The first patient treatment of electromagnetic-guided real time adaptive radiotherapy using MLC tracking for lung SABR

Jeremy T. Booth [a,b,] , Vincent Caillet [a,b], Nicholas Hardcastle [a,c], Ricky O'Brien [b], Kathryn Szymura [a], Charlene Crasta [a], Benjamin Harris [a], Carol Haddad [a], Thomas Eade [a], Paul J. Keall [b]

[a] Northern Sydney Cancer Centre, Level 1 Royal North Shore Hospital

[b] University of Sydney, Schools of Physics or Medicine, Sydney

[c] Centre for Medical Radiation Physics, University of Wollongong, Wollongong, Australia

Corresponding author: Dr Jeremy Booth
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

Abstract

Background and purpose: Real time adaptive radiotherapy that enables smaller irradiated volumes may reduce pulmonary toxicity. We report on the first patient treatment of electromagnetic-guided real time adaptive radiotherapy delivered with MLC tracking for lung stereotactic ablative body radiotherapy.

Materials and methods: A clinical trial was developed to investigate the safety and feasibility of MLC tracking in lung. The first patient was an 80-year old man with a single left lower lobe lung metastasis to be treated with SABR to 48 Gy in 4 fractions. In–house software was integrated with a standard linear accelerator to adapt the treatment beam shape and position based on electromagnetic transponders implanted in the lung. MLC tracking plans were compared against standard ITV-based treatment planning. MLC tracking plan delivery was reconstructed in the patient to confirm safe delivery.

Results: Real time adaptive radiotherapy delivered with MLC tracking compared to standard ITV-based planning reduced the PTV by 41% (18.7–11 cm^3) and the mean lung dose by 30% (202–140 cGy), V20 by 35% (2.6–1.5%) and V5 by 9% (8.9–8%).

Conclusion: An emerging technology, MLC tracking, has been translated into the clinic and used to treat lung SABR patients for the first time. This milestone represents an important first step for clinical real-time adaptive radiotherapy that could reduce pulmonary toxicity in lung radiotherapy.

Introduction

Stereotactic Ablative Body Radiotherapy (SABR) for lesions in the lung has shown substantially improved 5 year survival compared to conventionally fractionated treatments [1–3]. Comparison with surgery outcomes is favourable in weighted cohorts [4]. However, further application of lung SABR based on lesion size, proximity to central structures and dose level/fractionation has been limited by toxicity [5,6]. Legitimate reduction of margins with utilisation of more accurate, real-time motion adaptive, treatment delivery will directly reduce the irradiated volume and potentially toxicity.

For lung lesions, treatment delivery ideally needs to localise and adapt in real-time to account for variable inter- and intra-fraction tumour motion, to remove interplay for dynamic treatment, and to permit high efficiency. Critically, lung SABR planning is typically generated from 4DCT; growing evidence suggests motion at this single time point may not be representative of motion experienced during the short course treatment [7,8].

Real time guidance and adaptation has been clinically applied on specialised robotic and gimballed linear accelerators for lung SABR and both techniques have demonstrated significant reductions in treated volumes [9,10]. Another real-time image guidance and adaption technique, electromagnetic (EM) guided MLC tracking, is expected to match reductions in treated volumes to robotic and gimbal modalities [11,12]. MLC tracking began treating prostate cancer patients in 2013 [13] and demonstrated high fidelity of delivered dose, including dose painting, to moving targets [14]. However, to date MLC tracking has only been used clinically to treat prostate cancer, which exhibits occasional slow motion. In this work we apply MLC tracking to lung cancer, which exhibits constant and complex motion. We present the first-in-human study to clinically realise the benefits of real time adaptation on a standard linac for lung SABR. We describe our experience with the first patient.

Materials and methods

Clinical trial protocol and patients

The Lung Intensity Guided Hypofractionated Tumour tracking SABR (LIGHT SABR) study is a single institution investigator-led Phase I/II clinical trial with full local ethics approval and registration (NCT02514512). The primary endpoint is that 90% of treatments are delivered without MLC tracking related software failures, isolated as failure to deliver treatment with MLC tracking treatment caused directly by malfunction of the MLC tracking software. The trial will recruit 20 patients with stage I NSCLC or 1–3 oligometastases. Patients will be treated with electromagnetic-guided real-time adaptation with MLC tracking utilising Calypso lung transponders (Varian Medical Systems, Palo Alto) to provide the real-time motion signal. The workflow is shown in Fig. 1. The use of in-house MLC tracking software was registered with the Therapeutic Goods Administration in Australia utilising the Clinical Trial Notification system.

MLC tracking with electromagnetic-guidance

Three Calypso lung transponders were implanted one week prior to simulation using standard fiberoptic bronchoscopy with radial endobronchial ultrasound and X-ray image guidance. Transponders were placed as close as possible to the target lesion. Beacon migration and accuracy as a surrogate of lesion position were evaluated prior to treatment in 4DCT and during treatment with CBCT and fluoroscopic imaging. Beacon centroid to lesion centroid in each phase of the 4DCT was measured to describe the relative motion normalised to end of exhale. Surrogacy error was defined as the difference in beacon centroid and tumour centroid position in each phase. Prior to treatment, planning contours for PTV and transponders were overlayed on the CBCT to assess potential migration and alignment. Additionally, fluoroscopic imaging with a field encompassing lesion and transponders was acquired over three breathing cycles at two orthogonal angles prior to treatment for retrospective assessment of tumour/beacon motion with respiration; and fluoroscopic imaging was acquired during treatment for retrospective assessment of tumour motion during treatment.

The planning 4DCT scan was performed using an external surrogate for respiratory motion, Philips bellows (Philips Medical Systems, Cleveland) for 4DCT, with the patient free-breathing and positioned in a BodyFix^{TM} device with arms above head.

Treatment plans were created in the Eclipse planning system (v.11, Varian Medical Systems, Palo Alto) for a 6 MV dual RapidArc delivery utilising the AAA algorithm. The collimator was angled to align with the major motion axis of the lesion (superior–inferior) and the arcs rotated between 90 and 270 degrees (Varian IEC). Plan complexity was recorded using the modulation complexity score (MCS) which has been shown to correlate with delivery accuracy and can affect tracking performance above a 0.8 threshold [15,16]. Treatment planning was performed for MLC tracking, and for comparison (and back-up in case of MLC tracking failure) a ‘conventional’ ITV-based

plan was also created. MLC tracking plans utilised the end-of-exhale phase as a reference phase to define the $GTV_{Tracking}$, with the CTV defined as being equal to the GTV and a 5 mm CTV to PTV margin. The end-of-exhale phase assures a proper localisation and delineation of the tumour [17– 19] while the 5 mm margin has been described in the literature to be sufficient to account for tracking system latency up to 500 ms [20] and differences in tumour sizes and shape during respiration [21]. The exhale phase CT scan is likely to have the fewest imaging artefacts, and having the smallest lung volume, is likely to over-, rather than under-estimate the actual lung dose. The conventional plan was established for an ITV derived from the 4DCT which included the GTV in each breathing phase. The ITV was expanded by 5 mm to create the PTV. The conventional plan was calculated on a mean CT image from 4DCT. Both plans met the dose volume criteria of RTOG 0915 [22]. The fractionation scheme was 48 Gy in four fractions delivered to greater than 95% of the PTV. At treatment sessions the patient was aligned to lasers in the, BodyFix device and Philips bellows were attached to record the breathing signal during treatment. For each fraction, CBCT was acquired and a best-fit alignment to the transponders was performed. The PTV structure was then overlaid to confirm tumour coverage based on beacon localisation. The patient was treated with Calypso-guided MLC tracking [23]. We utilise the kernel density estimation prediction algorithm [24] to account for the system's 220 ms latency [13].

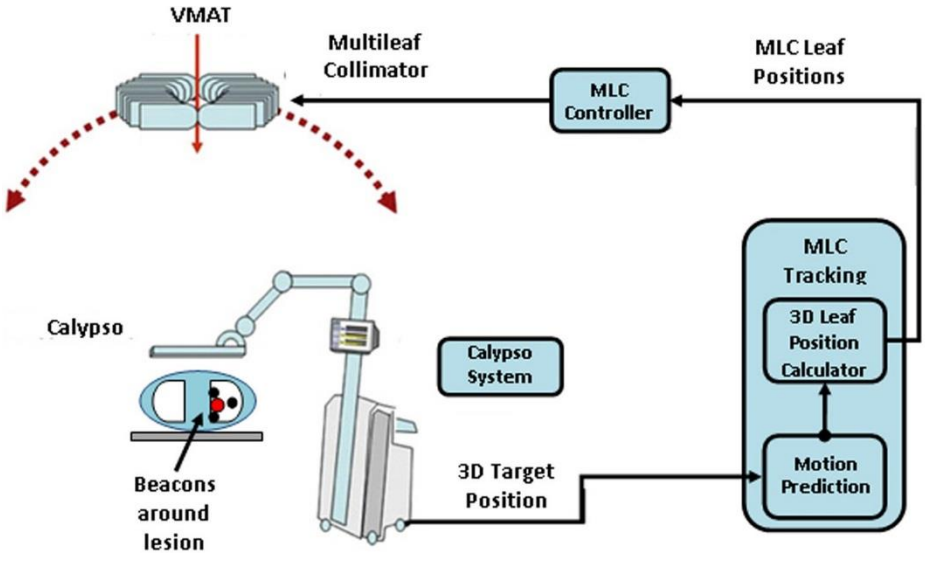

Fig. 1. Schematic of the MLC tracking control system used for the clinical trial. Electromagnetic transponders send real-time localisation to the MLC tracking system which updates the MLC pattern and sends these new leaf positions to the MLC controller for treatment at the linac.

Quality assurance (QA) regime

Quality assurance before, during and after treatment is essential, particularly with research software controlling the treatment unit. Standard quality assurance measures for SABR treatment were utilised including secondary monitor units check and fluence delivery [25]. Further quality measures, based on Failure Mode and Effects Analysis [26] and broad discussion with international thought leaders on MLC tracking safety, were implemented. These extra measures included:

- MLC tracking patient-specific QA incorporating review of over- and under-dose areas of patient plan with patient-specific motion [27],
- Checklist applied to additional MLC tracking-specific workflow steps,
- Pre-treatment delivery to a Delta4 phantom (ScandiDos, Swe- den) with and without motion (patient-specific with HexaMotion (Scandidos, Sweden)),
- Pre-treatment fluoroscopy to interrogate Calypso beacon motion migration and surrogacy to tumour, and post- treatment dose reconstruction [28,29].

MLC tracking errors were reported using the areas of under- and over-dose (A_u and A_o respectively) between the plan and delivery, as developed by Poulsen[29]. The under- and over-dose areas have been shown to correlate with dose delivery errors and clearly artic- ulate the contribution of leaf adjustment error, leaf fitting, and target localisation to the MLC tracking performance. Treatment log files including MLC motion, Calypso trajectories, kV and MV images and Philips bellows motion were recorded.

Dose reconstruction is a critical step as delivered dose for real-time adaptation will ultimately depend on the motion encountered. An isocentre shift method was utilised for volumes assumed to move with transponders (GTV and lung). The isocentre shift method considers each arc as many sub arcs each with isocentre shifted (in 2 mm bins) to mimic the motion. Treatment log files and the transponder trajectories were utilised to create a motion encoded treatment plan that was calculated in the planning system. Dose reconstruction was performed for spine and heart volumes assuming they were static. Reconstruction of the delivered conventional plan was performed for comparison. Delivery of the conventional plan assumed pre-treatment patient alignment and utilised treatment log files acquired in a dummy delivery and transponder motion from treatment sessions. The tracking plan was reconstructed on the end exhale phase CT while the conventional plan was reconstructed on the average CT. End-exhale GTV is used for both cases. For the reconstruction of the conventional plan, use of an average CT had <1% difference to calculation on the end exhale scan for this plan, which agrees with previous reports justifying dose calculation on average CT from 4DCT [30].

Results

We present data from the first patient treatment on 30th October 2015; an 80 y/o male with a single metastasis in the left lower lobe. He was positioned on his right side in a BodyFix bag due to the posterior distance to transponders from anterior chest wall preventing supine treatment (our normal setup) and patient performance preventing prone treatment. The internal peak to peak motion of the lesion at 4DCT was 10.8 mm, 4.8 mm, and 3.2 mm in the superior–inferior (SI), left–right (LR) and anterior–posterior (AP) directions, respectively. The surrogate accuracy of the transponder centroid to the GTV centre determined in each phase of the 4DCT showed mean discrepancies of 1.2 mm, 0.6 mm and 0.94 mm in the superior–inferior, lateral and anterior–posterior directions, respectively. Image artefacts in the 4DCT contributed to uncertainty in the determination of the surrogacy error; the beacon and GTV shape and size varied across the 10 breathing phases. The plan complexity for each plan was within acceptable range (<0.8) with MCS of 0.06 for the MLC tracking plan and 0.21–0.28 for the conventional ITV-based plan. The MLC tracking errors were minimal for delivery of the MLC tracking plan with mean A_uA_o of 2.26 cm^2 attributed to leaf adjustment (2.09cm^2), leaf-fitting (0.43cm^2 for arc 1 and 0.62cm^2 for arc2) and target localisation error (0.62cm^2 for arc 1 and 0.93cm^2 for arc2).

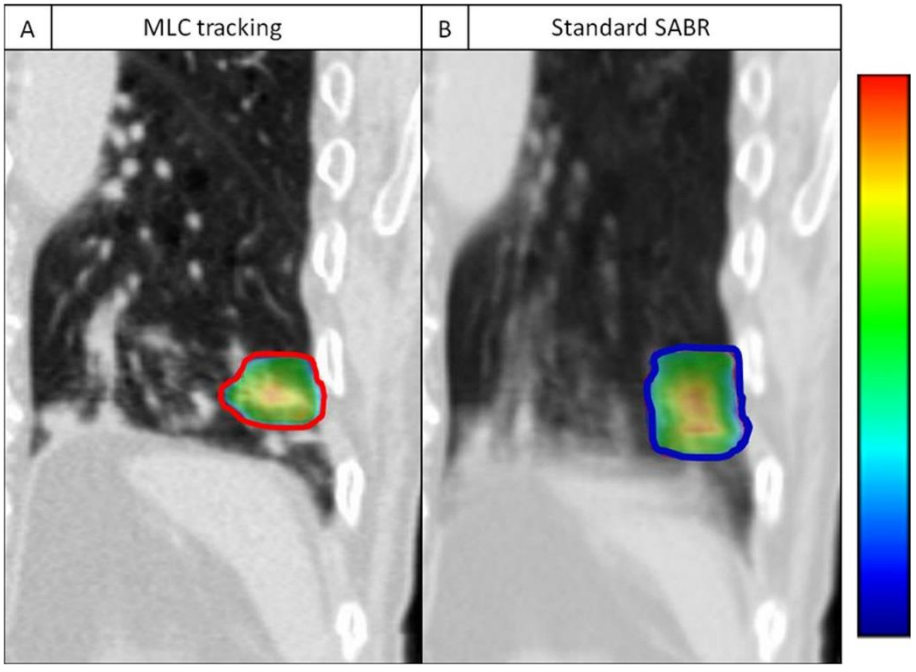

Fig. 2. Comparison of Planning Target Volumes shows a significant reduction (41%) in the volume with MLC tracking delivery (A) compared to standard ITV-based planning (B). The red contour indicates the PTV on end exhale phase of 4DCT used for MLC tracking and the blue contour indicates the PTV on mean of 4DCT used for the ITV-based plan. Coronal view.

The $PTV_{Tracking}$ was 18.7 cc, 41% smaller than the PTV for standard planning (29.8 cc) (Fig. 2). Targeting a smaller PTV translated to lower normal lung doses for this patient, with mean lung dose reduced by 31% or 0.6 Gy, V20 reduced by 35% or 48 cm^3 and V5 reduced by 9% or 50 cm^3. Dose maximum (D2%) reported to the spine was reduced from 5.1 to 3.8 Gy (33%). Plans had equivalent dose coverage for their respective PTV volumes.

Treatments had an average appointment time of 90 min. A significant proportion of time was allocated to ensuring correct patient rotation due to the beacon centroid being offset from tumour and patient being positioned in the lateral decubitus position. Transponders were located 2.5, 2.1 and 2.5 cm from the lesion edge, all anterior and lateral. Through the four treatment fractions, the internal motion of the transponders ranged between 15.0–16.5 mm, 3.4–3.7 mm, and 3.1–3.3 mm, in the SI, LR, and AP directions respectively, demonstrating substantially larger superior–inferior motion extent compared to simulation (Fig. 3). Fig. 3 shows motion of the transponders during treatment to be larger than the ITV (motion observed during 4DCT) 22%, 32% and 31% of the time, in the SI, LR and AP directions respectively. Motion extending out-side the PTV, a 5 mm expansion of the ITV, occurred during treatment 2%, 1% and 2% of the time, in the CC, LR and AP directions respectively. Critically, this infers that a geometric miss would have occurred if ITV-based treatment would have been delivered with only pre-treatment imaging. Furthermore, the components of the PTV margin expansion to account for inter-observer contouring variability, surrogacy accuracy and sub-clinical tumour growth, were utilised in full to account for tumour motion variation. Conventionally, SABR delivery does not deploy intra-treatment tumour monitoring so any geometric miss would have been undiscovered. The motion of the lesion and transponders with respiration captured in kV and MV images is shown in Fig. 4. A video of the kV and MV images acquired during treatment is provided as Supplementary material.

Fig. 5 shows the delivered dose reconstructed onto the respective planning CT datasets over the four days of treatment for MLC tracking delivery and the conventional ITV-based plan. The planned dose to the GTV is equivalent between MLC tracking and no tracking. However the delivered doses for no tracking are lower than that planned: the mean GTV D95 across fractions is 106 ± 2% (range 103–108%) compared to 110% planned. This difference occurred due to the systematically larger motion experienced with this patient during treatment compared to simulation. The MLC tracking delivery provided mean GTV D95 doses of 110 ± 0.5% (range 109–110%) compared to 111% planned. Fig. 5 demonstrates modest decreases in lung and heart doses and improved target coverage relative to the conventional plan. The MLC tracking delivery was also more reproducible (lower range of mean GTV D95 values) than the standard SABR delivery across fractions.

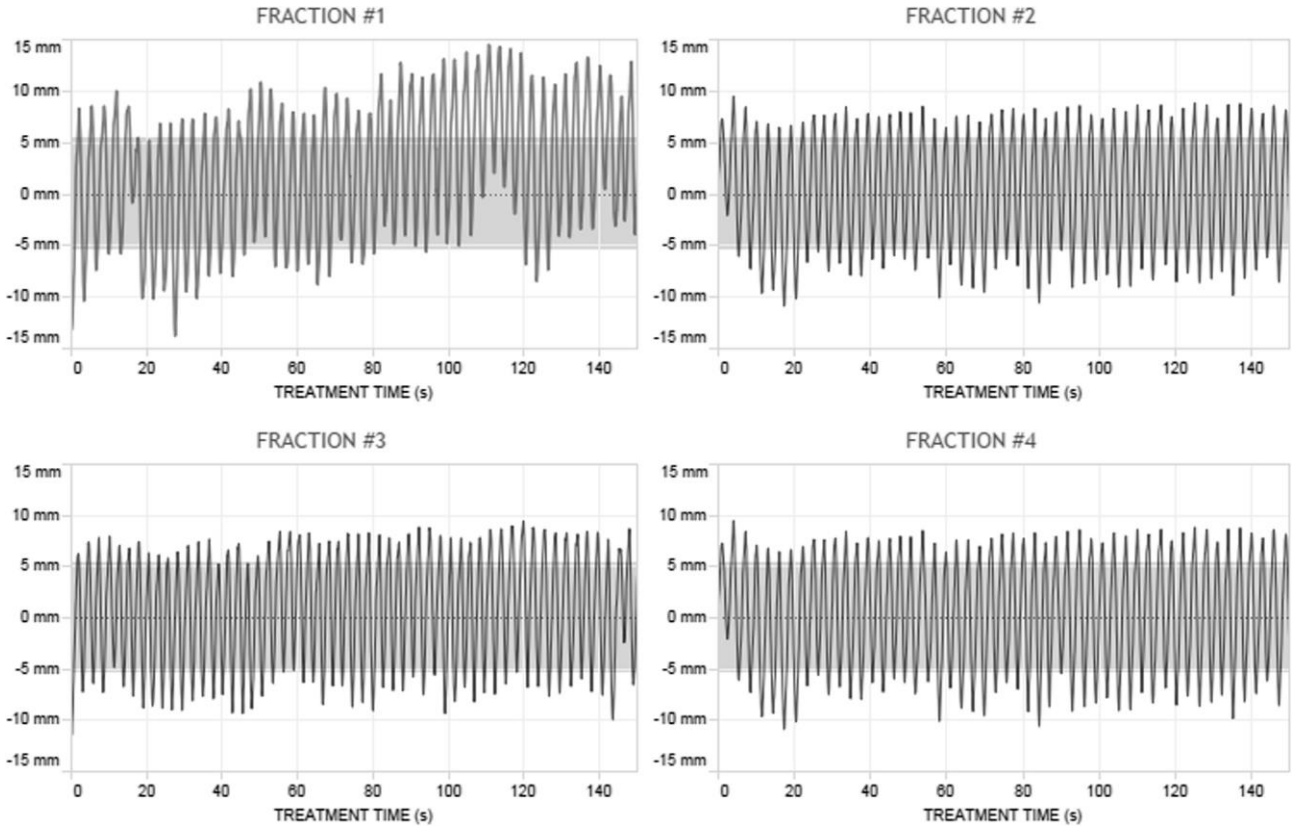

Fig. 3. Superior–inferior motion of the lung tumour (positive values represent motion in superior direction) for each of the four treatment fractions. The motion during 4DCT used to create the ITV of 10.8 mm is shown as a grey band in each plot. The tumour motion for all fractions was larger than that than expected from planning.

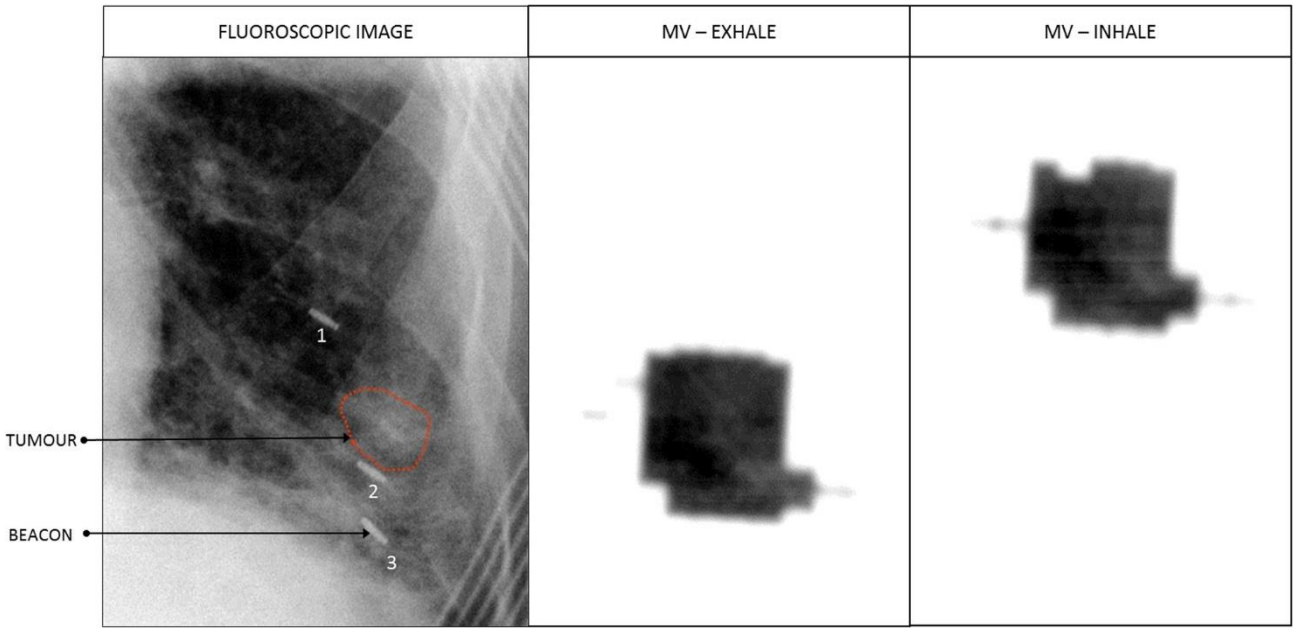

Fig. 4. Fluoroscopic image (left) showing three electromagnetic transponders and the tumour contour, and corresponding MV treatment images at inhale and exhale (right). A movie of the kV and MV images acquired during the treatment delivery is attached as supplementary material.

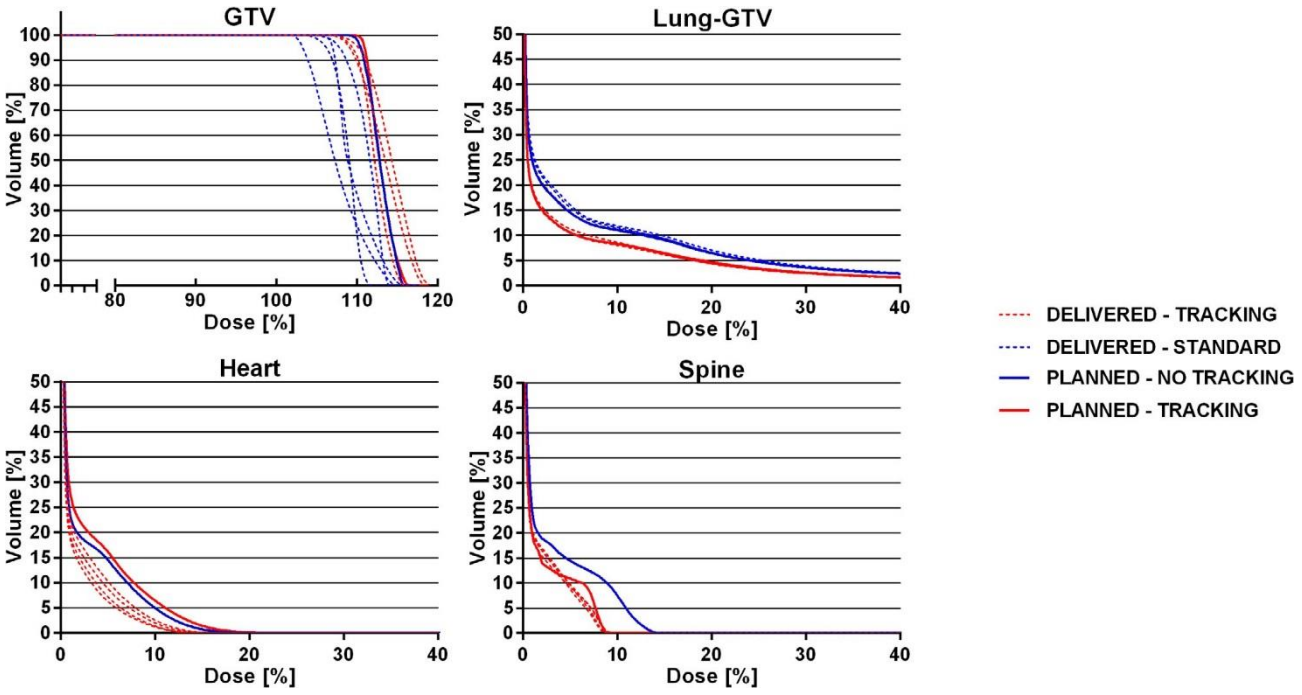

Fig. 5. Reconstructed delivered dose for the all fractions of the MLC tracking lung SABR patient showing delivered dose to target is maintained from planning and OAR dose is reduced for this patient. Dashed lines = dose for individual fractions; solid

Discussion

This paper reports on the first patient treatment with real-time adaptive treatment for lung cancer with MLC tracking. MLC tracking radiotherapy has previously been delivered to 28 prostate patients with 858 successful treatment fractions. MLC tracking for lung SABR is more complicated than prostate MLC tracking: respiratory motion is larger, more frequent and faster than prostate motion, SABR delivering larger dose per fraction, and there is an increased importance of system latency mitigation with the use of a prediction algorithm. The clinical issues are also different for lung SABR compared to prostate radiotherapy, with use of ITV based planning, baseline shifts of tumour position during respiration, irregular internal motion and in homogeneity.

The patient in this study benefited from real-time adaptive treatment with a 41% smaller target volume, which is comparable to that reported for adaptive delivery with robotic and gimbal devices [11,12]. The extent of motion was significantly larger at treatment compared to that seen during 4DCT acquisition. For the conventional ITV-based plan, motion exceeded the ITV ~30% of the time. For this case the PTV expansion of 5 mm has ensured coverage of the target is retained 98% of the time. However, the PTV expansion of 5 mm is derived to account for up to 5 mm inter-observer contouring variability, sub-clinical tumour extension and the measured 1-3 mm of surrogacy uncertainty with the beacon transponders.

Internal peak to peak transponder motion for this patient was significantly larger than the motion amplitude determined from simulation 4DCT. We believe that this is due to the sampling that occurs with standard 4DCT reconstruction, which score peak exhale and inhale minimally based on the short time in these positions, compared to the transponder locations during treatment which are reported 20 times per second.

The impact of MLC tracking will depend on the extent of tumour motion and patients with larger tumour motion will benefit from larger reductions in target volume and subsequent reductions in organ at risk doses. Even modest reduction of lung dose in absolute terms will benefit planning to isotoxic tolerances in the oligometastatic setting or for subsequent lesions. Furthermore, all patients potentially benefit if a baseline shift occurs from the gating enacted when the tumour moves outside the motion limits obtained from simulation. A similar level of dose coverage would have been achieved with a pure gating strategy; however, the efficiency of MLC tracking delivery is superior to gating strategies where a duty cycle of 30% is not uncommon. It should be noted however that introduction of flattening filter free delivery has reduced irradiation times, potentially improving the efficiency of gated treatments.

MLC tracking is highly accessible as it requires only two key components; real-time target guidance and a multi-leaf collimator. The great majority of linear accelerators currently sold now have the MLC. This study utilised real time target guidance from electromagnetic transponders as they are a proven robust position signal, but localisation could equally be derived from other methods such as X-ray fluoroscopy, real-time magnetic resonance imaging, or external surrogates. The electromagnetic transponders provide an internal surrogate of the tumour and their location will affect the accuracy of their surrogate motion. Further research is directed towards markerless MLC tracking that would not require implantation of transponders, a potential source of toxicity, replaced

with direct (image-based) tracking [31–34].

Reporting delivered dose poses some challenges to classical application of the ICRU volumes for MLC tracking. In real-time adaptive radiotherapy, the $PTV_{Tracking}$ can be considered time- resolved with its components defined in each respiratory phase to account for treatment uncertainty; in our implementation the PTV is equivalent across respiratory phases. This is contrasted to the PTV for conventional ITV-based planning, which should be defined in the classical way and is difficult to compare directly to $PTV_{Tracking}$. The more important metric is GTV coverage, which is maintained in this case. The PTV is a geometric tool to ensure GTV coverage, and for meaningful application with real-time adaptive treatment will require further data to development tolerances.

Clinical translational relevance

An emerging treatment delivery technology, MLC tracking has been translated in the clinic and used for real time adaptive radio- therapy with lung SABR for the first time. MLC tracking for real time adaptation with a standard linear accelerator improves target dose coverage, reduces organ at risk doses and is potentially highly accessible requiring only software change to be implemented on a modern linear accelerator.

Conflicts of interest

PJK is an inventor on the awarded US patents 7,469,035 and 8,971,489 that are related to MLC tracking. This work is supported by a Varian Medical Systems Collaborative Research Grant.

Acknowledgements

This work is supported by a Varian Medical Systems Collaborative Research Grant. PJK is supported by an NHMRC Senior Professorial Research Fellowship.

References

[1] Borst GR, Ishikawa M, Nijkamp J, Hauptmann M, Shirato H, Bengua G, et al. Radiation pneumonitis after hypofractionated radiotherapy: evaluation of the LQ (L) model and different dose parameters. Int J Radiat Oncol Biol Phys 2010;77:1596–603.

[2] Guckenberger M, Baier K, Polat B, Richter A, Krieger T, Wilbert J, et al. Dose–response relationship for radiation-induced pneumonitis after pulmonary stereotactic body radiotherapy. Radiother Oncol 2010;97:65–70.

[3] Timmerman R, Paulus R, Galvin J, Michalski J, Straube W, Bradley J, et al. Stereotactic body radiation therapy for inoperable early stage lung cancer. JAMA 2010;303:1070–6.

[4] Chang JY, Senan S, Paul MA, Mehran RJ, Louie AV, Balter P, et al. Stereotactic ablative radiotherapy versus lobectomy for operable stage I non-small-cell lung cancer: a pooled analysis of two randomised trials. Lancet Oncol 2015;16:630–7.

[5] Lo S, Sahgal A, Chang E, Mayr N, Teh B, Huang Z, et al. Serious complications associated with stereotactic ablative radiotherapy and strategies to mitigate the risk. Clin Oncol 2013;25:378–87.

[6] Lagerwaard FJ, Verstegen NE, Haasbeek CJ, Slotman BJ, Paul MA, Smit EF, et al. Outcomes of stereotactic ablative radiotherapy in patients with potentially operable stage I non-small cell lung cancer. Int J Radiat Oncol Biol Phys 2012;83:348–53.

[7] Purdie TG, Moseley DJ, Bissonnette J-P, Sharpe MB, Franks K, Bezjak A, et al. Respiration correlated cone-beam computed tomography and 4DCT for evaluating target motion in stereotactic lung radiation therapy. Acta Oncol 2006;45:915–22.

[8] Rietzel E, Chen GT, Choi NC, Willet CG. Four-dimensional image-based treatment planning: target volume segmentation and dose calculation in the presence of respiratory motion. Int J Radiat Oncol Biol Phys 2005;61:1535–50.

[9] Matsuo Y, Shibuya K, Nakamura M, Narabayashi M, Sakanaka K, Ueki N, et al. Dose–volume metrics associated with radiation pneumonitis after stereotactic body radiation therapy for lung cancer. Int J Radiat Oncol Biol Phys 2012;83: e545–9.

[10] Hoogeman M, Prévost J-B, Nuyttens J, Pöll J, Levendag P, Heijmen B. 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.

[11] Calliet V, Hardcastle N, Szymura K, Haddad C, Keall PJ, Booth JT. Justification of MLC tracking for lung SABR. Wellington, New Zealand: Engineering and Physical Sciences in Medicine; 2015.

[12] Suh Y, Sawant A, Venkat R, Keall PJ. Four-dimensional IMRT treatment planning using a DMLC motion-tracking algorithm. Phys Med Biol 2009;54:3821.

[13] Keall PJ, Colvill E, O'Brien R, Ng JA, Poulsen PR, Eade T, et al. The first clinical implementation of electromagnetic transponder-guided MLC tracking. Med Phys 2014;41:020702.

[14] Colvill E, Booth JT, O'Brien R, Eade TN, Kneebone AB, Poulsen PR, et al. MLC tracking improves dose delivery for prostate cancer radiotherapy: results of the first clinical trial. Int J Radiat Oncol Biol Phys 2015.

[15] Pommer T, Falk M, Poulsen PR, Keall PJ, O'Brien RT, Rosenschöld PM. The impact of leaf width and plan complexity on DMLC tracking of prostate intensity modulated arc therapy. Med Phys 2013;40:111717.

[16] McGarry CK, Agnew CE, Hussein M, Tsang Y, McWilliam A, Hounsell AR, et al. The role of complexity metrics in a multi-institutional dosimetry audit of VMAT. Br J Radiol 2016;89:20150445.

[17] Berbeco RI, Nishioka S, Shirato H, Chen GT, Jiang SB. Residual motion of lung tumours in gated radiotherapy with external respiratory surrogates. Phys Med Biol 2005;50:3655.

[18] Depuydt T, Poels K, Verellen D, Engels B, Collen C, Buleteanu M, 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.

[19] Persson GF, Nygaard DE, Hollensen C, Rosenschöld PM, Mouritsen LS, Due AK, et al. Interobserver delineation variation in lung tumour stereotactic body radiotherapy. Br J Radiol 2014;85:e654–60.

[20] Bedford JL, Fast MF, Nill S, McDonald FM, Ahmed M, Hansen VN, 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.

[21] Senthi S, Dahele M, Slotman BJ, Senan S. Investigating strategies to reduce toxicity in stereotactic ablative radiotherapy for central lung tumors. Acta Oncol 2014;53:330–5.

[22] Group RTO. 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.

[23] Keall PJ, Sawant A, Cho B, Ruan D, Wu J, Poulsen P, et al. Electromagnetic-guided dynamic multileaf collimator tracking enables motion management for intensity-modulated arc therapy. Int J Radiat Oncol Biol Phys 2011;79:312–20.

[24] Ruan D, Keall P. Online prediction of respiratory motion: multidimensional processing with low-dimensional feature learning. Phys Med Biol 2010;55:3011.

[25] Siva S, Kirby K, Caine H, Pham D, Kron T, Te Marvelde L, et al. Comparison of single-fraction and multi-fraction stereotactic radiotherapy for patients with 18 F-fluorodeoxyglucose positron emission tomography-staged pulmonary oligometastases. Clin Oncol 2015;27:353–61.

[26] Sawant A, Dieterich S, Svatos M, Keall P. Failure mode and effect analysis-based quality assurance for dynamic MLC tracking systems. Med Phys 2010;37:6466–79.

[27] Poulsen PR, Fledelius W, Cho B, Keall P. Image-based dynamic multileaf collimator tracking of moving targets during intensity-modulated arc therapy. Int J Radiat Oncol Biol Phys 2012;83:e265–71.

[28] Schmidt ML, Hoffmann L, Kandi M, Møller DS, Poulsen PR. Dosimetric impact of respiratory motion, interfraction baseline shifts, and anatomical changes in radiotherapy of non-small cell lung cancer. Acta Oncol 2013;52:1490–6.

[29] Poulsen PR, Schmidt ML, Keall P, Worm ES, Fledelius W, Hoffmann L. A method of dose reconstruction for moving targets compatible with dynamic treatments. Med Phys 2012;39:6237–46.

[30] Glide-Hurst CK, Hugo GD, Liang J, Yan D. A simplified method of four-dimensional dose accumulation using the mean patient density representation. Med Phys 2008;35:5269–77.

[31] Shieh C-C, Keall PJ, Kuncic Z, Huang C-Y, Feain I. Markerless tumor tracking using short kilovoltage imaging arcs for lung image-guided radiotherapy. Phys Med Biol 2015;60:9437.

[32] Rottmann J, Keall P, Berbeco R. Markerless EPID image guided dynamic multi-leaf collimator tracking for lung tumors. Phys Med Biol 2013;58:4195.

[33] Poulsen PR, Cho B, Sawant A, Ruan D, Keall PJ. Dynamic MLC tracking of moving targets with a single kV imager for 3D conformal and IMRT treatments. Acta Oncol 2010;49:1092–100.

[34] Cho B, Poulsen PR, Sloutsky A, Sawant A, Keall PJ. First demonstration of combined kV/MV image-guided real-time dynamic multileaf-collimator target tracking. Int J Radiat Oncol Biol Phys 2009;74:859–67.