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Editorial

Shooting the Star: Mitigating Respiratory Motion in Lung Cancer Radiotherapy

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Radiotherapy plays an important role in the management of lung cancer [1]. It is therefore essential to ensure that it is delivered accurately and precisely. Geometric uncertainties from unmitigated respiratory motion could degrade thoracic radiotherapy quality. Image guidance has enabled a more accurate assessment of respiratory motion and a number of respiratory motion management strategies have been developed [2,3]. Guidelines recommend the use of four-dimensional computed tomography (CT) planning with acknowledgement that additional tumour motion mitigation interventions could be beneficial in selected patients [4]. However, to date, only a few studies have reported the clinical or dosimetric benefits of these strategies. In this issue of *Clinical Oncology*, Bainbridge *et al.* [5] compare different respiratory motion management strategies in patients with non-small cell lung cancer (NSCLC) with a focus on isotoxic dose-escalated radiotherapy.

The aim of curative-intent radiotherapy is to deliver an ablative or radical tumour dose while respecting normal tissue dose constraints. In the past, lack of respiratory motion management approaches mandated the need for large population-based margins, resulting in increased normal tissue dose and toxicity [6]. Image-guided radiotherapy has enabled a personalised patient approach to account for respiratory motion. Advances in delivery (e.g. intensity-modulated radiotherapy) have led to additional dosimetric benefits in lung cancer [7]. However, lung cancer remains the leading cancer in cancer death, highlighting the unmet need to improve patient outcomes [8].

Three main strategies are under investigation to improve outcomes for lung cancer patients treated with curative-intent radiotherapy. The first is radiotherapy dose escalation, aiming to improve locoregional tumour control, which is strongly linked to survival in NSCLC [9]. Although dose escalation using conventional fractionation has led to survival detriments in NSCLC patients, as reported in the RTOG 0617 trial, there is interest in isotoxic dose-escalated radiotherapy and this is an area of active investigation [10]. The second strategy is to reduce normal tissue dose to limit radiotherapy-related morbidity and mortality [11,12]. Real-world and *post-hoc* trial data show an association between increasing radiotherapy dose to cardiopulmonary structures and serious heart toxicity and lymphopenia, leading to premature death [13–15]. The impetus for this strategy was strengthened following results from the LungART adjuvant radiotherapy trial in stage IIIA (N2) NSCLC. Although a significant reduction in mediastinal relapse was reported, higher acute and late cardiopulmonary toxicity was seen, which negated the likely survival benefit from postoperative radiotherapy [16]. A reduction in significant radiotherapy morbidity, such as grade $\geq$2 pneumonitis and oesophagitis, could also enable more patients with unresectable stage III NSCLC to receive adjuvant durvalumab, which has been shown to improve survival in this patient group [17]. The third strategy of combining radiotherapy with novel drugs is being investigated in the ongoing phase I platform CONCORDE trial [18].

Essential to the success of these strategies is the need for accurate and precise thoracic radiotherapy, achieved in part by respiratory motion management approaches. Four-dimensional CT planning, now available in most cancer centres, can assess and quantify tumour and normal tissue volume, location and motion resulting from the breathing cycle. CT images are acquired across several respirations and reconstructed at defined points of the breathing cycle. Four-dimensional cone beam CT (CBCT), now also available

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in many cancer centres, can be used to verify radiotherapy delivery. Motion artefacts are substantially reduced on both four-dimensional CT and four-dimensional CBCT compared with three-dimensional imaging, but can still occur, leading to under estimation of tumour motion [19]. Importantly, the images are not always representative, as they provide a snapshot in time. Other respiratory motion management strategies, such as breath-hold techniques and gating, are also used. Recent technological advances have led to further developments, including tumour tracking and magnetic resonance-guided adaptive radiotherapy (MRgART). However, despite the plethora of respiratory motion management strategies, the optimal strategy remains unknown. Therefore, clinical studies are needed to compare the benefits of these technologies in lung cancer patients.

Passive versus Active Respiratory Motion Management

Passive respiratory motion management makes use of four-dimensional imaging in a number of ways. The most common is where the tumour is outlined on all phases of the respiratory cycle and then combined to produce the internal target volume (ITV). Alternatively, mid-ventilation (MidV) or mid-position (MidP) approaches, first described by Wolthaus *et al.* [20,21], can be used, whereby the tumour is contoured on the phase closest to its time-averaged position or the images from all phases are rigidly deformed to produce a single image representing the time-weighted position, respectively. These approaches use patient-specific margins and often result in smaller target volumes, compared with the ITV-based technique, potentially reducing normal tissue irradiation. This was shown in a study of 79 lung cancer patients treated with stereotactic ablative radiotherapy (SABR) using the MidV technique [22]. A randomised trial including 44 patients with locally advanced NSCLC showed a significant reduction in the planning target volume (PTV) and mean lung dose with MidP compared with an ITV-based approach [23]. Another randomised trial of 54 patients with locally advanced NSCLC reported similar local control and progression-free survival but reduced rates of acute and late grade 3 pulmonary toxicity using the MidP compared with an ITV-based approach [24]. To date, studies have not directly compared the MidV and MidP techniques.

Deep inspiration breath-hold (DIBH) is an active respiratory motion management strategy that involves the delivery of radiotherapy during breath-hold. It results in increased lung volume and displacement of the heart and can therefore be used to reduce normal tissue dose [25,26]. Respiratory gating is another active respiratory motion management strategy. It relies on an external surrogate or internal fiducial(s) to monitor the patient's breathing pattern and enables the delivery of radiotherapy during a predefined window within the breathing cycle. Tumour tracking can be used alongside gating to continuously monitor the tumour. Again, it generally relies on the use of respiratory surrogates to help predict the tumour's path; however, marker-less tracking with kV imaging has also been reported [27]. Surface-guided radiotherapy using non-ionising visible light has similarly shown potential value in patient set-up and the monitoring of intra-fraction motion during lung SABR [28]. Prunaretty *et al.* [29] evaluated dosimetric differences between free-breathing, gating and tracking techniques in lung SABR planning. Mean target coverage was higher with free-breathing but this was attributed to the larger PTVs (45% and 35% larger compared with the tracking and gating, respectively). The volume of lung receiving 20 Gy was, however, much lower with tracking (17.5% and 33% lower than gating and free-breathing, respectively).

In this issue of *Clinical Oncology*, Bainbridge *et al.* [5] report the dosimetric differences between radiotherapy planned using the ITV-based approach compared with either the MidV or moderate DIBH (mDIBH) techniques in 21 NSCLC patients. A stepwise reduction in PTV was noted from the ITV to MidV to mDIBH approaches. mDIBH was associated with a statistically significant reduction in dose to the heart and lungs, resulting in a reduction of modelled lung and cardiac toxicities. This technique also showed greater potential for PTV dose escalation compared with the other approaches.

Looking ahead

Dynamic multileaf collimator tracking is an adaptive radiotherapy technique that can be implemented on a conventional linear accelerator (linac). It involves moving the treatment beam to follow tumour motion. A study by Caillet *et al.* [30] compared ITV-based PTVs to MidV and multileaf collimator tracking PTVs in 10 patients receiving SABR for early-stage NSCLC or thoracic oligometastases. Compared with the ITV-based approach, tracking reduced PTV by a mean of 37.3%, maintained target dose coverage and significantly reduced dose to normal tissues. The MidV technique also led to numerically improved dosimetry compared with the ITV-based approach, but this difference was not statistically significant.

MRgART (delivered on the MR-linac) offers another active respiratory motion management solution. The benefits of MRgART include the lack of radiotherapy dose (compared with CT/CBCT) and the ability to perform 'beam on' tumour gating/tracking with the option for daily adaptive radiotherapy (adapt to tumour position and shape) [31]. Dosimetric advantages have been reported and early clinical outcomes are encouraging [32]. However, additional research is needed to refine this approach and investigate clinical benefits compared with CT-based radiotherapy prior to wider clinical implementation.

Compared with photons, protons can be directed to stop inside the tumour (Bragg peak), reducing dose to normal tissues such as the heart and thoracic blood pool. The dosimetric advantages of protons in lung cancer could translate into outcome improvements via the three strategies mentioned above (enable safe dose-escalation, reduce normal tissue toxicity and enhance tolerability

when combined with novel drugs ± permit the use of higher novel drug dose). However, supporting level 1 evidence is lacking. Accrual is now ongoing in the phase III proton versus photon NSCLC trial (RTOG 1308; NCT01993810). Proton beam range uncertainty and sensitivity to tissue heterogeneity and motion could negatively impact target dose conformity, highlighting the importance of robust respiratory motion management approaches in this setting [33].

Conclusion

Respiratory motion management is essential to the delivery of high-quality thoracic radiotherapy. A multitude of strategies exist, but the optimal strategy remains unknown. The availability of equipment and local expertise often drive departmental adoption decisions. Radiotherapy departments should strive to expand access to evidence-based respiratory motion management strategies. With the results from Bainbridge *et al.* [5], there is a growing body of data supporting the dosimetric advantages of MidV or MidP positions and DIBH over an ITV-based approach [22,23]. However, larger clinical trials are needed to investigate the clinical benefits and cost-effectiveness of these approaches in the lung cancer population.

Conflicts of interest

The authors declare no conflicts of interest.

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