Review Article

Management of respiratory motion for lung radiotherapy: a review

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Abstract: In this review, various motion management techniques in lung radiotherapy treatment are discussed. Accounting for motion or reducing residual motion is crucial in facilitating dose escalation while reducing toxicity to critical organs near the target volume. The motion management techniques in this review are grouped into three main components: imaging, free breathing and breath hold. The importance of respiratory correlated imaging also known as 4 dimensional imaging, is emphasized in this review as it provides a more accurate representation of tumor motion and its acquisition challenges are reviewed in detail. Tumor delineation and consequently the planning target margins rely greatly on the quality and accuracy of image acquisition. Other factors such as reproducibility, patient selection, patient compliance, tumor location should also be considered when choosing the technique to be used. There is no one solution fits all or the 'best' technique when managing motion. The different techniques in delivering radiation while accounting for motion are also discussed, with the advantages and limitations of each of these techniques presented objectively.

Keywords: Lung cancer radiotherapy; motion management; 4-dimensional imaging; gating; tracking

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Introduction

Adapting radiotherapy to respiratory movements has always been a major concern in thoracic radiotherapy. The value of motion management has been further accentuated with the development of increasingly conformal radiotherapy, with intensity modulation techniques, using reduced irradiation fields, and especially with stereotactic hypo-fractionated radiotherapy becoming the standard in the treatment of early lung cancer. In addition, the use of proton therapy is becoming widespread over the last decade. Proton treatment presents a bigger challenge when being used in the treatment of lung cancers where interplay effects can significantly alter the dose distribution.

Traditionally, tumor motion is taken into account by adding a margin around the clinical target volume (CTV) in order to create the internal target volume (ITV). Positioning uncertainties are then accounted for by adding a margin to create the planning target volume (PTV). However, this strategy has its limitations. For tumors with significant respiratory motion, such as those near the diaphragm, the addition of various geometric margins leads to irradiation of a larger volume of healthy tissue, therefore increasing the risk of complications, and therefore reducing the possibility of dose escalation.

Technically, the safe delivery of thoracic radiotherapy involves multiple factors: accurate patient CT imaging, positioning, breathing motion. This review systematically presents various common available motion management techniques, outlining their advantages and disadvantages.

Search strategy

In November 2017, a literature search was performed on PubMed with the search terms "lung cancer radiotherapy", "motion management", "4D CT", "tracking", "gating",

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Table 1 Various techniques of motion management in lung radiotherapy

Imaging	Free breathing	Breath hold
Slow CT	Gating	Spirometric
4D imaging for treatment planning: CT, PET	Tracking	Non-spirometric
4D imaging for image guidance: MRI, CBCT	Abdominal compression	
	Continuous positive airway pressure	

"DIBH", "breath hold", "tumor motion", "slow CT", "4D PET", "4D MRI", "4D CBCT", "CPAP", "phase sorting", "amplitude sorting", "surrogates", "proton therapy" and "4D imaging". Articles were selected based on relevance and preference was given to more recent articles from 2010 onwards to November 2017. Articles before 2010 were also included if they presented new and useful research techniques.

Tumor motion uncertainties

Breathing induced organ motion is a source of uncertainty that affects the accuracy of radiotherapy planning and delivery. Tumor motion due to respiration in various locations of the lungs had been widely described. A study by Seppenwoolde *et al.* used golden fiducials inserted into tumors and tracked their motion using a real time tracking system, imaging the 3 dimensional co-ordinates at 30 images per second (1). They concluded that the largest motion was seen in the cranial- caudal direction in the lower lobe tumors near the diaphragm. These tumors were found to be more stable and spending more time in the exhale phase, and hysteresis has been commonly observed. Hysteresis describes that tumors can show paradoxical motion on inspiration and expiration. In addition, cardiac motion also contributes significant uncertainty, particularly if the tumor is close to the heart (2).

Motion management techniques

Many techniques are available to manage motion. For the purpose of this review and discussion we have organized the various techniques into three main groups. Various imaging techniques were developed to account for respiratory motion, such as slow CT scans and 4D imaging modalities. Free breathing techniques either use tracking, gating to keep track of tumor motion or devices such as abdominal compression and continuous positive airway pressure (CPAP) to limit the magnitude of breathing. The third group consists of both spirometric and non-spirometric breath hold techniques which attempts to stop the breathing motion rather than accounting for it (see *Table 1*).

Imaging

The above described uncertainties occur in relation to target localization as well as motion of structures within the thorax. Thus accurate radiotherapy requires acquisition of images at various steps along the radiotherapy chain. Imaging must take into account respiratory motion otherwise significant artifacts will be introduced into the CT images. These artifacts can decrease the quality of the CT scan and affect target volume delineation (3).

Slow CT

Prior to the advent of 4DCT, target margins were either too small, causing a geographical miss or too big, exposing normal tissues to unnecessary radiation (4). Fast helical or axial acquisition times are relatively faster than an average breathing cycle (4–6 secs), which results in multiple acquisitions in a breathing cycle. While it may visually look normal at a single slice, multiple consecutive slices depict tumor motion at arbitrary breathing phases, which causes a misrepresentation in tumor size, shape and location (5,6). Slow CT, on the other hand, acquires images at approximately the same time period as an average breathing cycle at around 4s per slice and therefore, depict the range of tumor motion more accurately. This comes at a loss to the spatial resolution as slow CT images are blurred, introducing uncertainties such as intra-observer variability in tumor delineation (2,7). Due to the significant blurring, it is not recommended to use this imaging technique for tumors near the mediastinum, chest wall or the diaphragm. Wurstbauer *et al.* evaluated 18 patients with slow CT and found that tumor volumes are bigger with the slow CT as compared to conventional CT imaging, internal margins are tighter and multiple slow CT scans of each patient show

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consistent depiction of the tumor at each scan (4). There are very few studies comparing tumor volumes drawn with slow CT and 4DCT. Nakamura *et al.* found that tumor volumes drawn on slow CT is smaller than the volume generated from a combination of all the phases of the 4DCT and that a mean of 8% of tumor volume drawn from slow CT is not encompassed by 4DCT (8). This meant that additional margins were required to be added to tumor volume drawn on slow CT. A more recent study by Jang *et al.* found that combining the volume drawn from slow CT (albeit modified slow CT with 2 s/slice) and from 2 extreme phases of 4DCT scan may be more useful and reliable when delineating mobile tumors as compared to using either one CT technique as the slow CT may provide additional motion information (7).

4-dimensional imaging

The challenge with precise imaging of lung tumors is correlating the CT scans with the patient's breathing cycle. Compounding factors such as the location of the tumor (1), hysteresis (1), irregular respiration (9,10), the techniques used to acquire the respiratory signal (11) and the scan parameters (12) all lead to uncertainties in tumor motion evaluation and delineation. Depending on the location of the lung tumor, some may exhibit larger variations in certain directions. For example, lower lobe unfixed tumors have shown to vary more in the cranial-caudal direction (1). Keall *et al.* presented tumor motion studies which concluded that tumor location, combined with the pathology of the tumor, can lead to various distinct patterns in displacement, direction and phase which make it even more difficult for clinicians and researchers to come up with a respiratory model which can be used to predict the tumor motion (2). This does not take into account the different breathing patterns each patient may have over a period of their course of treatment, from imaging to the completion of the radiotherapy treatment. However, the reproducibility of breathing can be mitigated with audio-visual coaching. Respiratory signals can be acquired with external surrogates. These include recording infrared marker blocks placed on patient's body, spirometers that records the air flow in and out of the patient, a pressure transducer that measures the pressure from the contraction and expansion of a belt around the patient's chest, laser surface scanning system which scans the patient surface and detected by a camera and a thermo-coupler which measures the temperature of the air flow in and out of the patient. While each technique has their own advantages and disadvantages, they provide, to a certain degree of accuracy, a respiratory signal, which is key to respiratory correlated CT images. A brief summary for the various 4D imaging modality is tabulated in *Table 2*.

4DCT

4DCT has been considered as the gold standard of imaging for lung radiotherapy. The rationale is that it gives information on the temporal changes of tumor and organs at risk, while at the same time, reducing image artifacts induced by motion which can be found in 3D-CT (19). Image acquisition can be done in helical or axial mode in synchronization with the respiratory signals obtained via methods mentioned above. In helical mode, multiple CT slices are acquired at each table position to capture the entire respiratory cycle. Due to the multiple acquisitions, the scanning duration is longer and the imaging dose is significantly higher than the conventional CT helical imaging (20). The acquired CT images are then sorted either via phase or amplitude into individual bins. Each bin is a 3D CT set of defined phases or amplitudes of the patient's breathing signal. Much has been studied on phase sorting and amplitude sorting of the CT acquisitions (21-23). In phase sorting, the breathing cycle is divided into equal time segments, typically 10 phases, corresponding to 10 3D-CT sets. The drawback with phase sorting is that it fails when the breathing pattern is irregular and not reproducible (5). This results in missing images or misaligned images due to the variations in amplitude (21).

In amplitude sorting, the CT images are sorted based on the amplitude values of the breathing cycle, from the end inspiration to the end expiration (peak-to-peak). By doing so, it is more robust to irregular breathing patterns and eliminates the misalignment issue faced during phase-sorting (13). Several studies have been done which concludes that amplitude sorting provides better image quality (14,24). However, with amplitude sorting, the temporal aspect of the imaging is diminished as it is not able to differentiate between the different time durations of the tumor at the same amplitude value. Also, with amplitude sorting, the problem of missing images may surface if a certain amplitude values (especially at end inhalation/exhalation) are not reached.

Both phase and amplitude sorting requires an external surrogate and the correlation between the external surrogate and tumor motion can affect the accuracy of the depiction of tumor motion. Thus, this motivates Hui *et al.*

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Table 2 Summary of 4D imaging modality for target delineation (13-18)

Techniques	Advantages	Disadvantages
4DCT Amplitude Binning	Respiratory-correlated CT images	Does not distinguish time duration at the same amplitude level
	Fewer motion related artifacts when breathing is irregular	Missing images if amplitude values at end-inhalation and end-exhalation are not reached
	Can be acquired with various systems that can produce respiratory signals	
4DCT Phase Binning	"Gold standard" for target delineation	Not suitable when breathing pattern is irregular and not reproducible
	Ease of use	Data may be misaligned due to varying slopes, period and amplitudes
	Respiratory-correlated CT images	
	Can be acquired with various systems that can produce respiratory signals	
4DPET/CT	Good tumor definition	Lack of ground truth in the accuracy of tumor segmentation methods
	Less inter-observer variability	Resource intensive
	Good definition of extent of movement	Requires additional training
	Reduced smearing due to respiration	Requires proper and efficient clinical workflow
	Additional information of lymph node status	Long acquisition time per bed position
		Quality affected by irregular breathing

to make use of Fourier transform of the CT image into frequency space and internal image-based motion indicators to produce a robust respiratory signal (25). A comparison with the Varian RPM signals shows that the waveform of the respiratory signal from both techniques were in good agreement and in regions where it does not match, the RPM-sorted images had more artifacts (25). One limitation is that it does not provide real time respiratory signal which it needed to correlate 4DCT and 4DCBCT.

It is important to note that 4DCT images taken during CT simulation are not representative of the breathing patterns of the patient throughout the course of treatment. One method that can potentially improve image quality of 4DCT images and the regularity and reproducibility of the respiratory signal is audio-visual biofeedback. The biofeedback may assist the patient to gauge the amplitude of the breathing with the visual aids and also able to control the frequency of the breathing with audio coaching. AV biofeedback has the potential to reduce artefacts caused by irregular breathing patterns, however, patient compliance and even lung function may limit the effectiveness of having an biofeedback system (26).

Classically motion is managed by using the CTV-PTV margin expansion which accounted for all variations on a population basis. With 4DCT, a personalized approach of individualizing each patient's margins that encompasses his or her breathing motion becomes possible. There are two established methods: the ITV method and the mid ventilation approach (27). For the ITV approach, all the 4DCT images are overlaid using a maximum intensity projection (MIP) of all phases, and the combined volume of the target in all phases is contoured as the ITV. This is regarded as the gross target volume that is to receive the full prescribed dose. Further margin is then added to give the PTV. The advantage of this approach is that any residual image artefacts in the 4DCT dataset are much reduced through the overlay of the image (28). Also, during the image guidance phase later, the matching for set up can be performed between the ITV in the 4DCT planning scan and the corresponding target in the cone beam CT scan. The mid-ventilation approach calculate the CTV-PTV margin differently by identifying the phase in which

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the target is closest to its mean position. This is the mid-ventilation phase and it best represents the time-weighted mean position of the target which is used for delineation and planning. The margin is then applied taking into account the extent of tumor motion. This approach can potentially have smaller PTV volumes compared to the ITV approach.

4DPET-CT

PET-CT imaging provides functional and anatomical imaging and it is widely used for target localization in radical radiotherapy for lung cancer. However, respiratory motion degrades PET images, affects attenuation correction of PET data and also overestimates the tumor volume (29). The acquisition time of PET images are significantly longer than a normal respiratory cycle (several minutes per bed position as compared to 4–5 s) and thus, are averaged over multiple breathing cycles. During the acquisition of the 4DPET-CT, an external surrogate detects the respiratory signal and the thorax is imaged with an average of 2–4 bed positions, each taking 7–10 mins. Acquisition mode is either prospective-gated PET or retrospective respiratory correlated dynamic PET (RCDPET) (30,31). Nehmeh *et al.* evaluated the prospective-gated PET, where the output from the RPM signal is used as a trigger to initiate the gating cycle of the PET scanner. At a user-defined phase of the breathing cycle, PET images will be acquired and are sorted into discrete bins. The number of bins and the duration of each bin are set by the user before the PET acquisition. The CT is used to correct for attenuation of the PET images. Respiratory motion affects the standardized uptake measurements (SUV) and thus images will appear blurred and the apparent volume of the tumor is also larger (30). This larger apparent volume is caused by smearing and not to be confused with the full extent of the tumor motion. Smearing, defined by Nehmeh *et al.*, is the ratio of gated to non-gated measurements performed on a tumor (30). With the 4DPET-CT, motion-induced smearing is reduced and thus, the tumor volume is smaller. With a reduction in the blurring, the maximum measured SUV increase by as much as 16% (29). In terms of volume delineation with 4DPET-CT, the volume of the GTV drawn on the 4D is generally larger than the volume drawn on 3DPET-CT. This study done by Aristophanous *et al.* suggests that 4DPET-CT takes into account the full extent of the tumor motion and reduces the probability of a geographical miss. 4DPET-CT imaging may be considered as a tool in treatment planning based on the location of the tumor, motion of the tumor and type of treatment to be given (15). Tumor located in the lower lobe or with motion of more than 3 mm has found to be an indication of 4DPET-CT (15). As mentioned above, gated-PET allows clinician to fully appreciate the full motion and also to distinguish between FDG-avid tumors from adjacent normal tissue. This is particularly important in advanced treatment planning such as in proton therapy, where dose painting requires accurate localization of the FDG-avid tumor (32).

Image guidance during RT

4DMRI

MRI imaging provides better soft tissue contrast with no additional radiation exposure to the patient. With such inherent imaging properties and also the potential to be able to correlate with the respiratory cycle, respiratory correlated MRI (4D-MRI) can be a powerful tool of imaging for tumor delineation and also to assess patient setup and intra-fractional movements (33). With the 4DCT, the acquisitions are snap shots and adjacent image slices may tend to sample the same breathing cycle. Therefore, in principle, a longer scan would depict a more robust average motion, which is more consistent with treatment conditions. However, the ability to acquire prolonged imaging is limited by the radiation dose. Therefore, MRI offers a potential solution to address motion artifacts with longer duration and repeat scanning with no unnecessary exposure. 4D MRI can be obtained by two known methods; 3D dynamic MRI (dMRI) acquisition and multi-slice fast 2D MRI acquisition, each with its own limitations and advantages (28). Recent study by Park *et al.* shows the feasibility of reconstructing 4D MRI from the multi slice 2D MRI using a computed body area as the respiratory signal (34). Another study by Tryggestad *et al.* demonstrated a technique for retrospectively sorting multi-slice 2D MRI images to produce "representative 4D MRI" with two applicable sequences acquired over a prolonged period of time. Prolonged acquisition can capture breathing variability and reduce volume inconsistencies (35).

4DCBCT

Respiration correlated CT is a powerful imaging tool for image guided radiotherapy. Like the 3DCBCT, it takes volumetric images of the patient on the treatment table

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Table 3 Summary of 4D image modality for pre-treatment image guidance (28,34,37-42)

Technique	Advantages	Disadvantages
4DCBCT	Good for evaluating tumor motion on the treatment table	Reduced CNR
	Reduced motion artifacts	Long acquisition time
	Feasibility for use in Lung SBRT	Image quality limited compared to planning CT
	Useful for adaptive planning	
4DMRI	Excellent soft tissue contrast	Presence of magnetic field in treatment room can disrupt dose distribution
	No additional imaging dose, good for prolonged imaging	MR planning not available

CNR, contrast to noise ratio.

before treatment delivery. This will then be registered with the 4DCT image set and shifts will be applied. Unlike 3DCBCT, 4DCBCT provides temporal and spatial information of the tumor motion, allows tumor localization at specific breathing phases and gives more confidence during gated treatment delivery that the breathing pattern during treatment and during simulation are not very different (36). Kilo-voltage projections are taken over 360 degrees with or without an external respiratory signal like that during CT simulation. Without the external signal, the projections are sorted via pixel values in a region of interest (ROI) at the air-tissue interface of the diaphragm. The changing mean pixel value in the ROI during inspiration and expiration serves as the 'respiratory signal' to sort the CT images via amplitude sorting (36). Due to the limited number of projections, the contrast to noise ratio (CNR) of 4DCBCT is reduced, however, motion artifacts that are usually found in 3DCBCT are reduced or eliminated with this technique (37). A brief summary for the various 4D pre-treatment imaging modalities is tabulated in *Table 3*.

Gating

Delivery of the treatment beam can be 'gated' or only delivered at specific respiratory phases or amplitudes determined during treatment planning (43). There are many devices available and a summary table is provided in *Table 4*. An external surrogate is used during treatment to determine the breathing cycle and a correlation between surrogate motion and tumor motion needs to be verified regularly so as to ensure that there is no geographical miss (12). There are two methods for gating, either by phase or amplitude. The choice of treatment methods depend on several factors: (I) the regularity of the breathing; (II) the ratio of time of beam on to treatment time, also known as duty cycle; and (III) residual motion of the tumor (16). Most commonly phase-based gating is used. However, it is dependent on the regularity of the breathing. If breathing is irregular, then phased-based gating might cause a mismatch between the treatment phase and the start and end phase values prescribed by the clinician during treatment planning. The consequence of such mismatch is that the patient's anatomy might not be in the intended position when the beam is delivered. Also, it will not be suitable, as the treatment will be prolonged because the tumor motion is not at the desired phase for treatment. It is shown by Riley *et al.* that irregularity in patient's breathing correlates to poorer dose distributions (27). In such situations, amplitude-based gating is preferred as the displacement values are based on the values of the breathing trace during treatment planning and treatment delivery. Abdelnour *et al.* concluded in their imaging study that amplitude based binning results in correctly binned images and that it is more sensitive to the actual location of the intended object (46). Another study by Rietzel *et al.* shows that amplitude based binning is optimal for reproducing images at accurate locations from cycle to cycle. Therefore, recent studies have shown that amplitude based gating may be potentially more accurate and consistent than phase-based gating. There is a trade off when deciding on the gating width between the residual motion of the tumor, potential lung toxicity and the duty cycle (47). Saito *et al.* studied the tradeoff between lung toxicity and treatment when gating at end-expiration (P2) or end-inspiration (P3) and found that for amplitude-based gating, difference in mean lung dose (MLD) between P2 and P3 was 0.5 Gy and the treatment time difference is 38 min (P2–P3) (47). The gating width is chosen based on which region the tumor has the least residual motion and

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Table 4 Summary of gating techniques (41,44,45)

Gating technique	Mechanism	Advantages	Disadvantages	Applications in proton therapy
RPM (Varian)	IR marker block placed on abdomen detected by IR camera. Marker block acts as an external surrogate to tumor motion. LINAC will beam on at pre-defined phases of respiratory motion	(I) Patient is treated in free-breathing; (II) allows for smaller treatment volumes	(I) Treatment time is extended; (II) assumption that signal of the fiducial markers is representative of tumor motion; (III) requires constant monitoring of tumor, additional imaging dose	(I) Feasible to use the RPM with proton therapy; (II) RPM provides respiratory signal correlated with the range modulation signal to enable gating control of the cyclotron beam current
Exac Trac Adaptive Gating System (Brainlab)	Pair of orthogonal kV X-ray tubes and amorphous Si diode imaging plates. Capable of tracking tumor through implanted fiducials and optical tracking of external fiducials			No published study with this system
Air Bellows (Philips)	Pressure transducer in the belt detects change in air pressure as the abdomen's stretches and contracts			Belt location needs to be out of the treatment field to minimize proton range uncertainty
Anzai Belt	Strain gauge in the belt detects abdominal motion by measuring pressure variations			
3D Surface Tracking GateCT and GateRT	GateCT captures surface images with user-defined tracking ROI for 4DCT reconstruction. GateRT is real time optical tracking of respiratory motion via user-defined ROI and allows gating when surface is in position			VisionRT feasible to use with proton treatment delivery system

ROI, region of interest.

usually this is at the end inhalation or at the end exhalation phase of breathing. End exhalation phase is chose as the gating window because the amplitude of respiration is more reproducible. However, at end exhalation, the lung is at a reduced volume and increased density and thus, the dosimetric parameters are not in favor at end-expiration (higher lung doses).

It is important that correlation between the external surrogate and the tumor motion be monitored regularly and when using only specific phases for gating, respiratory correlated pre-treatment imaging such as 4DCBCT or fluoroscopy with surgically implanted markers is acquired.

Tracking

Tumor tracking is one of the more advanced and complex treatment delivery, which, in principle, allows for the delivery system to track the tumor position in real time and continuously irradiate the tumor. This would, ideally, reduce the PTV, maintain dose coverage to the PTV, spare the OARs from being irradiated unnecessarily and also increase the duty cycle of the treatment. However, such a technique requires intensive real time imaging, precise prediction algorithm of the tumor motion based on external signals and minimal latency between the motion of the tracking beam and the motion of the object being tracked.

Up to date, there are three ways that tumor tracking can be implemented. The first method is initially implemented in UZ Brussels with the VERO system (48). This system is a single energy 6 MV linear accelerator with an MLC installed on an O-ring gantry. The O-ring gantry is able to rotate ±60° to facilitate non-coplanar treatment planning. The MLC is installed on orthogonal gimbals, which allows for a pan and tilt motion of the treatment beam. The pan and tilt amplitude is 4.4 cm in either directions, which is generally sufficient to track moving tumors. Imaging on

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the VERO consists of EPID for MV imaging and two orthogonal kV imaging systems for fluoroscopy, CBCT and also acquisition of orthogonal kV images. The system uses Exact-Trac infrared markers and also a 3rd order polynomial prediction function to compensate for system lag and latency. Preliminary results with the VERO system on 10 SBRT NSCLC patients have shown the feasibility of real time tumor tracking (RTTT) with visicoil planted near the GTV. Their study showed an average PTV reduction of about 35% as compared to conventional PTV_{ITV} volumes and also a reduction of mean lung dose (48). One limitation of the VERO system is the dependence on the 4D modeling and the fiducial insertion. If the model is not appropriate, then dynamic tracking cannot be performed accurately (49). Insertion of fiducial markers may also pose complications like pneumothorax, migration of the fiducial or localized pulmonary hemorrhage.

The second method of tumor tracking which is more commonly used is the Cyberknife system developed by Accuray. The Cyberknife system is a robotic arm capable of producing 6 MV photons coupled with X-ray imaging and a real-time respiratory motion-tracking camera. The treatment delivery and tumor tracking is based on a prediction model that correlates internal fiducials (located with orthogonal X-rays) and external surrogate (typically LED markers detected by a camera) (50). Unlike the VERO system, the Cyberknife's robotic arm has 6 degrees of freedom of control, which means that it can deliver radiation at multiple angles and directions. Several centers have reported their use of the Cyberknife in treating NSCLC. Brown *et al.*, in their 36 months study of Cyberknife radiosurgery of stage 1 lung cancer reported that local control and overall survival rates for image guided robotic SRS are comparable with surgical intervention (51). Their suggestion was to reduce the number of beams, hence the treatment time, as a long treatment time will increase proliferative rate of surviving tumor clonogens, not to use very small PTV margins, and to have fractionated treatment regimens instead of single fraction treatments. Another study by Collins *et al.* treating 20 stage 1 NSCLC patients with Cyberknife showed a 2 year Kaplan-Meier overall survival rate of 87% and local control of 100% with a median follow up time of 25 months. 3 of the patients had distant metastases while none reported local recurrences or severe treatment related complications (50).

Unlike the first two methods of tumor tracking, Dynamic Multi-leaf Collimator Tracking is not an additional machine in the arsenal of treatment delivery systems. In fact, it uses the MLCs that are already in conventional LINACs to continuously align the treatment field in sync with the respiratory motion. To date, DMLC has only been implemented in prostate cases while the feasibility of clinical use during lung SBRT is under development. The underlying principle of the DMLC system is to reposition each MLC leaf to achieve the desired dose distribution while the tumor moves in a combination of five moving patterns relative to the motion of the MLCs (52). These five possible moving patterns include:

(I) Tumor moves *parallel* to the leaf motion;
(II) Tumor moves *perpendicular* to the leaf motion;
(III) Tumor moves *along* the beam axis;
(IV) Tumor rotates *around* the beam axis;
(V) Tumor rotates *out of* the beam axis.

Caillet *et al.* retrospectively studied 10 lung SBRT plans with DMLC tracking delivered on a phantom. They found that there is a 30% reduction in the PTV, which is consistent with those found using Cyberknife or VERO. They also concluded that the strength of DMLC tracking is not to improve dose coverage, as they found it to be comparable with non-motion management technique, however, it significantly reduces the exposure to the OARs especially tumors near critical structures (53). Therefore, this could allow for tumoricidal dose escalation while sparing the OARs. A summary of the treatment delivery techniques is tabulated in *Tables 4* and *5*.

Continuous positive airway pressure (CPAP)

CPAP is a method of introducing constant pressurized air into the upper airways and lungs and it is currently used in the treatment of sleep apnea, COPD, acute respiratory failure with the goal that the patient's airways are continuously open thereby alleviating any obstruction. In the context of lung radiotherapy treatment, CPAP hyper-inflates the lung, increasing the lung volume, stabilizes the movement of the diaphragm and increases the distance of the tumor from critical structures. The first published work of CPAP in Lung SBRT was done by Goldstein *et al.*, who hypothesized that using CPAP will reduce the tumor excursion by decreasing the diaphragm motion and the tidal volume, thus, creating favorable conditions for dose escalation and reducing unnecessary exposure to critical organs (57). Preliminary results from their study show relative reduction of the ITV and PTV volumes compared to conventional free breathing plans, relative increase of lung volume by 32%, relative

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Table 5 Summary of motion tracking techniques (44,50,53-56)

Motion tracking technique	Mechanism	Advantages	Disadvantages	Applications in proton therapy
Synchrony System Cyberknife	Robotic arm with X-ray imaging and real-time respiratory motion-tracking camera	6 DOF	Limited beam output and field size	(I) RTTT for particle therapy consists of scanning magnets for lateral motion compensation and energy degrader to adjust beam energy; (II) feasibility of using planar scanning and energy switch in active scanning proton therapy
		Lesser margin expansion	Treatment can be lengthy for large tumors	
		No prolonged treatment time	Additional imaging dose with fluoroscopy	
		Non-invasive and fiducial free		
Vero Dynamic Tracking System (Brainlab)	Linac mounted on movable and rotating O-ring gantry Orthogonal gimbals allows pan and tilt motion.	MV PI and orthogonal kV imaging available	Additional imaging dose with fluoroscopy	
		Tracking performance shown to be similar in both pan and tilt direction		
Dynamic MLC Tracking (DMLC)	Prediction of future tumor position and calculation of new leaf positions which are relayed to the MLC controller	Leaf travel speed can match respiratory-induced tumor motion speed	2D MLC motion	
		Available on most Linacs	Out of plane motions will not be accounted for	
			Tracking performance varies with motion inline and perpendicular to MLC leaf	
			Additional imaging dose with fluoroscopy	

RTTT, real time tumor tracking.

reduction in lung V5, V10 and V20 and improved CT image quality (57). However, it must be noted that the small number of patient recruited limits the study and further developments are underway to test the feasibility of introducing CPAP with other treatment modalities such as proton beam therapy.

Breath hold techniques

This technique aims to create a static situation during treatment, and thus prevents interplay effects. Although these are likely of minor importance in modulated photon RT, they can significantly affect particle treatment plans. Especially for lung treatment, non-rigid deformations that relocate high-density (ribs) and low-density (soft tissue) regions can result in severe overshoots or undershoots. The other advantage of using breath hold is it allows for reduction of PTV margins. It can potentially move a significant amount of normal lung tissue outside the treatment field; it also increases the total lung volume, resulting in the improvement in lung parameters such as MLD, v20, v5 (58). The method was originally proposed by the Memorial Sloan Kettering Cancer Center (MSKCC) team in New York. The main disadvantage is that treatment and preparation time for DIBH patients is increased generally by about 30%. Patient collaboration is crucial and thus a lot of effort is spent on training the patients. There are also concerns that patients with poor lung reserves are unable to hold their breaths multiple times during the treatment.

Deep inspiratory breath hold (DIBH) is where a patient attempts a maximum reproducible inhalation during simulation and treatment. DIBH can be implemented using spirometric devices or non-spirometric methods such as chest wall movement (59). The involuntary breath-hold consists of an active breathing control unit, which uses a

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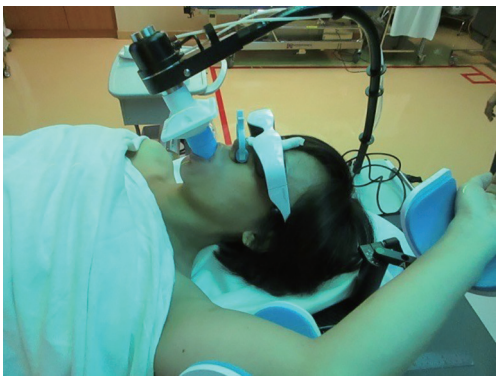

Figure 1 Patient set-up for DIBH technique with the SDX Spirometric Gating System. DIBH, deep inspiratory breath hold.

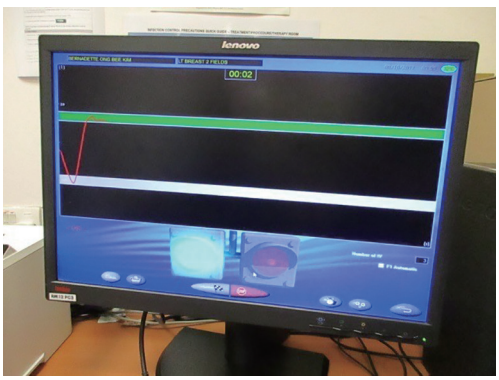

Figure 2 SDX Spirometric Gating System. Green bar shows the breath hold region where radiation will be delivered.

valve to close the airway to manage patients' breath-hold (Elekta's ABC). The voluntary breath-hold technique uses video guidance (SDX, Muret, France) to instruct the patient to inhale to reach a certain signal position on the glasses (60) (see *Figures 1*,*2*). The key difference between them is who initiate the control of the of breath hold. Details are described in the *Table 6* showing different breath hold devices.

Breath hold with visual feedback requires optimal patient compliance and has been shown to be accurate for lung lesions, with intra-fraction reproducibility of <3 mm. Both intra-breath hold and inter-breath hold measurements during feedback-guided voluntary breath hold with computer-controlled visual feedback resulted in a reproducibility of GTV centroid positions of <1.3 mm magnitude, largest being the S-I movement (65).

Dosimetric advantages for reduced lung and cardiac doses had been shown repeatedly for DIBH RT in advanced lung cancer treatments. Clinical outcomes had also been published by Giraud *et al.*, the largest study to date comparing different DIBH techniques which showed that there are significant reductions in acute pulmonary toxicities correlating with the dosimetric reductions (60).

DIBH-CBCT (in lung IGRT) has the advantage of improved image quality although the acquisition time is longer than that of FB CBCT. This approach provides superior image quality, particularly for middle-lobe and lower-lobe lung tumors and it also improves soft tissue contrast in upper abdominal lesions. First experiences report feasibility, speed, and better inter-observer variability of DIBH CBCT for even lung SBRT

Discussion and conclusions

The application of motion management techniques in lung radiotherapy has been shown, at least dosimetrically, to improve coverage of treatment volume and also reduce unnecessary exposure to critical organs. In this review, we have presented an overview of the various motion management techniques, from imaging modalities, free breathing techniques to breath hold devices. Each has its own advantages and disadvantages. There is no consensus or a standard guideline regarding the application of motion management.

How do we go about selecting the patient for the different techniques remain a question of heated debates, often it depends of the availability of resource of that treatment center. While it is not necessary to have all the various techniques in a radiation oncology department's arsenal, it is imperative that there should include 4D imaging capability for more accurate representation of tumor motion. It is also important to note that there is no one technique fits all for treatment of lung cancer as the effectiveness of a motion management technique depends on patient selection, staging, dose fractionation, tumor location, patient's lung function and patient's ability to comply to instructions. Of all the techniques, 4DCT imaging is the most prevalent. Modern CT simulation scanners will include a 4D imaging as a standard component, reflecting its widespread clinical use.

Long-standing issues such as the sorting method for 4D reconstruction, uncertainties with using external surrogates for acquiring the respiratory signal, obtaining the optimal PTV margin for good tumor coverage while at the same time minimizing unnecessary exposure to

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Table 6 Summary of breath hold techniques (44,61-64)

Breath hold technique	Mechanism	Advantages	Disadvantages
Non-spirometric			
RPM (Varian)	IR marker block placed on abdomen detected by IR camera. Marker block acts as an external surrogate to tumor motion. Linac will beam on when the respiratory signal is at user-defined threshold	Clinical feasibility	Reproducibility of the RPM marker block on patient anatomy
		Ease of use	Slight change in lung volume may not be detected by the marker block
		Non-invasive	
Abches (APEX Medical Inc.)	Two point systems that detect motion amplitude of the abdomen and chest and displayed by an indicator for patient to see. Operator will adjust three dials to mark end-inspiration, expiration and reference level for FB	Clinical feasibility	Lacks audio coaching
		Reproducibility of tumor position during lung SBRT	Not suitable for patients with low breath hold capacity and difficulty in communication
		Ease of use	Not suitable if patients are unable to monitor their own respiration
		Can be used for multiple sites	
		No electrical components	
Spirometric			
Active Breathing Coordinator (ELEKTA)	Turbine-based spirometer with visual feedback. Patient controls radiation treatment by pressing a hand switch, which blocks airflow at a pre-determined and reproducible tidal volume	(I) Clinical feasibility; (II) audio-visual feedback improves reproducibility; (III) gated treatment delivery when the breath hold volume is reached	Relatively invasive in nature for the patients as breath hold is controlled forcibly by a valve which will only be released when the patient hand held switch is released
SDX Spirometry Gating System (DYN'R)	Reisch-pneumotachometer based spirometer with visual feedback. Patient given a visual cue to indicate the start/end of voluntary breath hold		Gating module is not compatible for all treatment delivery system

normal tissues and critical organs have been discussed. Several solutions have surfaced from these studies. For instance, audio-visual biofeedback has shown to improve reproducibility in compliant patient's respiratory signal, which improves 4D image reconstruction, regardless with amplitude or phase sorting. Future developments include using patient's anatomic structures to acquire respiratory signal, which reduces latency issues that are present with current techniques with external surrogates, to improve the robustness of radiotherapy treatments. The potential of MRI in radiotherapy should also be realized, as it provides no radiation dose and better tissue contrast. With the improvement of more sophisticated technology, we will be able to see a paradigm shift in radiotherapy where MRI technology will be omnipresent in simulation, planning, pre-treatment verification and even treatment delivery.

The importance of motion management in proton therapy has been emphasized in many research studies. The effect of motion in proton therapy is less forgiving than it is in photon therapy as small changes in density in the path of the treatment can potentially have a significant impact on the dose distribution. For dynamic treatments, implementing robust planning strategies such as full 4D optimization and the type of dose calculation algorithm used can reduce contribution of the interplay effect to the uncertainty in dose distribution. Breath-hold techniques (minimizing motion) are relatively easier to implement for proton therapy, however, tracking and gating, with its advantages over breath hold, do pose their own set of challenges. Up to date, there are no gold standard of motion

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management in proton therapy but like conventional photon therapy, advanced 4D imaging has an important role to play in ensuring accurate target delineation and dose delivery.

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