Radiotherapy and Oncology 155 (2021) 131–137

Contents lists available at ScienceDirect

Radiotherapy and Oncology

journal homepage: www.thegreenjournal.com

Original Article

MLC tracking for lung SABR is feasible, efficient and delivers high-precision target dose and lower normal tissue dose

Jeremy Booth [a,b,*], Vincent Caillet [a,c], Adam Briggs [a], Nicholas Hardcastle [d,e], Georgios Angelis [a,b], Dasantha Jayamanne [a,f], Meegan Shepherd [a], Alexander Podreka [a], Kathryn Szymura [a], Doan Trang Nguyen [c,g], Per Poulsen [h], Ricky O'Brien [c], Benjamin Harris [i], Carol Haddad [a], Thomas Eade [a,f], Paul Keall [c]

[a] Northern Sydney Cancer Centre, Royal North Shore Hospital, Sydney, Australia; [b] Institute of Medical Physics, School of Physics; [c] ACRF Image X Institute, Central Clinical School, University of Sydney; [d] Department of Physical Sciences, Peter MacCallum Cancer Centre, Melbourne; [e] Centre for Medical Radiation Physics, University of Wollongong; [f] Northern Clinical School, University of Sydney; [g] School of Biomedical Engineering, University of Technology Sydney; [h] Department of Oncology and Danish Center for Particle Therapy, Aarhus University Hospital, Aarhus, Denmark; [i] Department of Respiratory and Sleep Medicine, Royal North Shore Hospital, Sydney, Australia

ARTICLE INFO

Article history:
Received 12 August 2020
Received in revised form 20 October 2020
Accepted 24 October 2020
Available online 3 November 2020

Keywords:
Lung SABR
Adaptive radiotherapy
MLC tracking

ABSTRACT

Background and purpose: The purpose of this work is to present the clinical experience from the first-in-human trial of real-time tumor targeting via MLC tracking for stereotactic ablative body radiotherapy (SABR) of lung lesions.

Methods and materials: Seventeen patients with stage 1 non-small cell lung cancer (NSCLC) or lung metastases were included in a study of electromagnetic transponder–guided MLC tracking for SABR (NCT02514512). Patients had electromagnetic transponders inserted near the tumor. An MLC tracking SABR plan was generated with planning target volume (PTV) expanded 5 mm from the end-exhale gross tumor volume (GTV). A clinically approved comparator plan was generated with PTV expanded 5 mm from a 4DCT-derived internal target volume (ITV). Treatment was delivered using a standard linear accelerator to continuously adapt the MLC based on transponder motion. Treated volumes and reconstructed delivered dose were compared between MLC tracking and comparator ITV-based treatment.

Results: All seventeen patients were successfully treated with MLC tracking (70 successful fractions). MLC tracking treatment delivery time averaged 8 minutes. The time from the start of CBCT to the end of treatment averaged 22 minutes. The MLC tracking PTV for 16/17 patients was smaller than the ITV-based PTV (range −1.6% to 44% reduction, or −0.6 to 18 cc). Reductions in mean lung dose (27 cGy) and V20Gy (50 cc) were statistically significant ($p < 0.02$). Reconstruction of treatment doses confirmed a statistically significant improvement in delivered GTV D98% ($p < 0.05$) from planned dose compared with the ITV-based plans.

Conclusion: The first treatments with lung MLC tracking have been successfully performed in seventeen SABR patients. MLC tracking for lung SABR is feasible, efficient and delivers high-precision target dose and lower normal tissue dose.

Introduction

Tumor motion in the thorax and abdomen is three dimensional, complex and can vary within and between fractions [1,2]. Motion during treatment may exceed that measured during the 4DCT used for planning [3–5]. This motion complexity is optimally managed by real-time adaptive radiation therapy, where the radiation beam-target alignment is maintained during treatment obviating the need for an ITV. Real-time adaptation corrects the delivery for motion at treatment, including motion variations and baseline shifts. The clinical potential of such techniques should enable fidelity of dose painting to targets (with functional imaging) for improved outcomes and shrinking of high dose volumes to further alleviate treatment related toxicity. Inherent safety is achieved from the real-time motion monitoring during treatment delivery beyond that of pre-treatment imaging.

Real-time adaptive radiotherapy has been clinically implemented in the CyberKnife system [6] (Accuray Inc. Sunnyvale, USA), RadiXact [7], (Accuray Inc. Sunnyvale, USA) and Vero systems [8] (BrainLab AG, Feldkirchen, Germany) demonstrating an

* Corresponding author at: Northern Sydney Cancer Centre, Level 1 Royal North Shore Hospital, Reserve Rd St Leonards, NSW 2065, Australia.
E-mail address: Jeremy.Booth@health.nsw.gov.au (J. Booth).

https://doi.org/10.1016/j.radonc.2020.10.036
0167-8140/

increased target accuracy [9–11]. MLC tracking is a form of real-time adaptive radiotherapy enabled on a conventional linear accelerator (linac) utilizing the MLC to adapt to location and pose changes during treatment representing a potentially highly accessible motion management solution. First experimentally conceptualized in 2001 [12], MLC tracking has been implemented on all major linac vendors (Varian [13], Siemens [14] and Elekta [15,16]) in a research setting and was first clinically implemented in 2013 for prostate cancer [17]. The preliminary result for the first lung SABR patient was reported previously [18].

The present study reports the results of the first clinical trial of real-time adaptive radiotherapy using electromagnetic transponder-guided MLC tracking for lung SABR. We report on the feasibility, efficiency, dosimetric accuracy, and clinical outcomes of the MLC tracking treatments.

Methods and materials

Seventeen patients with primary NSCLC (n = 7) or metastases (n = 10) underwent electromagnetic transponder-guided MLC tracking in this ethics-approved clinical trial (NCT02514512). A technical summary of the MLC tracking is provided in Supplementary Materials. The patient cohort is summarized in Table 1.

The study outline is shown in Fig. 1. The primary hypothesis was that MLC tracking is feasible. Treatment efficiency was measured. Secondary outcomes included: evaluation of transponder implantation safety and migration, comparison of target volumes between MLC tracking and ITV-based, comparison of treatment plans between MLC tracking and ITV-based, comparison of delivered vs. planned dose between MLC tracking and ITV-based, and recording patient outcomes. Further study results are provided in Supplementary Materials, including geometric accuracy, excursion rate, patient reported outcomes and analysis of visual feedback.

Table 1
Characteristics of 17 patients who underwent radiotherapy.

Variable	n = 17 (%)
Age at recruitment (y)	
Mean (range)	72 (40–89)
Patient Gender	
Female	4 (24)
Male	13 (76)
Diagnosis	
Primary non-small cell lung cancer	7 (41)
Metastases*	10 (59)
Lesion size (cc)	
Mean (range)	5.4 (0.4–15.0)
Performance status ECOG	
0	12 (71)
1	5 (29)
2–4	0 (0)
Tumor location	
Lower left lobe	4 (24)
Lower right lobe	6 (35)
Upper left lobe	3 (18)
Upper right lobe	3 (18)
Lingula	0 (0)
Middle right lobe	1 (6)
Fractionation, Gy (No. fractions)	
48 (4)	15 (88)
50 (5)	2 (12)
Patient treatment orientation	
Supine	10 (59)
Prone	6 (35)
Lateral decubitus	1 (6)
Peak-to-peak tumor motion from 4DCT, cm	
Mean (range)	0.9 (0.3–1.8)

*Primary site for metastases were (n): colorectal (3), head and neck (2), endometrial (1), pancreas (1), hepatocellular carcinoma/liver (1), thyroid (1), renal cell cancer (1). Only individual metastases were treated per patient.

Primary Endpoint – Feasibility of MLC tracking. The primary endpoint of feasibility is defined as successful delivery of at least 90% of the treatment fractions. A successful delivery requires correct software control of the MLC to follow the target motion without MLC tracking software failure. The primary hypothesis was tested using maximum likelihood estimation (MATLAB binofit function, MathWorks, USA).

Endpoint – Treatment efficiency. The mean time taken for CBCT imaging and review (CBCT start to the start of the first treatment field) and the mean time for treatment delivery (first treatment field to last) was recorded from the logfiles from each fraction.

Secondary Endpoint – Transponder implantation, migration, and motion. Two (n = 3) or three (n = 14) cylindrical anchored lung transponders (14 mm long, 2 mm diameter) were implanted under sedation one week prior to simulation using standard fiber optic bronchoscopy with X-ray image guidance. Transponder implantation was planned to surround the lesion. Prior to treatment, planning contours for PTV and transponders were overlaid on the CBCT scan to assess potential migration and alignment. During treatment the transponder location is transmitted 25 times per second with sub-mm accuracy [19,20]. Fluoroscopic X-ray imaging of the lung was acquired at two orthogonal angles for 2–3 breaths to visually inspect transponder/lesion motion prior to each treatment.

Transponder motion was recorded from 4DCT, CBCT and fluoroscopy at treatment for quantitative assessment. A tumor excursion percentage is reported as the percentage of time that the lesion moves outside the PTV during treatment delivery.

Secondary Endpoint – Comparison of PTV between MLC tracking and ITV-based plans. A planning 4DCT scan was performed using an external surrogate for respiratory motion, the Varian Real-time Position Management (RPM) system (Varian Medical Systems, Palo Alto, CA), with the patient free-breathing and positioned in a vacuum immobilization device with arms above head.

Contours for treatment planning were drawn for MLC tracking, and for comparison, to be used if MLC tracking was unavailable or failed, for an ITV-based plan. MLC tracking contours were drawn on the end-of-exhale phase as a reference phase to define the GTV with the clinical target volume (CTV) defined as being equal to the GTV. A 5 mm expansion was applied to form the PTV. The end-of-exhale phase assures a proper localization and delineation of the tumor [21–23] while the 5 mm margin has been described in the literature to be sufficient to account for tracking system latency up to 500 ms [24] and differences in tumor sizes and shape during respiration [25]. The exhale phase CT scan is likely to have the fewest imaging artifacts, and having the smallest lung volume, is likely to over- rather than under-estimate the actual lung dose. Contours for the ITV-based plan were derived from the 4DCT which included the union of GTVs in each breathing phase. The ITV was expanded by 5 mm to create the PTV. We tested the hypothesis that PTV for MLC tracking will be smaller than for ITV-based planning. This hypothesis was considered statistically significant if p-value <0.05 using the Wilcoxon signed rank test.

Secondary Endpoint – Comparison of MLC tracking and ITV-based plan dosimetry. Treatment plans were created in the Eclipse planning system (v13.6, Varian Medical Systems, Palo Alto) for a 6 MV dual RapidArc delivery utilizing the AAA algorithm. The collimator was angled to align the MLC leaves with the major motion axis of the lesion (i.e. superior-inferior in most cases) and the arcs rotated between 0 and 180 degrees (Varian IEC). MLC tracking plans utilized the end-of-exhale phase as a reference phase for dose calculation. The ITV-based plan was calculated on a mean CT image from 4DCT. Both plans met the dose volume criteria of RTOG 0915 [26] and were clinically approved. The fractionation scheme was either 48 Gy in four fractions or 50 Gy in five fractions

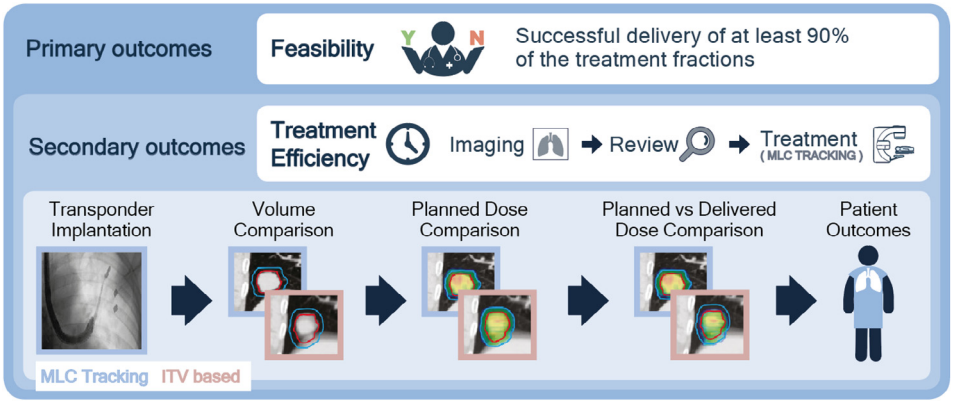

Fig. 1. Study outline. Patients received MLC tracking treatment. Primary outcome is feasibility with a range of geoemtric, dosimetric and clinical secondary outcomes. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

delivered to at least 95% of the PTV. Mean lung dose (MLD) and lung V20Gy are defined per RTOG as lung subtracting GTV/ITV. We tested the hypothesis that MLC tracking provided lower lung dose (MLD and V20Gy) compared to ITV-based planning is statistically significant if p-value <0.05 using the Wilcoxon signed rank test.

Secondary Endpoint – Comparison of delivered vs planned dose between MLC tracking and ITV-based plans. At treatment sessions, the patient was aligned to lasers in the vacuum immobilization device. Motion of transponders were monitored and aligned for final patient positioning in the treatment room. For each fraction, CBCT was acquired and a best-fit alignment to the transponders was performed. The PTV contour was overlaid to review tumor coverage.

The dose reconstruction method of Poulsen [27] was applied to estimate the delivered dose with MLC tracking and ITV-based plans, as described previously [28]. As 4D CBCT was not available for this study, the dose reconstruction was performed on the planning 4DCT scan. Briefly, for targets, transponder motion traces and MLC logfiles were encoded into the treatment plan recalculated in the treatment planning system on the planning dataset. The variation in delivered dose across fractions was compared against the planned dose for MLC tracking and the ITV-based plans. For each patient we record the range of [planned-delivered] dose for each metric e.g. GTV D100% as a measure of fidelity in delivery.

Secondary Endpoint – Patient outcomes (survival, toxicity and quality of life). For all patients we collected any site of failure (local, regional or distant). Local failure was based on either PET avid disease, positive biopsy findings or progressive growth on subsequent CTs as deemed by the Multi-Disciplinary Team (MDT). Patients had CT scans prior to clinical follow-up, at 3 month intervals during the first 2 years followed by 4 month intervals in the 3rd and 4th years and a 6 month interval in the 5th year. Toxicity was assessed utilizing the Common Terminology Criteria for Adverse Events (CTCAE v4.0) at baseline and every 3 months after treatment to 2 years. Quality of life was assessed using the European Organization for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire-Core 30 (QLQ-C30) and the Quality of Life Questionnaire Lung Cancer 13 (QLQ-LC13). Patients were asked to complete the EORTC-QLQ-C30, EORTC-QLQ-LC13 and Pain Thermometer at baseline on initial visit, first day of treatment, last day of treatment and every 3 months following treatment for 2 years. These results were reported in the Supplementary Material.

Overall survival (OS) and progression free survival (PFS) are estimated using the Kaplan-Meier method. Time to first failure is estimated with cumulative incidence adjusting for competing risks. Time to local failure is also estimated assuming that ongoing assessments are made after other failures are observed.

Results

All 70 MLC tracking treatment fractions for 17 patients were successful i.e. treated without failure of MLC tracking software. Maximum likelihood analysis yielded an estimated success rate of 100%, with 99% confidence intervals of (93%, 100%). Therefore, we accept the primary hypothesis that MLC tracking is feasible.

The mean time taken for CBCT imaging and review was 14 minutes (range 4–50 min). The mean time for treatment delivery was 8 minutes (range 2–26 min). The mean time from start of CBCT to end of last field was 22 minutes (range 15–40 min).

No bleeding, hematoma, leakage, infection or other complications were observed in relation to the transponder implantations. For 3 patients, 1 of 3 implanted transponders was not tracked by the Calypso system. For one of these patients, a transponder was outside the detection volume; for the other two patients it was shown that a group of two provided a superior surrogate based on 4DCT review (and confirmed with fluoroscopy on first day). No migration of any transponders between simulation and treatment, or during treatment, was observed.

The mean lesion motion amplitude in the 4DCT scan was 5.9 mm (range 1.7–11.7 mm) in the superior-inferior (SI), 2.2 mm (range 0.9–5.5 mm) in the left–right (LR), and 3.9 mm (range 1.2–12.9 mm) in the anterior-posterior (AP) direction. The mean GTV motion amplitude during treatment was larger than at 4DCT, ranging from 2.4 – 39.4 mm in the SI, 1.5–13.4 mm in the LR, and 1.6–19.8 mm in the AP directions. In one patient, a single transponder was placed in a neighboring lobe, and all three transponders were tracked.

Motion of the transponders during treatment was observed to be larger than captured during CT simulation [4,18]. Motion extending outside the PTV, a 5 mm expansion of the ITV, is reported as the tumor excursion percentage. Data from the 17 patients estimates tumor excursion for the ITV-based plans would have occurred on average 3.3%, 0.02%, and 0.7% of the time, in the SI, LR, and AP directions respectively. Four patients exhibited an SI excursion rate on at least one day of more than 5%. The average (and range) of excursion rate for this subgroup was 15.4% (7.9–24.5%), 16.1% (4.9–31.6%), 8.7% (3.3–14.9%), and 9.6% (0–27.5%). Conventionally, SABR delivery does not deploy intra-treatment tumor monitoring so any geometric miss would have been undiscovered.

Fig. 2 shows the reducing PTV with MLC tracking relative to the ITV-based PTV. The mean (standard deviation (SD), range) of the

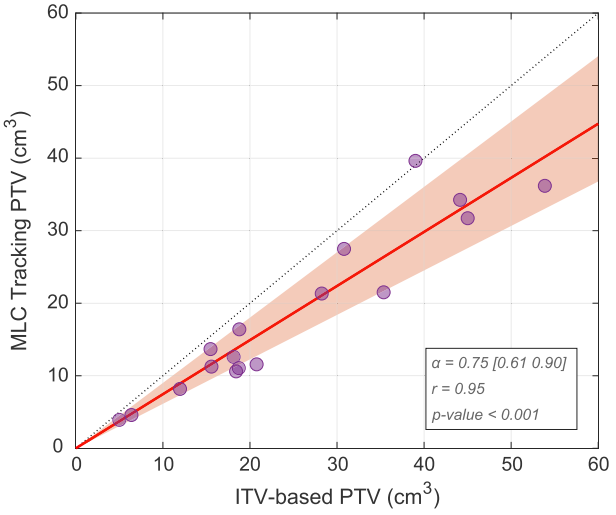

Fig. 2. Scatter plot of MLC tracking PTV against ITV-based PTV. The dotted line corresponds to the line of equality, while the thick solid line corresponds to the linear regression fit ($a = 0.746$, Pearson $r = 0.945$). The shaded area represents the 95% confidence interval of the estimated regression slope (0.613, 0.901). The reduction in PTV size between MLC tracking and ITV-based planning is significant ($p < 0.001$).

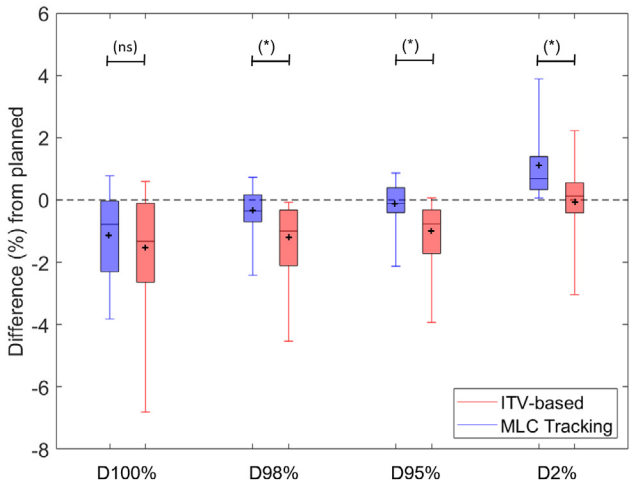

Fig. 3. Percentage difference between accumulated planned and delivered GTV dose per patient ($n = 17$) for key target dose metrics comparing MLC tracking (blue) with ITV-based plans (red). Boxes indicate quartiles, median (line) and average (cross), while whiskers indicate the minimum and maximum. Key: (ns) not significant and (*) significant for $p < 0.02$). (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

PTV with MLC tracking and ITV-based planning was 18.6 cc (11.4, 3.9–39.6) and 25.0 cc (14.2, 5.0–53.9), respectively. The mean (SD, range) of the PTV reduction with MLC tracking was 26.4% (12.6%, −1.6–44.3%) or 6.4 cc (5.1 cc, −0.6 cc–17.7 cc) compared to the ITV-based PTV. A single case (Patient 17) with PTV = 39 cc exhibited a slightly larger PTV with MLC tracking (increase of 1.6% or 0.6 cc). The lesion for this patient experienced very small motion along the SI direction (<3 mm) providing minimal internal margin for motion. As CTV is contoured on average CT for ITV-based planning and on end-exhale phase image, the difference has been attributed within the intra-observer uncertainty range of contouring. The Wilcoxon signed-rank test p-value of the PTVs with MLC tracking compared to those with ITV-based planning was less than 0.001, confirming the hypothesis that the PTV reduction is statistically significant.

All treatment plans for MLC tracking and for ITV-based planning met the planning dose constraints. Planned MLD reduced from 2.91 Gy for ITV-based planning to 2.64 Gy for MLC tracking. In relative terms, MLD was reduced on average by 27 cGy (SD 40 cGy) with reductions ranging from −37 (increase) to 123 cGy. This reduction in MLD was statistically significant (Wilcoxon signed-rank test $p < 0.02$). The volume of lung (excluding GTV) receiving 20 Gy was reduced from 297 cc for ITV-based planning to 247 cc (8.7%) for MLC tracking. In relative terms, V20Gy was reduced by 50 cc (SD 52 cc) ranging from −20 (increase) to 196 cc with MLC tracking. This reduction in V20Gy was statistically significant (Wilcoxon signed-rank test $p < 0.02$). Five of seventeen patients demonstrated a higher MLD and 1/17 patients demonstrated a higher lung V20Gy with the MLC tracking plan despite having a smaller PTV. This difference is attributed to a combination of factors including small motion, dose calculation in the exhale phase rather than on an average CT, and plan quality.

Dose reconstruction of the delivered target dose with MLC tracking showed improved fidelity of the planned dose compared to the ITV-based plan in terms of accuracy and reproducibility. Fig. 3 shows the percentage difference between planned GTV dose metrics (D100%, D98%, D95%, and D2%) and reconstructed delivered doses including actual motion. Average dosimetric delivery accuracy was improved for D98% and D95% for the MLC tracking plans compared with the ITV-based plans. Specifically, the mean difference between planned and delivered GTV D100% was reduced from −1.7% (ITV plan) to −1.1% (MLC tracking plan), −1.4% to −0.4% for D98% and −1.2% to −0.1% for D95%. GTV D2% difference from planned increased with MLC tracking compared with ITV-based by 1.1% on average and up to 3.7%. This increase in D2% localized as a central hotspot is a common dose artifact for MLC tracking [29]. PTV D98% for MLC tracking was 99.4 ± 1.4% (planned) and 96.0 ± 3.9% (delivered) compared to ITV-based with 99.8 ± 20.6% (planned) and 92.0 ± 8.9% (delivered). PTV D2% for MLC tracking was 116.2 ± 3.4% (planned) and 117.3 ± 3.8% (delivered) compared to ITV-based with 116.8 ± 4.5% (planned) and 116.6 ± 4.4% (delivered).

The delivered doses are more reproducible with MLC tracking for D100%, D98% and D95%. The mean difference between treated and planned GTV D100% was −1.1 ± 2.3% for MLC tracking and −1.7 ± 2.4% for ITV-based. Differences for GTV D98% was −0.4 ± 1.4% for MLC tracking and −1.4 ± 1.7% for ITV-based. Differences for GTV D95% was −0.1 ± 1.3% for MLC tracking and −1.2 ± 1.7% for ITV-based. Differences for GTV D2% was 1.1 ± 1.4% with MLC tracking and −0.1 ± 1.6% for ITV-based.

Fig. 4 shows the best and worst case dose volume histograms (DVHs) for MLC tracking patients assessed by difference in PTV D95% values between plan and actual value. DVHs for all patients are shown in Supplementary Fig. 1. Unlike previous experience with MLC tracking for prostate where the same plan is used for tracking and non-tracking, for lung SABR, the respiratory motion led to different target volumes and different dose distributions between tracking and non-tracking. Each day's treatment delivery will encounter different motion providing different delivery accuracy evident in the thin line DVH curves, as compared to the thick lines marking the planned DVH. Fig. 5 shows dose distributions for best and worst cases for both MLC tracking and ITV-based plans. These dose distributions show the total dose over 4 or 5 fractions.

The median follow-up for our cohort of patients was 27.5 months with 5 deaths recorded, with 4 patients succumbing to their disease. There were 2 local failures with a median time to local failure of 17.0 months. The time to local failure for the two failures were 9.8 and 24.1 months. The PFS for the entire group was 16.8 months. There were 2 patients with CTCAE grade 2 toxicity (both pneumonitis), with no patients having grade 3 or greater toxicity. Further detail including Quality of Life (QoL) data is provided in Supplementary Data.

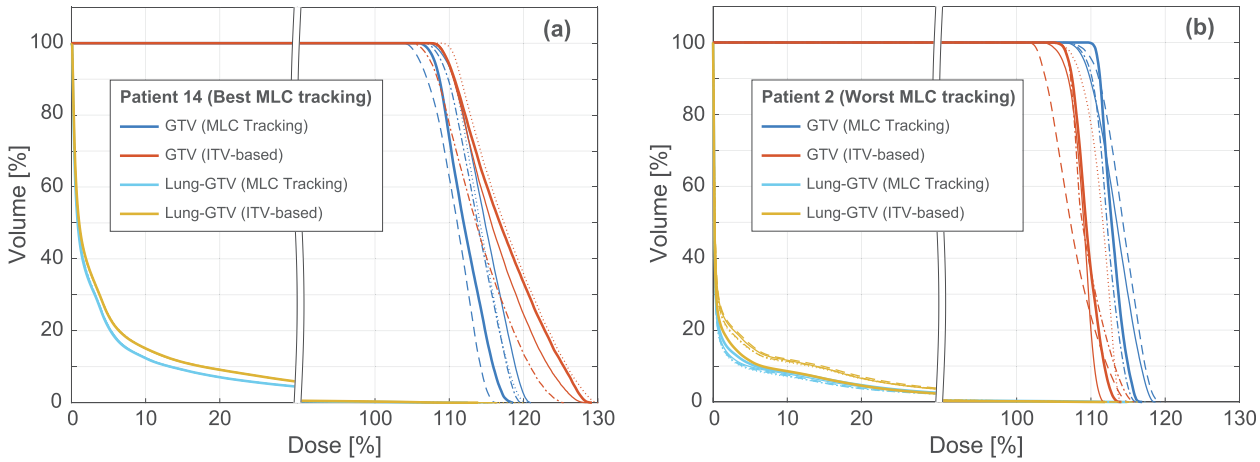

Fig. 4. Dose Volume Histograms for 'best' and 'worst' cases for MLC tracking rated by difference between planned and delivered PTV D95% value. Planned dose (thick curves) is shown against daily delivered doses at each fraction (thin curves: solid, dashed, dotted, and dot-dashed for 4 fractions). The GTV for MLC tracking (dark blue) and ITV (red), as well as the normal lung (subtracting target) for MLC tracking (light blue) and ITV-based plan (orange) are shown. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

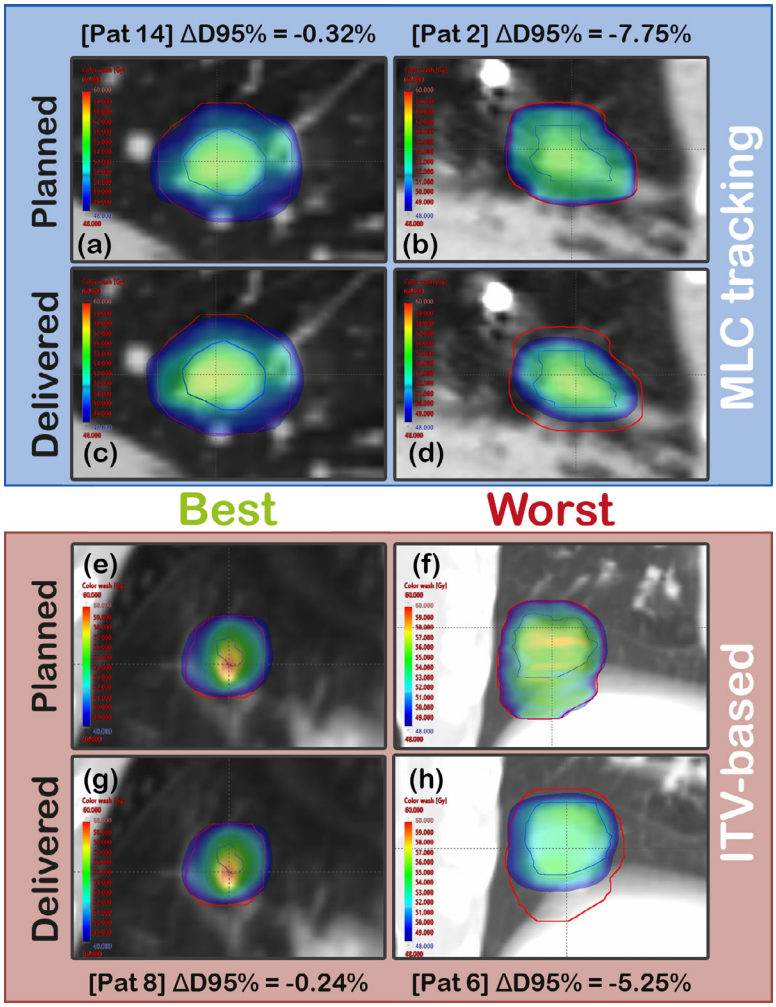

Fig. 5. Dose distributions for 'best' and 'worst' cases ranked by difference between planned and delivered PTV D95% value. GTV shown as blue contour and PTV as red contour. All doses represent a full course of treatment. (a–d) MLC tracking examples. (e–h) ITV-based cases.

Discussion

The first real-time adaptive trial using MLC tracking for lung SABR has been performed. MLC tracking produced reductions in PTV in line with other real-time motion management techniques, such as CyberKnife [30], RadiXact [31] and Vero [22]. MLC tracking is potentially highly accessible since it requires only software additional to a standard linac with real-time motion monitoring [32].

This study was designed to test feasibility of MLC tracking across a typical lung SABR patient cohort with a range of disease sites and tumors exhibiting large and small motion. We expected MLC tracking to do no worse than the comparator ITV-based plans, and within the accuracy of our reporting this has been demonstrated for all courses of treatment. Some individual fractions demonstrated inferior tumor dose coverage compared with the plan. In these 'worst' cases, there were multiple contributing factors including system latency requiring prediction which introduced uncertainty and error in the presence of irregular motion. Real-time adaptation systems, such as RadiXact, Vero and Unity have reported system latencies of 70 ms [31], 48 ms [22] and 20 ms [16], respectively. Commercial MLC tracking systems have lower system latency than our research system (220 ms, see Supplementary Materials) allowing a superior response to irregular motion, which proved to be challenging to predict and control at the time of treatment for some fractions in this study.

ITV-based planning will produce larger PTVs than respiratory gated or breath hold techniques, which provide similar PTVs to MLC tracking [33,34]. The mid-ventilation technique compares similarly to ITV-based approach [28,35]. Despite this larger PTV, the delivered dose with an ITV-based plan will be influenced predominantly by the tumor motion at treatment. We have shown previously for this patient cohort, and elsewhere [3,5] that lesions affected by respiratory motion generally exhibit (50%) greater peak-to-peak motion at treatment than measured during 4DCT. Importantly, baseline drifts were observed during treatment in this cohort. Baseline drifts are deleterious to the accuracy of any delivery technique that operates without lesion motion management during delivery. We used real-time transponder tracking to monitor motion during setup, CBCT and treatment fractions with MLC tracking activated. The notable wait time between CBCT and first treatment field (mean 14 min; max 50 min) due to extra care with alignment between transponders and soft tissue, rotation and potential repeat CBCT, did not affect the accuracy of MLC tracking.

MLC tracking has been shown to deliver treatment with high precision enabling reductions in dose delivered to healthy lung. This study has shown reductions in MLD up to 123 cGy and average 27 cGy are achievable. MLD has been shown to indicate toxicity. Barriger et al. [36] show rates of grade 2+ radiation pneumonitis at 4.3% where MLD < 4 Gy, and 17.6% with MLD > 4 Gy. Chang et al. [37] show an increase in grade 2+ radiation pneumonitis with MLD above 6 Gy. In this study, all plans (ITV-based and MLC tracking) met MLD constraints of 4 Gy and therefore no lung toxicity reduction is expected for this cohort.

The secondary endpoints of the trial were patient outcomes. The median follow-up for the cohort was 27.5 months. There were 2 local failures with the actuarial 1 year OS 88%, 2 year OS 88% and 1 year PFS 53%, 2 year 39%. The rate of grade 2 toxicity was low (11.7%) with no higher grade 3–5 toxicity. For the QoL data please see the Supplementary Material.

There were limitations to this study; patient orientation, inclusion of patients with small motion, and study size. We would have treated all of the patients in the supine orientation. However, limitations with the detectable lesion depth (maximum of 17 cm) of the motion monitoring equipment led to 7 of 17 patients requiring non-standard prone or lateral decubitus orientation. Treatment in prone orientation may have caused slower and less robust patient setup compared to our standard supine orientation. As a feasibility study, we included all patients to gain an understanding across a range of clinical scenarios, no patient received a worse treatment. Considering the rapid delivery and automation of real-time adaptation, we suggest that with care in patient selection (e.g. central lesions) and implementation (e.g. gating if motion towards, not away from, dose limiting structure) that MLC tracking should be safe and efficient for all patients, not only those patients with lower lobe disease. This study required 17 of 20 patients to achieve statistical significance for primary hypothesis that MLC tracking is feasible. A larger study is needed to draw conclusions on any clinical benefit, though there are clear dosimetric benefits.

Real-time adaptive radiotherapy has been commercially available for 15 years; to date all versions have used kV X-rays, transponders and/or optical surface tracking to synchronize treatment delivery with lesion/surrogate centroid motion. The next level of sophistication in real-time radiotherapy might be systems that track real-time dose accumulation to a rigid or deforming target volume, or consider accumulated dose to organs at risk. Such systems are emerging but require real-time anatomy as input to link to real-time dose adaptation. MRI-Linacs have been implemented with MLC tracking to provide high soft tissue contrast for guidance [16,38], so when combined with real-time dose prediction should lead to full automation in alignment, control and delivery. For X-ray and optical guidance systems, there continues to be development of motion models and direct tracking techniques with increasing accuracy for a range of tumor targets. Real-time adaptive radiotherapy aligns with contemporary areas of development in intelligent systems and automation that should see existing barriers overcome and such techniques deployed broadly in the future.

In conclusion, the first trial with MLC tracking has been successfully performed in seventeen lung cancer patients. MLC tracking for lung SABR is feasible, efficient and delivers high-precision target dose and lower normal tissue dose.

Conflict of interest statement

In the interests of full disclosure of a conflict of interest, Dr Keall is an inventor on the awarded US patents 7,469,035 and 8,971,489 that are related to MLC tracking. Dr Booth has a collaborative research agreement with Varian Medical Systems to support this clinical trial.

Data sharing statement

Research data are not available at this time.

Sources of funding

The authors acknowledge Varian Medical Systems and Royal North Shore Hospital No2 Trust for supporting this study.

Clinical trial information

Trial information can be found at clinicaltrials.gov NCT02514512.

Acknowledgements

The authors thank Clare Banks, Helen Ball, Danielle Chrystall, Julia Johnson, Emily Hewson, and the entire Radiotherapy Unit at Northern Sydney Cancer Centre. Scott Johnson and Varian Medical

Systems are thanked for their support in facilitating the clinical implementation, including a loan of hardware and software.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.radonc.2020.10.036.

References

[1] Suh Y et al. An analysis of thoracic and abdominal tumour motion for stereotactic body radiotherapy patients. Phys Med Biol 2008;53:3623.
[2] Shah AP et al. Real-time tumor tracking in the lung using an electromagnetic tracking system. Int J Radiat Oncol Biol Phys 2013;86:477–83.
[3] Jones BL, Schefter T, Miften M. Adaptive motion mapping in pancreatic SBRT patients using Fourier transforms. Radiother Oncol 2015;115:217–22.
[4] Steiner E et al. Both four-dimensional computed tomography and four-dimensional cone beam computed tomography under-predict lung target motion during radiotherapy. Radiother Oncol 2019;135:65–73.
[5] Ge J et al. Planning 4-dimensional computed tomography (4DCT) cannot adequately represent daily intrafractional motion of abdominal tumors. Int J Radiat Oncol Biol Phys 2013;85:999–1005.
[6] Hoogeman M et al. Clinical accuracy of the respiratory tumor tracking system of the cyberknife: assessment by analysis of log files. Int J Radiat Oncol Biol Phys 2009;74:297–303.
[7] First Cancer Patient Treated With Accuray Radixact System With Synchrony Motion Tracking. Imaging Technology News online article 21/8/2020 [cited 21/9/2020]; Available from: https://www.itnonline.com/content/first-cancer-patient-treated-accuray-radixact-system-synchrony-motion-tracking.
[8] Van den Begin R et al. Motion management during SBRT for oligometastatic cancer: results of a prospective phase II trial. Radiother Oncol 2016;119:519–24.
[9] Chang SD et al. An analysis of the accuracy of the CyberKnife: a robotic frameless stereotactic radiosurgical system. Neurosurgery 2003;52:140–7.
[10] Matsuo Y et al. Evaluation of dynamic tumour tracking radiotherapy with real-time monitoring for lung tumours using a gimbal mounted linac. Radiother Oncol 2014;112:360–4.
[11] Prévost J-B et al. Stereotactic radiotherapy with real-time tumor tracking for non-small cell lung cancer: clinical outcome. Radiother Oncol 2009;91:296–300.
[12] Keall P et al. Motion adaptive x-ray therapy: a feasibility study. Phys Med Biol 2001;46:1.
[13] Sawant A et al. Management of three-dimensional intrafraction motion through real-time DMLC tracking. Med Phys 2008;35:2050–61.
[14] Tacke MB et al. Real-time tumor tracking: automatic compensation of target motion using the Siemens 160 MLC. Med Phys 2010;37:753–61.
[15] Fast MF et al. Dynamic tumor tracking using the Elekta Agility MLC. Med Phys 2014;41.
[16] Glitzner M et al. MLC-tracking performance on the Elekta unity MRI-linac. Phys Med Biol 2019;64:p. 15NT02.
[17] Keall PJ et al. The first clinical implementation of electromagnetic transponder-guided MLC tracking. Med Phys 2014;41.
[18] Booth JT et al. The first patient treatment of electromagnetic-guided real time adaptive radiotherapy using MLC tracking for lung SABR. Radiother Oncol 2016;121:19–25.
[19] Murphy MJ et al. The effect of transponder motion on the accuracy of the Calypso Electromagnetic localization system. Int J Radiat Oncol Biol Phys 2008;72:295–9.
[20] Parikh P et al. 4D verification of real-time accuracy of the Calypso system with lung cancer patient trajectory data. Int J Radiat Oncol Biol Phys 2005;63:S26–7.
[21] Berbeco RI et al. Residual motion of lung tumours in gated radiotherapy with external respiratory surrogates. Phys Med Biol 2005;50:3655.
[22] Depuydt T et al. Treating patients with real-time tumor tracking using the Vero gimbaled linac system: implementation and first review. Radiother Oncol 2014;112:343–51.
[23] Persson GF et al. Interobserver delineation variation in lung tumour stereotactic body radiotherapy. Br J Radiol 2014;85:e654–60.
[24] Bedford JL et al. Effect of MLC tracking latency on conformal volumetric modulated arc therapy (VMAT) plans in 4D stereotactic lung treatment. Radiother Oncol 2015;117:491–5.
[25] Senthi S et al. Investigating strategies to reduce toxicity in stereotactic ablative radiotherapy for central lung tumors. Acta Oncol 2014;53:330–5.
[26] Group, R.T.O.. RTOG 0915, a randomized phase II study comparing 2 Stereotactic Body Radiation Therapy (SBRT) schedules for medically inoperable patients with stage I peripheral non-small cell lung cancer. Philadelphia (PA): RTOG; 2009.
[27] Poulsen PR et al. A method of dose reconstruction for moving targets compatible with dynamic treatments. Med Phys 2012;39:6237–46.
[28] Caillet V et al. MLC tracking for lung SABR reduces planning target volumes and dose to organs at risk. Radiother Oncol 2017;124:18–24.
[29] Poulsen PR et al. Simulated multileaf collimator tracking for stereotactic liver radiotherapy guided by kilovoltage intrafraction monitoring: Dosimetric gain and target overdose trends. Radiother Oncol 2020;144:93–100.
[30] Yang Z-Y et al. Target margin design for real-time lung tumor tracking stereotactic body radiation therapy using CyberKnife Xsight Lung Tracking System. Sci Rep 2017;7:1–11.
[31] Schnarr E, et al., Feasibility of real-time motion management on the Radixact™ System. 2017.
[32] Keall PJ et al. The first clinical implementation of real-time image-guided adaptive radiotherapy using a standard linear accelerator. Radiother Oncol 2018;127:6–11.
[33] Wolthaus JW et al. Comparison of different strategies to use four-dimensional computed tomography in treatment planning for lung cancer patients. Int J Radiat Oncol Biol Phys 2008;70:1229–38.
[34] Ehrbar S et al. ITV, mid-ventilation, gating or couch tracking–A comparison of respiratory motion-management techniques based on 4D dose calculations. Radiother Oncol 2017;124:80–8.
[35] Bellec J et al. ITV versus mid-ventilation for treatment planning in lung SBRT: a comparison of target coverage and PTV adequacy by using in-treatment 4D cone beam CT. Radiat Oncol 2020;15:1–10.
[36] Barriger RB et al. A dose–volume analysis of radiation pneumonitis in non–small cell lung cancer patients treated with stereotactic body radiation therapy. Int J Radiat Oncol Biol Phys 2012;82:457–62.
[37] Chang JY et al. Clinical outcome and predictors of survival and pneumonitis after stereotactic ablative radiotherapy for stage I non-small cell lung cancer. Radiat Oncol 2012;7:152.
[38] Yun J et al. First demonstration of intrafractional tumor-tracked irradiation using 2D phantom MR images on a prototype linac-MR. Med Phys 2013;40:051718.