure of radiation-induced lung toxicity, and it has been suggested that pulmonary function declines in a dose-dependent manner post-treatment [44]. To better predict and prevent lung toxicities after SBRT, prospective data is needed. However, reports on PFT changes after SBRT for lung tumours are mainly from retrospective studies and contradictory [45–48]. Our findings albeit after a short follow-up showed no significant acute decline in lung function parameters. However, the relatively heterogenous intervals between pre- and post-treatment PFT in our analysis, with many short-term PFTs, limit our results since PFT metrics can decline 24 months post SBRT [49].

Furthermore, oMRgRT workflows require time consuming OAR delineation during online adaptation. Our group recently published data on deep learning autosegmentation (DLAS) for thoracic OARs using MRI planning data with DLAS contours preferred over physician contours. DLAS can surely promote reduction in total treatment times and thus improve overall patient comfort [50].

Based on our results, showing small to moderate dosimetric improvements and similar doses to organs at risk between non-adapted and adapted plans and taking into consideration that online plan adaptation can be time consuming, we can infer that the dosimetry benefits achieved with online plan adaptation for peripheral tumours likely do not

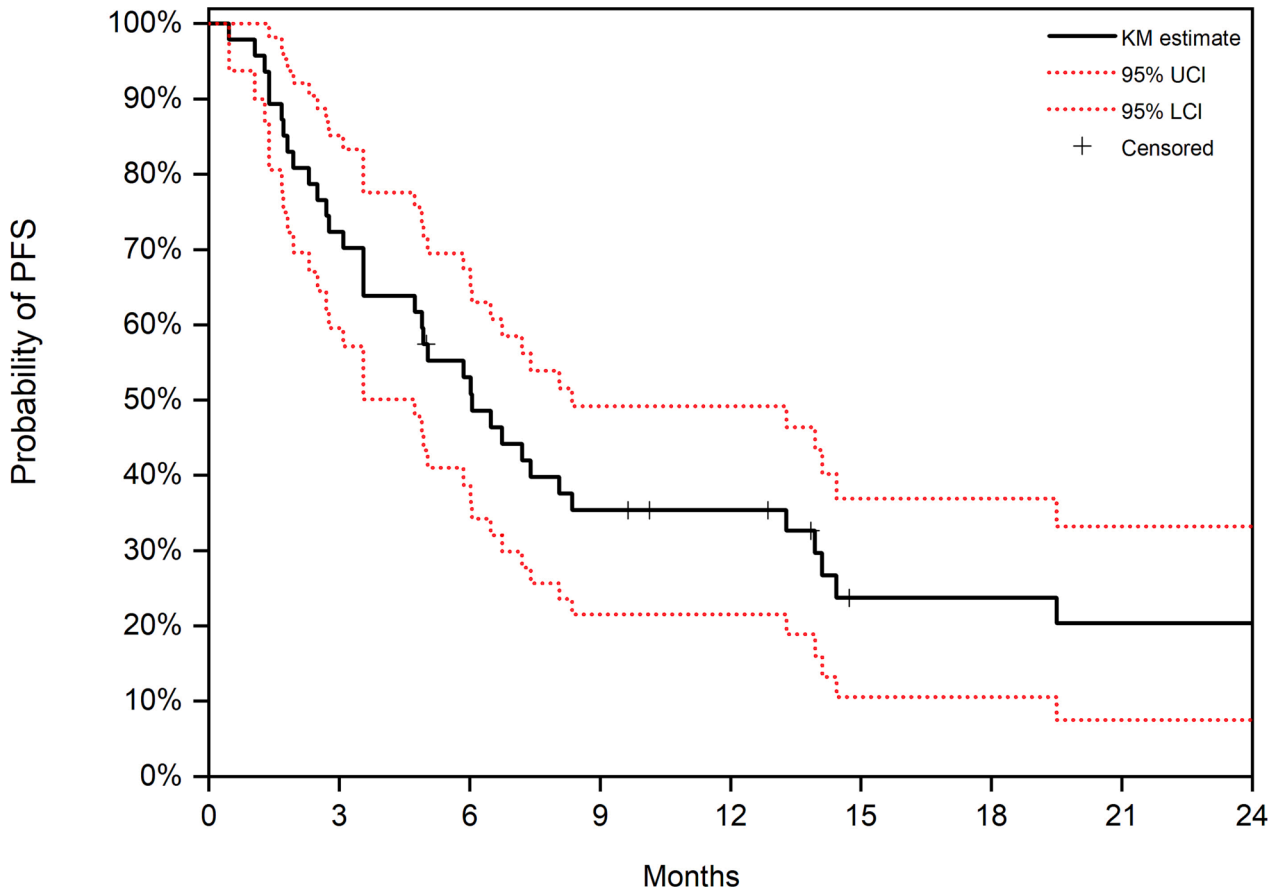


**Fig. 7.** Kaplan-Meier estimate of progression-free survival (PFS) probability. 1- and 2-year estimated PFS rates were 35.4% (95% CI: 21.5 – 49.2%) und 20.3% (95% CI: 7.5 – 33.2%), respectively.

**Table 3**
Summary of all treatment-related adverse events classified per the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) version 5.0 up to three months post-treatment (six months post-treatment for pneumonitis where applicable). Data is presented as an absolute number (percentage). The most common all-grade treatment-related toxicity was radiation pneumonitis (30%).

| Adverse events n (%) (CTCAE v. 5.0) | Grade 1 | Grade 2 | Grade 3 | Grade 4 | Grade 5 | All grades |
|---|---|---|---|---|---|---|
| Radiation pneumonitis (n = 50) | 9 (18) | 5 (10) | – | – | 1 (2) | 15 (30) |
| Dyspnoea (n = 51) | 4 (8) | 2 (4) | – | – | – | 6 (12) |
| Cough (n = 51) | 3 (6) | – | – | – | – | 3 (6) |
| Fatigue (n = 51) | 1 (2) | 1 (2) | – | – | – | 2 (4) |

result in any significant clinical benefit. Conversely, we are currently investigating dosimetry benefits and clinical outcomes of online plan adaption in our cohort of patients treated exclusively to ultra-(central) locations. The results of this analysis and further investigations at the level of accumulated dose using the approach by Rabe et al. would certainly be of interest and could complement the current literature and aid in future clinical decision making in this setting [51].

Acknowledging the limitations of the current analysis, loss to follow-up as well as individual preferences or characteristics of personnel involved in treatment planning could potentially bias our analysis. Finally, the results reflect the experience at a single tertiary cancer with a limited number of patients and a relatively heterogenous cohort.

Further studies will be indispensable to precisely evaluate the benefit of stereotactic oMRgRT in different subgroups of lung tumour patients.

## Conclusions

Online adaptive multi-fraction MR-guided SBRT is an effective, safe and generally well tolerated treatment option for lung tumours achieving excellent local control rates with significantly improved dose coverage of target volumes.

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None.

## CRediT authorship contribution statement

**Svenja Hering:** Data curation, Formal analysis, Investigation, Methodology, Validation, Visualization, Writing – original draft, Writing – review & editing. **Alexander Nieto:** Data curation, Formal analysis, Investigation, Methodology, Validation, Visualization, Writing – review & editing. **Sebastian Marschner:** Conceptualization, Investigation, Methodology, Validation, Writing – review & editing. **Jan Hofmaier:** Conceptualization, Investigation, Methodology, Validation. **Nina-Sophie Schmidt-Hegemann:** Conceptualization, Investigation, Methodology, Validation, Writing – review & editing. **Vanessa da Silva Mendes:** Conceptualization, Investigation, Methodology, Validation, Writing – review & editing. **Guillaume Landry:** Conceptualization, Investigation, Methodology, Project administration, Resources, Supervision, Validation, Writing – review & editing. **Maximilian Niyazi:** Conceptualization, Funding acquisition, Investigation, Methodology, Project administration, Resources, Supervision, Validation, Writing –

review & editing. **Farkhad Manapov:** Conceptualization, Funding acquisition, Investigation, Methodology, Project administration, Resources, Supervision, Validation, Writing – review & editing. **Claus Belka:** Conceptualization, Funding acquisition, Investigation, Methodology, Project administration, Resources, Supervision, Validation, Writing – review & editing. **Stefanie Corradini:** Conceptualization, Funding acquisition, Investigation, Methodology, Project administration, Resources, Supervision, Validation, Writing – review & editing. **Chukwuka Eze:** Conceptualization, Data curation, Formal analysis, Funding acquisition, Investigation, Methodology, Project administration, Resources, Software, Supervision, Validation, Visualization, 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: The Department of Radiation Oncology of the LMU University Hospital, LMU Munich has research agreements with ViewRay Inc., Elekta, Brainlab, and C-RAD. ViewRay Inc. did not fund this study and was not involved and had no influence on the study design, the collection or analysis of data, or on the writing of the manuscript. MN reports research grants and speaker fees/travel support from Brainlab, ViewRay, AstraZeneca. FM reports a research grant from AstraZeneca and honoraria from AstraZeneca, Novartis, Roche, Lilly, Elekta and Brainlab. FM serves on the advisory board of AstraZeneca, Novartis. CB reports receiving grants or contracts from ViewRay, Brainlab, and Elekta; payment or honoraria from Bristol-Myers Squibb, Roche, Merck, AstraZeneca, Opasca, C-RAD, Elekta, and ViewRay; receiving support for attending meetings or travel from Bristol-Myers Squibb, Roche, Merck, AstraZeneca, Elekta, and View Ray; and having a leadership or fiduciary role with ESTRO, all outside the submitted work. SC reports research grants and speaker fees/travel support from Elekta, Viewray and Brainlab. CE reports consulting fees from Novartis outside the submitted work.

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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.2024.100736.

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