Received:
1 February 2015

Revised:
30 April 2015

Accepted:
7 May 2015

doi: 10.1259/bjr.20150100

Cite this article as:

Korremán SS. Image-guided radiotherapy and motion management in lung cancer. *Br J Radiol* 2015; **88**: 20150100.

ADVANCES IN RADIOTHERAPY SPECIAL FEATURE: REVIEW ARTICLE

Image-guided radiotherapy and motion management in lung cancer

S S KORREMAN, PhD

Department of Science, Systems and Models, Roskilde University, Roskilde, Denmark

Address correspondence to: Dr Stine S Korreman

E-mail: stine.korreman@gmail.com

ABSTRACT

In this review, image guidance and motion management in radiotherapy for lung cancer is discussed. Motion characteristics of lung tumours and image guidance techniques to obtain motion information are elaborated. Possibilities for management of image guidance and motion in the various steps of the treatment chain are explained, including imaging techniques and beam delivery techniques. Clinical studies using different motion management techniques are reviewed, and finally future directions for image guidance and motion management are outlined.

Image-guided radiotherapy (IGRT) implies the use of in-room imaging to localize the target with the aim of guiding the treatment beam to an accurate aim. Based on the images, compensating actions may be taken to adjust for variations found in the images. Variations can be of both rigid and non-rigid nature, and occur on different time scales. Specific to image guidance for radiotherapy in the lungs, is the phenomenon that breathing causes geometric anatomical changes to take place in the patient within the time scale of a radiotherapy fraction that are (more or less) predictable and cyclic. This phenomenon at the same time poses great challenges to implementation of image guidance for lung radiotherapy, as well as great opportunities. Over the last approximately 15 years, almost overwhelming attention has been given to this subject in particular in the radiotherapy physics society, and great technical advances have been made, which have changed the clinical practice of lung radiotherapy. This review systematically covers both technical aspects and clinical implementation of various strategies for image guidance in lung radiotherapy. Focus will be given to techniques aimed at compensating for breathing dynamics, although it should be stated now that a fully comprehensive review would be much too vast to fit in the space available in a single article.

BASIC CONCEPTS OF LUNG IMAGE-GUIDED RADIOTHERAPY

Motion characteristics of target, lung and nearby structures

Motion characteristics of thoracic structures have been investigated and presented in a number of studies, both with

regard to the cyclic breathing motion on the short time scale of seconds and minutes, and variations on longer time scales of days and weeks.

In a previous review,¹ this author has collected data from a number of early studies of motion of organs and structures in the thoracoabdominal region (Table 1). Notable is that motion takes place in all three orthogonal directions and may be of a considerable extent up to several centimetres, especially in the craniocaudal direction. For tumours in the lung, motion extent and characteristics may depend on location of the tumour, tumour size, lung function and whether or not the tumour is attached to structures. Additional to this, there are cycle-to-cycle variations in breathing, hysteresis and changes on a longer time scale of days and weeks.

The hysteresis phenomenon is well documented in, for instance, the classic and often cited study by Seppenwoolde et al² (Figure 1a). In this figure, the potentially large extent of motion is confirmed, as is the occurrence of motion in all three directions, at the same time as the hysteresis is visually illustrated by the differences between inspiration and expiration paths in the drawn trajectories.

In the recent years, several studies have investigated in detail cycle-to-cycle variation in breathing pattern, as these variations are crucial in relation to implementation of real-time motion management techniques. An example of such a study is reported in Worm et al,⁴ where sequences of

Table 1. Dynamics of normal structures with respiration

Structure	Mean excursion (mm) (range) ^a						Number of studies	Number of patients over all studies reported
	Free breathing			Deep breathing				
	SI	AP	ML	SI	AP	ML		
Lungs	10.3 (1–31.9)	6.4 (0–24.4)	(1–10)	9.3 (0.1–70)	7.8 (0.5–18.8)	4.2 (1.1–17.6)	7	62
Diaphragm	14.9 (2.6–38.2)			44.6 (3.1–96)			10	112
Liver	12.3 (4.9–30.4)	(max. 5.2)	(max. 4.6)	38 (25–57)			6	59
Chest wall	7.3 (2–15)	2.3 (0–8)	(5–7)		16 (0.7–37.3)	11.7 (0.5–64.1)	6	88
Heart	18.1 (12–25)	2.4					2	20

AP, anterior-posterior; max., maximum; ML, medio-lateral; SI, superior-inferior.

^aThis table contains an overview of the results of a number of studies concerning organ motion with respiration. For each organ, the mean value (or the range) of the organ excursion over several studies is reported, and the number of studies used to obtain the mean as well as the total number of patients is given. The table is reproduced from Korreman¹ with permission from IOP, and references for the studies can be found there.

breathing have been investigated for a series of patients undergoing stereotactic body radiotherapy (SBRT) for liver cancer. The study showed that the cycle-to-cycle variability had a standard deviation of approximately 20% of the mean total motion extent over all cycles.

Finally, variations related to breathing take place on longer time scales as well. This was, for instance, quantified for 56 patients with lung cancer in Sonke et al,³ as illustrated in Figure 1b using a representation similar to that in Figure 1a. It is demonstrated by this study that breathing varies from day to day in reference to the surrounding structures, with a mean magnitude of variations of 3.9 mm.

From imaging for treatment planning to treatment delivery

Given that all of the above stated variations take place in relation to target localization and motion of structures in the lung, it is also evident that accurate radiotherapy requires images to be acquired at various stages of the radiotherapy chain and with high degrees of temporal and spatial resolution.

Imaging for treatment planning consists of a CT scan possibly combined with a positron emission tomography (PET) or even a MR scan. In a standard CT scan of the thoracic region, motion of structures on time scales comparable to that of slice acquisition and scan acquisition introduces artefacts in the CT image of the patient. These effects have been extensively studied,^{5–7} and although they are well known, they are not easily predicted or accounted for in clinical practice for standard CT scanning. With the aim of minimizing artefacts stemming from motion, four-dimensional CT (4DCT) scanning is now becoming standard for imaging for treatment planning for lung cancer radiotherapy. The 4DCT scan displays the breathing motion of all structures in the scan region as it occurs in the breathing cycles taking place during the scan period. Depending on the specifications of the scanner and the scan settings, the image quality resulting from such a scan varies, but generally, there are markedly less artefacts than in a standard scan.

Modern CT scanners used for treatment planning scanning can be acquired with 4DCT capability as a standard. For PET-CT scanners, four-dimensional (4D) capability may be available for the CT part but not for the PET part. Motion has a significantly different effect in PET scans than in CT scans, because the time scale of a PET acquisition is much longer than the time scale of the breathing cycle. As the PET acquisition thus spans a large number of breathing cycles, the effect is a blurring of the signal over the motion trajectory of the target.⁸ A 4DPET scan consisting of a number of scans representing different phases of the breathing cycle may be produced by sorting the counts according to when in the breathing cycle they were recorded.⁹ Some scanners come with this capability, but it is not as widely available and used as 4DCT scanning is.

The quality and representativeness of a 4DCT scan depends highly on the regularity of the patient's breathing. The more irregular the breathing, the more artefacts will be present in the 4DCT scan,¹⁰ and the less representative the scan can be for the

Figure 1. (a) Orthogonal projections of the trajectories of the 21 tumours on (left) the coronal (LR-CC) and (right) the sagittal (AP-CC) plane. The tumours are displayed at the approximate position, based on the localization mentioned in the treatment chart. Reproduced from Seppenwoolde et al.² (b) Graphical representation of systematic (arrows) and random (ellipses) baseline variations projected on coronal and sagittal views of a schematic bronchial tree. Colours reflect average amplitude. Reproduced from Sonke et al.³ with permission from Elsevier.

patient's breathing pattern. However, we have recently shown in a phantom study that even for highly irregular motion, a 4DCT scan will represent the target shape and trajectory at least as good as a standard scan.¹¹ However, the 4DCT scan will always only be an image of the motion taking place in a few breathing cycles on that particular day—a “snapshot cycle image” so to speak.

Although the 4DCT scan provides significant information to the radiotherapy process of the volumetric breathing dynamics in the patient, the snapshot nature of the image means that it cannot supply information regarding intercycle variations and variations on time scales longer than seconds.

How the information—and lack of information—obtained in a 4DCT scan is used in the radiotherapy process depends on

the choice of motion management strategy employed, as will be seen in the Motion management strategies section. In all cases, IGRT includes additional imaging in the treatment room in relation to treatment fraction(s), in two, three or four dimensions. In two-dimensional (2D) images, mainly bony structures are visible, especially when the megavoltage (MV) beam is used for imaging where the contrast is low. In kilovoltage (kV) images, soft-tissue contrast is higher, and especially when three-dimensional (3D) cone-beam CT (CBCT) imaging is used, it may be possible to set up directly to soft-tissue structures. Semi-3D imaging may be performed by combining information from two orthogonal 2D images. Options for imaging in the treatment room do not as a standard include high-quality volumetric 4D techniques (at least not yet), although both 4D CBCT imaging and fluoroscopic imaging are increasingly available with new

and upgraded treatment machines. CT on rails, with a full-scale CT scanner physically adjacent to the treatment machine can provide in-room full-scale 4DCT imaging, although only used to a limited extent in few clinics.

An entirely different option for gaining information specifically on the position of single points in the patient (typically in the tumour) over time, is that of implanting radiofrequency beacons, which can be monitored in real time (for instance the Calypso® system, see the Techniques for imaging motion section).

When variations take place on the same time scale as a treatment fraction, imaging during treatment may be relevant. This can take place either during beam on time, or in-between beams. The purpose of imaging during treatment will either be verification for possible intervention if tolerance levels are exceeded, or dynamic beam adaptation such as motion tracking.

An alternative option should be mentioned, namely that of “freezing” the motion rather than imaging and accounting for it, which can be achieved by employing breath-hold during imaging and treatment. Breath-hold is a well-known and early technique used in diagnostics for achieving CT images with reduced artefacts, and CT images obtained during a breath-hold are of a better quality than those obtained in a 4DCT scan—as is seen in an example in Figure 2.^{12,13} When employed in CT scanning for radiotherapy planning, a crucial point, however, is the reproducibility of the breath-hold that must be mimicked in the treatment situation, making in-room imaging (with breath-hold) even more important.¹⁴

Techniques for imaging motion

A number of techniques are available for imaging in the treatment room as well as for treatment planning. In the treatment room, radiographic and fluoroscopic kV imaging capabilities are now standard for new machines. This may be either as equipment mounted on the linear accelerator (linac) gantry, mostly in an orthogonal geometry to the treatment MV beam, or as independent units mounted in the ceiling or floor of the room in an orthogonal (or at least stereoscopic) geometry. Two orthogonal (or stereoscopic) imaging units may be combined to give semi-3D information, while gantry-mounted imaging units can additionally be used for CBCT imaging, yielding true 3D images, as well as for 2D radiographic/fluoroscopic imaging. For CBCT scanning, the acquisition time is long compared with the breathing cycle time, and the image will therefore contain a blurred image of the target position over several breathing cycles. Time-resolved CBCT scanning (4D CBCT) yielding a set of 3D images corresponding to different phases of the breathing cycle has been developed, although it is not widely available yet.¹⁵

Visibility of lung tumours in kV images is often quite good and is sufficient for matching with digitally reconstructed radio-graphs from the treatment planning CT scan. This is especially true for 3D (and 4D) CT imaging. However, for valid high-precision tumour-tracking purposes, especially in real time, it is more optimal to implant markers for increased visibility. When markers are implanted, an added benefit is that the tumour is visible even in MV images, for instance, from the treatment beam during beam delivery. Marker implantation carries a risk of side effects, depending on how the implantation is performed—the

Figure 2. CT scans of two patients with large deviations in gross target volume (GTV) between scans: conventional three-dimensional CT (3DCT) (left), four-dimensional CT (4DCT) midventilation bin (middle) and breath-hold CT (BHCT; right). The upper row shows images from a patient with a tumour in the right lower lobe. The delineated GTV size was 64.9, 45.2 and 34.9 cm³, respectively, and the craniocaudal (CC) tumour motion was 2.4 cm. The lower row shows a patient with an apical tumour in the left lower lobe. The GTV size was 4.2, 3.0 and 2.1 cm³, respectively, and CC tumour motion was 0.6 cm. Reproduced from Persson¹³ with permission.

risk of pneumothorax for percutaneous implantation is reported to be up to 30% including all levels of severity and up to 10% requiring intervention.^{16,17} Alternative to the percutaneous method, implantation may be performed bronchoscopically as in for instance reported in Harada et al.¹⁸

Common for all methods of imaging motion, is that it is often relevant to monitor breathing through an external surrogate simultaneously. This can be performed through many different techniques—optical recording of reflective optical markers or light-emitting diodes positioned on the surface of the patient, spirometry for volume measurement of air flowing in and out of the lungs, measurement of the temperature of in- and out-flowing air, with a thermocouple placed under the nose, measurement of pressure produced by chest expansion with piezoelectric ceramics placed in an elastic abdominal strap, patient surface rendering by use of lasers. All these surrogates give respiratory cyclic signals that are one dimensional in the sense that they (mostly) only monitor a single property (pressure, temperature, flow, position) as a function of time. The surrogates reflecting position (such as optical markers) have the potential of giving 3D positional information when stereoscopic imaging of several markers is performed or in the case of surface rendering.

A method for monitoring which gives direct information on target position without imaging is the implantation of radio-frequency beacons in the patient—for instance, using the Calypso system. The implantation process carries the risks related to implantation as described previously, especially since the beacons are quite large. The advantage is that the target position monitoring process becomes less complicated, since the target position is directly monitored without the necessity of extensive imaging and image processing.¹⁹

MOTION MANAGEMENT STRATEGIES

When motion is present in the treatment region of the patient, this needs to be accounted for both in treatment preparation and in treatment delivery. The past approximately 15 years of development has made it possible to do so on an individual basis and even in real time. The classic method of using the clinical target volume to planning target volume (CTV-to-PTV) margin to account for all variations on a population basis can now be replaced by more and more sophisticated individual approaches.

Encompassing treatment field margins

When a 4DCT scan is available for planning, there is an immediate potential for applying individualized treatment field margins to encompass the breathing motion. Two different methods for doing this in practice have been established—(1) definition of the internal target volume (ITV) and (2) the midventilation approach. Both are in use in clinical practice and have been reported in the literature, for instance, in Sonke et al.²⁰ and in Hanna et al.²¹ The two methods take two quite different approaches to achieving the same goal—calculating an adequate CTV-to-PTV margin to account for the breathing motion observed in the 4DCT scan.

Using the ITV approach, the all images of the 4DCT scan are overlaid using, for instance, a maximum intensity projection of

all phases, and the combined volume of the target in all phases of the breathing cycle is outlined as the ITV.²² The ITV is then considered the gross target of irradiation ensuring full irradiation of the target over the entire breathing cycle. On the ITV, further margins are subsequently added to give the planning target volume (PTV). In relation to the image guidance perspective, there are two advantages of the approach. At the planning stage, residual image artefacts in the target shape and volume in the 4DCT scan are to a large degree eliminated by the overlay of the images of all the phases. When subsequently performing in-room image guidance, matching for set-up can be performed between the ITV in the 4DCT planning scan and the corresponding target in the CBCT scan.^{23,24}

In the midventilation approach, the trajectory of the target in the 4DCT scan is analysed, and the phase in which the target is closest to its mean position is identified—this is termed the midventilation phase.²⁵ This phase is then used for delineation and treatment planning. The motion extent of the target throughout breathing can be measured from the trajectory and used in the combined margin applied to the target. In this approach, it is often also argued that the margin to account for breathing motion should be calculated by quadratic addition of the breathing variation.²⁶ (This is in opposition to the ITV approach where the margin for breathing is *de facto* linearly added.) For the midventilation approach, image-guided set-up can be performed by matching the target in the midventilation phase of the 4DCT scan to the target in the corresponding midventilation phase of a 4D CBCT scan or matching can be attempted using the full motion in both scans.²⁷

Gating and breath-hold techniques

Going a step further in motion management, it may be relevant to utilize the knowledge of breathing motion to decrease the treatment field margins, especially when toxicity is a limiting factor and/or of high concern. This can be achieved by reducing the breathing motion of the target during irradiation, through only irradiating the target when it is within a limited pre-defined window of the breathing trajectory. The approach of turning the beam on and off in synchronization with the breathing cycle is termed respiratory gating. An illustration of the principle of respiratory gating is shown in Figure 3a.

For treatment delivery, the gating phase of the breathing cycle needs to be identified and positionally verified, and the beam must be triggered on and off accordingly for the duration of the beam delivery. A breathing monitoring device for providing the trigger signals is required, and there are several commercially available systems on the market for this. Breathing monitoring devices for respiratory gating most often rely on surrogates for the actual motion of the target, such as an external optical skin marker or a pressure sensor, as described in the Techniques for imaging motion section.

For respiratory gating, image guidance is of utmost importance as has been shown in Korreman et al.²⁸ This is owing to the inert variable degree of irregularity of breathing, and the resulting lack of predictability of breathing motion. The correspondence between the breathing motion of an external surrogate and the

Figure 3. (a) Normal breathing shown with the principle of respiratory gating of beam delivery. (b) Breathing with breath-hold shown with the principle of beam delivery during breath-hold. For both (a, b) the horizontal lines indicate the thresholds within which the beam can be turned on. The vertical dashed lines indicate the points in time at which the beam should be turned on and off, respectively.

breathing motion of the target may change markedly—therefore, when external surrogates are used for motion monitoring, the correspondence between surrogate motion and target motion needs to be established and verified on a regular basis, not only from fraction to fraction but also within each treatment fraction. If this is not performed, geographical miss may be risked, with underdosage of the target as a result.²⁸ Image guidance adequate for this purpose includes 4D CBCT, respiratory correlated fluoroscopy or repeated radiographs combined with suitable software to establish a quantification of the target position in the images.

In order to perform treatment planning for respiratory gating, the planning phase of the 4DCT scan appropriate for gating can initially be selected as the planning scan. Parameters for

choice of gating phase will typically include stability, time spent in the phase and proximity of nearby organs at risk. For high stability and large fraction of time spent in the gating window, end-expiration will be the phase of choice. On the other hand, dosimetric concerns for organs at risk may in some cases point to the inspiration phase as the optimal phase for gating.²⁹

The breath-hold approach is somewhat simpler than cyclic respiratory gating in several aspects, although it relies on the same basic principle of turning the beam on and off based on target position (Figure 3b). The continuous detection of breathing phase as well as the potential lack of consistent correlation with surrogate monitored motion are not issues, although target position still needs to be verified during breath-hold.^{30,31} For

increased stability of breath-hold procedures, the Active Breathing Coordinator™ (Elekta AB, Stockholm, Sweden) uses a combination of a valve system shutting off air flow and a visual guidance to the patient.³² As for free breathing, breath-hold during expiration is more stable than during inspiration, but the choice of whether to use expiration or inspiration breath-hold will depend not only on stability but also on dosimetric concerns.

For both respiratory gating in free breathing and breath-hold techniques, it has been shown that reproducibility and stability can be enhanced by use of patient training and coaching techniques, using both audio and visual guidance^{33,34} (see the Decision making strategies for motion management section).

Motion tracking

The ultimate solution for accounting for target motion during treatment is to aim the treatment beam continuously and dynamically at the moving target. This is also the most demanding solution in terms of image guidance requirements.

There are several systems for motion-tracking treatment on the market.

Since its first use in 2002, the Synchrony system for Cyberknife® (BrainLab AG, Feldkirchen, Germany) has been in clinical use in an increasing number of clinics, and several articles have reported investigations as well as clinical protocols using the system.^{35–37} The Cyberknife robotic arm is programmed to move synchronously with the breathing cycle, in a trajectory following the projected 3D motion of the target. The target motion is not monitored directly, but before treatment is started, a sequence of orthogonal radiographic images is recorded from which the target breathing motion is derived in three dimensions. At the same time, a mathematical correlation model between the target motion and the motion of a set of external optical markers on the surface of the patient is established. During beam on, the motion of the external optical markers is monitored and the correlation model is used to direct the beam at the corresponding target positions dynamically. Intermittent radiographic images are acquired throughout beam on time, to provide verification of target position and to update the correlation model.

The newer Vero® (BrainLab AG) dynamic tracking system is in clinical use in only few clinics (only two reported in literature^{38,39}). The machinery is very different from that of the CyberKnife, using a gimbaled treatment head mounted on an O-ring, but the principles of the tracking monitoring and driving systems are very similar to those of the CyberKnife described above. External optical markers are placed on the patient surface, and orthogonal fluoroscopic imaging sequences are initially used to establish a mathematical correlation model between the motion of the external markers and the target. During beam on, the motion of the external markers is monitored and the correlation model is used to direct the beam (with pan and tilts of the gimbaled head) dynamically at the modelled target position. During beam delivery, orthogonal radiographic images are acquired regularly, and the images are used post beam delivery for evaluation of the need for recalculation of the correlation model.

Dynamic multi-leaf collimator (MLC) tracking for a standard gantry-based linac has recently been used clinically for the first time,⁴⁰ although not for lung cancer but prostate cancer treatment. MLC tracking for lung cancer is still in development.^{41–43} In MLC tracking, the MLC leaves shaping the treatment beam are programmed to move in accordance with the target motion during breathing. This leaf motion can be superposed on intensity-modulated radiotherapy (IMRT) or dynamic arc leaf motion.^{44–46} In relation to the development of MLC tracking, focus is on beam delivery, and specific image guidance protocols are not established. Development issues relate primarily to positioning of the leaves and jaws. Image guidance techniques available in the treatment room can be used in the tracking process in various ways. The standard linac does not have orthogonal radiographic imaging capabilities, like the CyberKnife and the Vero machines, but some rooms may have additional radiographic imaging equipment installed, such as the BrainLab ExacTrac® X-ray system (BrainLab). Monitoring of the breathing by, for instance, an optical tracking system may additionally be available in the treatment room. Several alternatives of direct or indirect motion monitoring and positional verification are investigated for MLC tracking implementation.^{47–49}

Finally, tracking by couch counter-motion is under investigation by several groups but is not clinically implemented.^{50,51}

Treatment planning for motion tracking can be performed either for all phases of the full 4DCT scan for a 4D optimized treatment plan⁴⁴ or to a single phase for a static plan, which may be subsequently translated according to breathing motion.

Decision-making strategies for motion management

It is still a question of heated debate, which motion management strategy to use for which patients. A standard or guideline for decision-making regarding motion management has not been established in the radiotherapy community, rather the community is divided by different basic views on the issue.

It has been shown that the median motion extent of lung tumours is around 5 mm, and only around 20% of patients with lung cancer have tumours with motion >1 cm.^{26,52,53} For motion less than approximately 13 mm, respiratory gating or motion tracking can reduce treatment field margins by <2 mm⁵³ compared with a midventilation approach. The effects of motion management on treatment field margins are rather small in general because it is only one component of random nature in the entire uncertainty chain, and especially small for lung cancer radiotherapy because of the smeared out penumbra in the low-density lung tissue.

A cost-effectiveness decision criterion for choice of motion management in treatment delivery based on motion extent alone would therefore imply that only few patients would be eligible for respiratory gating or motion tracking. However, an additional parameter relevant for decision-making is the dose to nearby organs at risk. Dose to organs at risk is very much dependent on individual features in each case, and there are no easily quantifiable simple parameters that can pre-determine eligibility for motion management. Calculation of doses to

organs at risk in the treatment planning system is doable for respiratory gating or breath-hold techniques (where calculations can be carried out in one single phase of breathing), but for motion-encompassing techniques and tracking techniques, calculation should really be performed in all phases of breathing and accumulated, and treatment planning systems do not have that capability in full. Proximity of target to organs at risk may be a parameter indicating potential relevance of respiratory gating or tracking, but it will be a matter of individual assessment.

Regularity of breathing relates to a feasibility criterion that may also determine eligibility for use of motion management techniques in treatment delivery. The success of both respiratory gating and motion-tracking techniques rely on the ability of the patient to breathe in a regular and predictable pattern. The more irregular and unpredictable the pattern, the more likely the motion management is to fail, for instance, by lack of consistency in the correspondence between motion of the target and of the external motion surrogate used for driving the beam position. Also for this, there is no easily quantifiable parameter to indicate adequate regularity of breathing. Training and real-time coaching in regular breathing may increase the regularity of breathing for many patients.^{54,55}

Motion management techniques that do not imply beam delivery interference include 4D scanning for treatment planning and respiratory correlation of in-room imaging for localization and verification of target position. Treatment planning based on respiratory correlated imaging should always be applied for lung cancer. A 4DCT scan will give information on motion extent and proximity of target of organs at risk, which can be used in the decision-making strategy for further motion management. Also, the 4DCT scan will be less prone to image artefacts of the target, enabling more accurate delineation. In-room imaging should also as a default be performed with inclusion of respiratory information for pre-treatment set-up, as it has been demonstrated that this gives a large potential for increasing accuracy and thereby enabling reduction of treatment field margins.^{26,53,56}

Obviously in each department, availability of equipment is the first parameter determining the image guidance and motion management strategies used. With purchase of new equipment, importance of image guidance and motion management will be weighed, with consideration to the patient groups, work load and performance expected for the machine operation.

CLINICAL PROTOCOLS

In this section, examples are given of high-level use of image guidance and motion management protocols reported in recent literature. As the literature reports mostly investigations of innovative and experimental methods rather than general clinical practice, it is not easy to find state-of-the-art protocols in literature.

A good example of routine clinical use of image guidance and motion management for lung cancer radiotherapy with curative intent can be found in the official Danish recommendations for lung cancer radiotherapy from the Danish Oncological Lung Cancer Group from 2014 (www.dolg.dk/strålerekommandationer.php in Danish). In these recommendations, treatment planning

should be performed based on a 4DCT scan, in which the magnitude of breathing motion is estimated. Based on the CT scan, either the midventilation approach or ITV approach (or similar method in which breathing motion is taken into account) is used for margin encompassing of the breathing motion. It is suggested that a breath-hold CT scan is additionally acquired in order to give an artefact-free guide for tumour shape and size to aid in target delineation. For treatment delivery, image guidance is recommended on a daily basis in accordance with and supporting the added CTV-to-PTV margin. Specific recommendations for choice of image guidance method (2D, 3D or 4D) and action levels are not given, but it is implicit that the CTV-to-PTV margin must be adequate to support the specific choice, and individually calculated at each clinic and for each protocol. Guidelines for margin calculation are also given, based on relevant literature.^{57–63}

In the Danish guidelines, there are no recommendations regarding respiratory gating, breath-hold or motion tracking. None of these techniques are used on a routine basis, although they may be applied in some clinics for specific cases where normal tissue constraints or target dose prescription cannot otherwise be achieved.

Use of a breath-hold technique during beam delivery in clinical practice has been reported, for instance, in Brock et al.⁶⁴ at the Royal Marsden Hospital. The Active Breathing Coordinator was used in deep inspiration breath-hold, in order to minimize irradiation of lung tissue. No reduction of treatment field margins was applied, but the increased lung volume (mean increase of 41% measured in a deep inspiration CT scan compared with volume in a free breathing CT scan) implied reduction of the relative lung volume irradiated and presumably therefore also a corresponding reduction of irradiated lung tissue. Imaging for treatment planning was performed as deep inspiration breath-hold CT scanning (free breathing CT was performed for comparison). Repeated breath-hold CT scans showed that target position changed markedly between fractions, and the study recommends image guidance be used on a daily basis.

Clinical use of 4D CBCT for daily set-up imaging has been reported for SBRT for lung tumours [early stage non-small-cell lung cancer (NSCLC)] at the Netherlands Cancer Institute in Sonke et al.²⁰ Patients were routinely scanned using 4DCT scanning, and treatment planning was carried out using the midventilation approach. Patients' individual PTV margins were calculated based on the individual magnitude of breathing motion. On each treatment day, 4D CBCT was used to match the midventilation target position from the planning 4DCT scan to the mean position of the breathing motion on the treatment day. No motion management was used during beam delivery except the motion-encompassing margin. Significant reductions of PTV margins were applied compared with the margins that would have been necessary with no motion management in image guidance. In a subsequent article by Peulen et al.,⁶⁵ clinical outcome for this protocol (with a slightly larger PTV margin) is reported at 98% local control and 67% overall survival at 2 years.

Clinical use of motion tracking for lung cancer has been reported using both the CyberKnife^{66,67} and the Vero^{38,39} systems. The CyberKnife motion-tracking system has been in

clinical use since 2005, and clinical outcome results are reported in the referenced literature for lung cancer treatment (Stage 1 NSCLC). In these reported results, standard 3D CT scanning was used for treatment planning, and the treatment beams were rigidly translated according to the monitored motion. Image guidance was performed according to the protocol described in the Motion tracking section. Local control and overall survival at 2 years was reported to be 96% and 62%, respectively. Clinical use of the Vero system has only recently been commenced. In the first reported study, treatment planning was carried out in the expiration phase of a 4DCT scan, and image guidance was performed according to the protocol described in the Motion tracking section. Owing to the early stage of implementation of this technique, outcome results are not yet available, but it is to be expected that results comparable to those of the CyberKnife system motion tracking can be achieved.

PERSPECTIVES AND FUTURE DIRECTIONS

Special issues for proton therapy

Motion management for proton therapy is a special issue, which has been covered in a number of papers (see, for instance, Hui et al,⁶⁸ Lu et al⁶⁹ and Zhao et al;⁷⁰ Bert and Durante;⁷¹ and Wink et al⁷²). The challenge of proton therapy for moving targets is specifically that the effects of motion on target coverage and irradiation of adjacent structures is potentially much larger than for photon irradiation. For protons, the position of the narrow Bragg peak is highly dependent on the beam energy and on the amount and density of tissue penetrated by the beam during its travel through the patient. Motion in the patient anatomy that changes the configuration of structures with different densities can therefore have a potentially large impact on the dose distribution. The effects depend on whether passive scattering proton beams or spot scanning beams are used, where the respiratory motion of the target may interfere with the scanning motion of the proton beam creating interplay effects changing the dose deposition pattern markedly.⁷³ There are studies showing varying degree of effects for both passive beams and scanning beams.^{74,75} In general, it can be said that image guidance needs to be at least as comprehensive for proton therapy as for photon therapy, and in some cases, safe implementation of proton therapy requires more extensive image guidance schemes than does proton therapy, in effect limiting the implementation of proton therapy for lung.

Dose painting and motion

The delivery of heterogeneous dose distributions based on functional imaging with high spatial resolution and large dose gradients within the target volume is termed dose painting. The

high spatial resolution and large dose gradients add to the necessity of high accuracy in both pre-treatment imaging and dose delivery. Uncertainties in the treatment chain have detrimental effects on the correspondence between deposited dose and the dose prescription map, as has been shown in, for instance, Korreman et al.⁷⁶ A clinical multicentre Phase II trial is presently running for a very simple dose painting strategy, applying a dose boost volume within the target to the high uptake (>50% standardized uptake value) volume from a fluorine-18 flu-deoxyglucose PET scan.⁷⁷ The protocol involves a midventilation approach to treatment planning, use of patient-specific treatment field margins and set up in the treatment room using image guidance with institutional policies. As there are only two dose levels in the protocol and not high degree of heterogeneity, it is expected that this provides sufficient accuracy.

New technological developments and increasing standardization of four-dimensional imaging

An interesting new technological development that has been emerging in the recent years is that of the combined treatment machine with MRI, the MRIdian by ViewRay⁷⁸ or various versions of the MR-linac^{79–81} (although the MR-linac is not yet in clinical use). MRI has superior soft-tissue contrast compared with imaging using ionizing radiation and can be performed simultaneously with beam delivery. The potential of using this for image guidance for lung cancer in the treatment room are promising,^{82,83} and may well constitute the next large step in development of image-guided radiotherapy.

The existing imaging technology using CT and PET scanners as well as in-room electronic portal imaging devices is being continuously developed with respect to both hardware and software to provide images of higher and higher quality and resolution, in both 2D, 3D and 4D. Examples of hardware developments are dual-energy CT scanning; time-of-flight PET scanning; combined uses of CT, MR and PET; and refined filters for detectors.⁸⁴ As these technologies are refined so is the software following them, and their use will to a larger and larger extent become standard. The field of 4D imaging has been in fast development since 2000 and has changed the field of radiotherapy for lung cancer, as described in this review. Many issues continue to challenge the clinical implementation, and research and development is ongoing (see, for instance, the summary of the 4D treatment planning workshop 2013 in Knopf et al⁸⁵), however, radiotherapy including 4D image guidance (and dynamic beam delivery) has become standard in many clinics, and its dissemination in clinical practice will continue.

REFERENCES

1. Korreman SS. Motion in radiotherapy: photon therapy. *Phys Med Biol* 2012; **57**: R161–91. doi: [10.1088/0031-9155/57/23/R161](https://doi.org/10.1088/0031-9155/57/23/R161)
2. Seppenwoolde Y, Shirato H, Kitamura K, Shimizu S, van Herk M, Lebesque JV, et al. Precise and real-time measurement of 3D tumor motion in lung due to breathing and heartbeat, measured during radiotherapy. *Int J Radiat Oncol Biol Phys* 2002; **53**: 822–34. doi: [10.1016/S0360-3016\(02\)02803-1](https://doi.org/10.1016/S0360-3016(02)02803-1)
3. Sonke JJ, Lebesque J, van Herk M. Variability of four-dimensional computed tomography patient models. *Int J Radiat Oncol Biol Phys* 2008; **70**: 590–8. doi: [10.1016/j.ijrobp.2007.08.067](https://doi.org/10.1016/j.ijrobp.2007.08.067)
4. Worm ES, Høyer M, Fledelius W, Hansen AT, Poulsen PR. Variations in magnitude and directionality of respiratory target motion throughout full treatment courses of stereotactic body radiotherapy for tumors in the

- liver. *Acta Oncol* 2013; **52**: 1437–44. doi: [10.3109/0284186X.2013.813638](https://doi.org/10.3109/0284186X.2013.813638)
5. Shirato H, Shimizu S, Kitamura K, Nishioka T, Kagei K, Hashimoto S, et al. Four-dimensional treatment planning and fluoroscopic real-time tumor tracking radiotherapy for moving tumor. *Int J Radiat Oncol Biol Phys* 2000; **48**: 435–42. doi: [10.1016/S0360-3016\(00\)00625-8](https://doi.org/10.1016/S0360-3016(00)00625-8)
 6. Chen GT, Kung JH, Beaudette KP. Artifacts in computed tomography scanning of moving objects. *Semin Radiat Oncol* 2004; **14**: 19–26. doi: [10.1053/j.semradiol.2003.10.004](https://doi.org/10.1053/j.semradiol.2003.10.004)
 7. Persson GF, Nygaard DE, Brink C, Jahn JW, Munck af Rosenschöld P, Specht L, et al. Deviations in delineated GTV caused by artefacts in 4DCT. *Radiation Oncol* 2010; **96**: 61–6. doi: [10.1016/j.radonc.2010.04.019](https://doi.org/10.1016/j.radonc.2010.04.019)
 8. Nehmeh SA, Erdi YE, Ling CC, Rosenzweig KE, Squire OD, Braban LE, et al. Effect of respiratory gating on reducing lung motion artifacts in PET imaging of lung cancer. *Med Phys* 2002; **29**: 366–71. doi: [10.1118/1.1448824](https://doi.org/10.1118/1.1448824)
 9. Nehmeh SA, Erdi YE, Rosenzweig KE, Schoder H, Larson SM, Squire OD, et al. Reduction of respiratory motion artifacts in PET imaging of lung cancer by respiratory correlated dynamic PET: methodology and comparison with respiratory gated PET. *J Nucl Med* 2003; **44**: 1644–8.
 10. Clements N, Kron T, Franich R, Dunn L, Roxby P, Aarons Y, et al. The effect of irregular breathing patterns on internal target volumes in four-dimensional CT and cone-beam CT images in the context of stereotactic lung radiotherapy. *Med Phys* 2013; **40**: 021904. doi: [10.1118/1.4773310](https://doi.org/10.1118/1.4773310)
 11. Aznar MC, Persson GF, Kofoed IM, Nygaard DE, Korreman SS. Irregular breathing during 4DCT scanning of lung cancer patients: is the midventilation approach robust? *Phys Med* 2014; **30**: 69–75. doi: [10.1016/j.ejmp.2013.03.003](https://doi.org/10.1016/j.ejmp.2013.03.003)
 12. Persson GF, Nygaard DE, Munck Af Rosenschöld P, Richter Vogelius I, Josipovic M, Specht L, et al. Artifacts in conventional computed tomography (CT) and free breathing four-dimensional CT induce uncertainty in gross tumor volume determination. *Int J Radiat Oncol Biol Phys* 2011; **80**: 1573–80. doi: [10.1016/j.ijrobp.2010.10.036](https://doi.org/10.1016/j.ijrobp.2010.10.036)
 13. Persson GF. *Uncertainties in target definition for radiotherapy of peripheral lung tumours*. PhD thesis. Copenhagen, Denmark: University of Copenhagen; 2011.
 14. Weiss E, Robertson SP, Mukhopadhyay N, Hugo GD. Tumor, lymph node, and lymph node-to-tumor displacements over a radiotherapy series: analysis of interfraction and intrafraction variations using active breathing control (ABC) in lung cancer. *Int J Radiat Oncol Biol Phys* 2012; **82**: e639–45. doi: [10.1016/j.ijrobp.2011.08.021](https://doi.org/10.1016/j.ijrobp.2011.08.021)
 15. Sonke JJ, Zijp L, Remeijer P, van Herk M. Respiratory correlated cone beam CT. *Med Phys* 2005; **32**: 1176–86. doi: [10.1118/1.1869074](https://doi.org/10.1118/1.1869074)
 16. Trumm CG, Häussler SM, Muacevic A, Stahl R, Stintzing S, Paprottka PM, et al. CT fluoroscopy-guided percutaneous fiducial marker placement for CyberKnife stereotactic radiosurgery: technical results and complications in 222 consecutive procedures. *J Vasc Interv Radiol* 2014; **25**: 760–8. doi: [10.1016/j.jvir.2014.01.004](https://doi.org/10.1016/j.jvir.2014.01.004)
 17. Patel A, Khalsa B, Lord B, Sandrasegaran K, Lall C. Planting the seeds of success: CT-guided gold seed fiducial marker placement to guide robotic radiosurgery. *J Med Imaging Radiat Oncol* 2013; **57**: 207–11. doi: [10.1111/j.1754-9485.2012.02445.x](https://doi.org/10.1111/j.1754-9485.2012.02445.x)
 18. Harada T, Shirato H, Ogura S, Oizumi S, Yamazaki K, Shimizu S, et al. Real-time tumor-tracking radiation therapy for lung carcinoma by the aid of insertion of a gold marker using bronchofiberscopy. *Cancer* 2002; **95**: 1720–7. doi: [10.1002/cncr.10856](https://doi.org/10.1002/cncr.10856)
 19. Shah AP, Kupelian PA, Waghorn BJ, Willoughby TR, Rineer JM, Mañon RR, et al. Real-time tumor tracking in the lung using an electromagnetic tracking system. *Int J Radiat Oncol Biol Phys* 2013; **86**: 477–83. doi: [10.1016/j.ijrobp.2012.12.030](https://doi.org/10.1016/j.ijrobp.2012.12.030)
 20. Sonke JJ, Rossi M, Wolthaus J, van Herk M, Damen E, Belderbos J. Frameless stereotactic body radiotherapy for lung cancer using four-dimensional cone beam CT guidance. *Int J Radiat Oncol Biol Phys* 2009; **74**: 567–74. doi: [10.1016/j.ijrobp.2008.08.004](https://doi.org/10.1016/j.ijrobp.2008.08.004)
 21. Hanna GG, van Sörnsen de Koste JR, Dahele MR, Carson KJ, Haasbeek CJ, Michielssen R, et al. Defining target volumes for stereotactic ablative radiotherapy of early-stage lung tumours: a comparison of three-dimensional 18F-fluorodeoxyglucose positron emission tomography and four-dimensional computed tomography. *Clin Oncol (R Coll Radiol)* 2012; **24**: e71–80. doi: [10.1016/j.clon.2012.03.002](https://doi.org/10.1016/j.clon.2012.03.002)
 22. Underberg RW, Lagerwaard FJ, Slotman BJ, Cuijpers JP, Senan S. Use of maximum intensity projections (MIP) for target volume generation in 4DCT scans for lung cancer. *Int J Radiat Oncol Biol Phys* 2005; **63**: 253–60. doi: [10.1016/j.ijrobp.2005.05.045](https://doi.org/10.1016/j.ijrobp.2005.05.045)
 23. Yin FF, Wang Z, Yoo S, Wu QJ, Kirkpatrick J, Larrier N, et al. Integration of cone-beam CT in stereotactic body radiation therapy. *Technol Cancer Res Treat* 2008; **7**: 133–9. doi: [10.1177/153303460800700206](https://doi.org/10.1177/153303460800700206)
 24. Knap MM, Hoffmann L, Nordsmark M, Vestergaard A. Daily cone-beam computed tomography used to determine tumour shrinkage and localisation in lung cancer patients. *Acta Oncol* 2010; **49**: 1077–84. doi: [10.3109/0284186X.2010.498434](https://doi.org/10.3109/0284186X.2010.498434)
 25. Wolthaus JW, Schneider C, Sonke JJ, van Herk M, Belderbos JS, Rossi MM, et al. Mid-ventilation CT scan construction from four-dimensional respiration-correlated CT scans for radiotherapy planning of lung cancer patients. *Int J Radiat Oncol Biol Phys* 2006; **65**: 1560–71. doi: [10.1016/j.ijrobp.2006.04.031](https://doi.org/10.1016/j.ijrobp.2006.04.031)
 26. Wolthaus JW, Sonke JJ, van Herk M, Belderbos JS, Rossi MM, Lebesque JV, 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. doi: [10.1016/j.ijrobp.2007.11.042](https://doi.org/10.1016/j.ijrobp.2007.11.042)
 27. Sweeney RA, Seubert B, Stark S, Homann V, Müller G, Flentje M, et al. Accuracy and inter-observer variability of 3D versus 4D cone-beam CT based image-guidance in SBRT for lung tumors. *Radiat Oncol* 2012; **7**: 81. doi: [10.1186/1748-717X-7-81](https://doi.org/10.1186/1748-717X-7-81)
 28. Korreman SS, Juhler-Nøttrup T, Boyer AL. Respiratory gated beam delivery cannot facilitate margin reduction, unless combined with respiratory correlated image guidance. *Radiation Oncol* 2008; **86**: 61–8. doi: [10.1016/j.radonc.2007.10.038](https://doi.org/10.1016/j.radonc.2007.10.038)
 29. Giraud P, Morvan E, Claude L, Mornex F, Le Pechoux C, Bachaud JM, et al. Respiratory gating techniques for optimization of lung cancer radiotherapy. *J Thorac Oncol* 2011; **6**: 2058–68. doi: [10.1097/JTO.0b013e3182307ec2](https://doi.org/10.1097/JTO.0b013e3182307ec2)
 30. Kimura T, Murakami Y, Kenjo M, Kaneyasu Y, Wadasaki K, Ito K, et al. Interbreath-hold reproducibility of lung tumour position and reduction of the internal target volume using a voluntary breath-hold method with spirometer during stereotactic radiotherapy for lung tumours. *Br J Radiol* 2007; **80**: 355–61. doi: [10.1259/bjr/31008031](https://doi.org/10.1259/bjr/31008031)
 31. Josipovic M, Aznar MC, Persson GF. Deep inspiration breath hold radiotherapy of lung cancer: the good, the bad and the ugly case. *Acta Oncol* 2014; **53**: 1446–8. doi: [10.3109/0284186X.2014.922216](https://doi.org/10.3109/0284186X.2014.922216)
 32. Cheung PC, Sixel KE, Tirona R, Ung YC. Reproducibility of lung tumor position and reduction of lung mass within the planning target volume using active breathing control (ABC). *Int J Radiat Oncol Biol Phys* 2003; **57**: 1437–42. doi: [10.1016/j.ijrobp.2003.08.006](https://doi.org/10.1016/j.ijrobp.2003.08.006)
 33. George R, Chung TD, Vedam SS, Ramakrishnan V, Mohan R, Weiss E, et al. Audio-visual biofeedback for respiratory-gated radiotherapy: impact of audio instruction and audio-visual biofeedback on respiratory-gated radiotherapy. *Int J Radiat*

- Oncol Biol Phys* 2006; **65**: 924–33. doi: [10.1016/j.ijrobp.2006.02.035](https://doi.org/10.1016/j.ijrobp.2006.02.035)
34. Damkjær SM, Aznar MC, Pedersen AN, Vogelius IR, Bangsgaard JP, Josipovic M. Reduced lung dose and improved inspiration level reproducibility in visually guided DIBH compared to audio coached EIG radiotherapy for breast cancer patients. *Acta Oncol* 2013; **52**: 1458–63. doi: [10.3109/0284186X.2013.813073](https://doi.org/10.3109/0284186X.2013.813073)
 35. Nioutsikou E, Seppenwoolde Y, Symonds-Taylor JR, Heijmen B, Evans P, Webb S. Dosimetric investigation of lung tumor motion compensation with a robotic respiratory tracking system: an experimental study. *Med Phys* 2008; **35**: 1232–40. doi: [10.1118/1.2842074](https://doi.org/10.1118/1.2842074)
 36. Brown WT, Wu X, Fayad F, Fowler JF, Garcia S, Monterosso MI, et al. Application of robotic stereotactic radiotherapy to peripheral stage I non-small cell lung cancer with curative intent. *Clin Oncol (R Coll Radiol)* 2009; **21**: 623–31. doi: [10.1016/j.clon.2009.06.006](https://doi.org/10.1016/j.clon.2009.06.006)
 37. Pepin EW, Wu H, Zhang Y, Lord B. Correlation and prediction uncertainties in the cyberknife synchrony respiratory tracking system. *Med Phys* 2011; **38**: 4036–44. doi: [10.1118/1.3596527](https://doi.org/10.1118/1.3596527)
 38. Depuydt T, Poels K, Verellen D, Engels B, Collen C, Bulteana 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. doi: [10.1016/j.radonc.2014.05.017](https://doi.org/10.1016/j.radonc.2014.05.017)
 39. Solberg TD, Medin PM, Ramirez E, Ding C, Foster RD, Yordy J. Commissioning and initial stereotactic ablative radiotherapy experience with Vero. *J Appl Clin Med Phys* 2014; **15**: 4685. doi: [10.1120/jacmp.v15i2.4685](https://doi.org/10.1120/jacmp.v15i2.4685)
 40. Falk M, Pommer T, Keall P, Korreman S, Persson G, Poulsen P, et al. Motion management during IMAT treatment of mobile lung tumors—a comparison of MLC tracking and gated delivery. *Med Phys* 2014; **41**: 101707. doi: [10.1118/1.4896024](https://doi.org/10.1118/1.4896024)
 41. Falk M, Munck af Rosenschöld P, Keall P, Cattell H, Cho BC, Poulsen P, et al. Real-time dynamic MLC tracking for inversely optimized arc radiotherapy. *Radiother Oncol* 2010; **94**: 218–23. doi: [10.1016/j.radonc.2009.12.022](https://doi.org/10.1016/j.radonc.2009.12.022)
 42. Pommer T, Falk M, Poulsen PR, Keall PJ, O'Brien RT, Munck af Rosenschöld P. The impact of leaf width and plan complexity on DMLC tracking of prostate intensity modulated arc therapy. *Med Phys* 2013; **40**: 111717. doi: [10.1118/1.4824434](https://doi.org/10.1118/1.4824434)
 43. Fast MF, Nill S, Bedford JL, Oelfke U. Dynamic tumor tracking using the Elekta Agility MLC. *Med Phys* 2014; **41**: 111719. doi: [10.1118/1.4899175](https://doi.org/10.1118/1.4899175)
 44. Suh Y, Sawant A, Venkat R, Keall PJ. Four-dimensional IMRT treatment planning using a DMLC motion-tracking algorithm. *Phys Med Biol* 2009; **54**: 3821–35. doi: [10.1088/0031-9155/54/12/014](https://doi.org/10.1088/0031-9155/54/12/014)
 45. Zimmerman J, Korreman S, Persson G, Cattell H, Svatos M, Sawant A, et al. DMLC motion tracking of moving targets for intensity modulated arc therapy treatment: a feasibility study. *Acta Oncol* 2009; **48**: 245–50. doi: [10.1080/02841860802266722](https://doi.org/10.1080/02841860802266722)
 46. Gui M, Feng Y, Yi B, Dhople AA, Yu C. Four-dimensional intensity-modulated radiation therapy planning for dynamic tracking using a direct aperture deformation (DAD) method. *Med Phys* 2010; **37**: 1966–75. doi: [10.1118/1.3319498](https://doi.org/10.1118/1.3319498)
 47. Korreman S, Mostafavi H, Le QT, Boyer A. Comparison of respiratory surrogates for gated lung radiotherapy without internal fiducials. *Acta Oncol* 2006; **45**: 935–42. doi: [10.1080/02841860600917161](https://doi.org/10.1080/02841860600917161)
 48. Xu Q, Hamilton RJ, Schowengerdt RA, Alexander B, Jiang SB. Lung tumor tracking in fluoroscopic video based on optical flow. *Med Phys* 2008; **35**: 5351–9. doi: [10.1118/1.3002323](https://doi.org/10.1118/1.3002323)
 49. Poulsen PR, Cho B, Keall PJ. A method to estimate mean position, motion magnitude, motion correlation, and trajectory of a tumor from cone-beam CT projections for image-guided radiotherapy. *Int J Radiat Oncol Biol Phys* 2008; **72**: 1587–96. doi: [10.1016/j.ijrobp.2008.07.037](https://doi.org/10.1016/j.ijrobp.2008.07.037)
 50. Menten MJ, Guckenberger M, Herrmann C, Krauß A, Nill S, Oelfke U, et al. Comparison of a multileaf collimator tracking system and a robotic treatment couch tracking system for organ motion compensation during radiotherapy. *Med Phys* 2012; **39**: 7032–41. doi: [10.1118/1.4761868](https://doi.org/10.1118/1.4761868)
 51. D'Souza WD, Naqvi SA, Yu CX. Real-time intra-fraction-motion tracking using the treatment couch: a feasibility study. *Phys Med Biol* 2005; **50**: 4021–33. doi: [10.1088/0031-9155/50/17/007](https://doi.org/10.1088/0031-9155/50/17/007)
 52. Keall PJ, Mageras GS, Balter JM, Emery RS, Forster KM, Jiang SB, et al. The management of respiratory motion in radiation oncology report of AAPM Task Group 76. *Med Phys* 2006; **33**: 3874–900. doi: [10.1118/1.2349696](https://doi.org/10.1118/1.2349696)
 53. Korreman S, Persson G, Nygaard D, Brink C, Juhler-Notttrup T. Respiration-correlated image guidance is the most important radiotherapy motion management strategy for most lung cancer patients. *Int J Radiat Oncol Biol Phys* 2012; **83**: 1338–43. doi: [10.1016/j.ijrobp.2011.09.010](https://doi.org/10.1016/j.ijrobp.2011.09.010)
 54. Haasbeek CJ, Spoelstra FO, Lagerwaard FJ, van Sörnsen de Koste JR, Cuijpers JP, Slotman BJ, et al. Impact of audio-coaching on the position of lung tumors. *Int J Radiat Oncol Biol Phys* 2008; **71**: 1118–23. doi: [10.1016/j.ijrobp.2007.11.061](https://doi.org/10.1016/j.ijrobp.2007.11.061)
 55. Goossens S, Senny F, Lee JA, Janssens G, Geets X. Assessment of tumor motion reproducibility with audio-visual coaching through successive 4D CT sessions. *J Appl Clin Med Phys* 2014; **15**: 4332. doi: [10.1120/jacmp.v15i1.4332](https://doi.org/10.1120/jacmp.v15i1.4332)
 56. Grills IS, Hugo G, Kestin LL, Galerani AP, Chao KK, Wloch J, et al. Image-guided radiotherapy via daily online cone-beam CT substantially reduces margin requirements for stereotactic lung radiotherapy. *Int J Radiat Oncol Biol Phys* 2008; **70**: 1045–56. doi: [10.1016/j.ijrobp.2007.07.2352](https://doi.org/10.1016/j.ijrobp.2007.07.2352)
 57. van Herk M, Remeijer P, Rasch C, Lebesque JV. The probability of correct target dosage: dose-population histograms for deriving treatment margins in radiotherapy. *Int J Radiat Oncol Biol Phys* 2000; **47**: 1121–35.
 58. Steenbakkers RJ, Duppen JC, Fittion I, Deurloo KE, Zijp LJ, Comans EF, et al. Reduction of observer variation using matched CT-PET for lung cancer delineation: a three-dimensional analysis. *Int J Radiat Oncol Biol Phys* 2006; **64**: 435–48. doi: [10.1016/j.ijrobp.2005.06.034](https://doi.org/10.1016/j.ijrobp.2005.06.034)
 59. Persson GF, Nygaard DE, Hollensen C, Munck af Rosenschöld P, Mouritsen LS, Due AK, et al. Interobserver delineation variation in lung tumour stereotactic body radiotherapy. *Br J Radiol* 2012; **85**: e654–60. doi: [10.1259/bjr/76424694](https://doi.org/10.1259/bjr/76424694)
 60. Nielsen TB, Hansen VN, Westberg J, Hansen O, Brink C. A dual centre study of setup accuracy for thoracic patients based on cone-beam CT data. *Radiother Oncol* 2012; **102**: 281–6. doi: [10.1016/j.radonc.2011.11.012](https://doi.org/10.1016/j.radonc.2011.11.012)
 61. Josipovic M, Persson GF, Logadottir A, Smulders B, Westmann G, Bangsgaard JP. Translational and rotational intra- and inter-fractional errors in patient and target position during a short course of frameless stereotactic body radiotherapy. *Acta Oncol* 2012; **51**: 610–17. doi: [10.3109/0284186X.2011.626448](https://doi.org/10.3109/0284186X.2011.626448)
 62. Gottlieb KL, Hansen CR, Hansen O, Westberg J, Brink C. Investigation of respiration induced intra- and inter-fractional tumour motion using a standard Cone Beam CT. *Acta Oncol* 2010; **49**: 1192–8. doi: [10.3109/0284186X.2010.498834](https://doi.org/10.3109/0284186X.2010.498834)
 63. Ottosson W, Baker M, Hedman M, Behrens CF, Sjöström D. Evaluation of setup accuracy for NSCLC patients; studying the impact of different types of cone-beam CT matches based on whole thorax, column vertebralis,

- and GTV. *Acta Oncol* 2010; **49**: 1184–91. doi: [10.3109/0284186X.2010.500303](https://doi.org/10.3109/0284186X.2010.500303)
64. Brock J, McNair HA, Panakis N, Symonds-Taylor R, Evans PM, Brada M. The use of the active breathing coordinator throughout radical non-small-cell lung cancer (NSCLC) radiotherapy. *Int J Radiat Oncol Biol Phys* 2011; **81**: 369–75. doi: [10.1016/j.ijrobp.2010.05.038](https://doi.org/10.1016/j.ijrobp.2010.05.038)
 65. Peulen H, Belderbos J, Rossi M, Sonke JJ. Mid-ventilation based PTV margins in Stereotactic Body Radiotherapy (SBRT): a clinical evaluation. *Radiother Oncol* 2014; **110**: 511–16. doi: [10.1016/j.radonc.2014.01.010](https://doi.org/10.1016/j.radonc.2014.01.010)
 66. van der Voort van Zyp NC, Prevost JB, Hoogeman MS, Prévost J, van der Holt B, Levendag PC, et al. Stereotactic radiotherapy with real-time tumor tracking for non-small cell lung cancer: clinical outcome. *Radiother Oncol* 2009; **91**: 296–300. doi: [10.1016/j.radonc.2009.02.011](https://doi.org/10.1016/j.radonc.2009.02.011)
 67. Ahn SH, Han MS, Yoon JH, Jeon SY, Kim CH, Yoo HJ, et al. Treatment of stage I non-small cell lung cancer with CyberKnife, image-guided robotic stereotactic radiosurgery. *Oncol Rep* 2009; **21**: 693–6.
 68. Hui Z, Zhang X, Starkschall G, Li Y, Mohan R, Komaki R, et al. Effects of interfractional motion and anatomic changes on proton therapy dose distribution in lung cancer. *Int J Radiat Oncol Biol Phys* 2008; **72**: 1385–95. doi: [10.1016/j.ijrobp.2008.03.007](https://doi.org/10.1016/j.ijrobp.2008.03.007)
 69. Lu HM, Brett R, Sharp G, Safai S, Jiang S, Flanz J, et al. A respiratory-gated treatment system for proton therapy. *Med Phys* 2007; **34**: 3273–8. doi: [10.1118/1.2756602](https://doi.org/10.1118/1.2756602)
 70. Zhao L, Sandison GA, Farr JB, Hsi WC, Li XA. Dosimetric impact of intrafraction motion for compensator-based proton therapy of lung cancer. *Phys Med Biol* 2008; **53**: 3343–64. doi: [10.1088/0031-9155/53/12/019](https://doi.org/10.1088/0031-9155/53/12/019)
 71. Bert C, Durante M. Motion in radiotherapy: particle therapy. *Phys Med Biol* 2011; **56**: R113–44. doi: [10.1088/0031-9155/56/16/R01](https://doi.org/10.1088/0031-9155/56/16/R01)
 72. Wink KC, Roelofs E, Solberg T, Lin L, Simone CB 2nd, Jakobi A, et al. Particle therapy for non-small cell lung tumors: where do we stand? A systematic review of the literature. *Front Oncol* 2014; **4**: 292. doi: [10.3389/fonc.2014.00292](https://doi.org/10.3389/fonc.2014.00292)
 73. Paganetti H, Jiang H, Trofimov A. 4D Monte Carlo simulation of proton beam scanning: modelling of variations in time and space to study the interplay between scanning pattern and time-dependent patient geometry. *Phys Med Biol* 2005; **50**: 983–90. doi: [10.1088/0031-9155/50/5/020](https://doi.org/10.1088/0031-9155/50/5/020)
 74. Matney J, Park PC, Bluett J, Chen YP, Liu W, Court LE, et al. Effects of respiratory motion on passively scattered proton therapy versus intensity modulated photon therapy for stage III lung cancer: are proton plans more sensitive to breathing motion? *Int J Radiat Oncol Biol Phys* 2013; **87**: 576–82. doi: [10.1016/j.ijrobp.2013.07.007](https://doi.org/10.1016/j.ijrobp.2013.07.007)
 75. Dowdell S, Grassberger C, Sharp GC, Paganetti H. Interplay effects in proton scanning for lung: a 4D Monte Carlo study assessing the impact of tumor and beam delivery parameters. *Phys Med Biol* 2013; **58**: 4137–56. doi: [10.1088/0031-9155/58/12/4137](https://doi.org/10.1088/0031-9155/58/12/4137)
 76. Korreman SS, Ulrich S, Bowen S, Deveau M, Bentzen SM, Jeraj R. Feasibility of dose painting using volumetric modulated arc optimization and delivery. *Acta Oncol* 2010; **49**: 964–71. doi: [10.3109/0284186X.2010.498440](https://doi.org/10.3109/0284186X.2010.498440)
 77. van Elmpt W, De Ruysscher D, van der Salm A, Lakeman A, van der Stoep J, Emans D, et al. The PET-boost randomised phase II dose-escalation trial in non-small cell lung cancer. *Radiother Oncol* 2012; **104**: 67–71. doi: [10.1016/j.radonc.2012.03.005](https://doi.org/10.1016/j.radonc.2012.03.005)
 78. Mutic S, Dempsey JF. The ViewRay system: magnetic resonance-guided and controlled radiotherapy. *Semin Radiat Oncol* 2014; **24**: 196–9. doi: [10.1016/j.semradi.2014.02.008](https://doi.org/10.1016/j.semradi.2014.02.008)
 79. Keall PJ, Barton M, Crozier S. The Australian magnetic resonance imaging-linac program. *Semin Radiat Oncol* 2014; **24**: 203–6. doi: [10.1016/j.semradi.2014.02.015](https://doi.org/10.1016/j.semradi.2014.02.015)
 80. Fallone BG. The rotating biplanar linac-magnetic resonance imaging system. *Semin Radiat Oncol* 2014; **24**: 200–2. doi: [10.1016/j.semradi.2014.02.011](https://doi.org/10.1016/j.semradi.2014.02.011)
 81. Raaymakers BW, Lagendijk JJ, Overweg J, Kok JG, Raaijmakers AJ, Kerkhof EM, et al. Integrating a 1.5 T MRI scanner with a 6 MV accelerator: proof of concept. *Phys Med Biol* 2009; **54**: N229–37. doi: [10.1088/0031-9155/54/12/N01](https://doi.org/10.1088/0031-9155/54/12/N01)
 82. Shi X, Diwanji T, Mooney KE, Lin J, Feigenberg S, D'Souza WD, et al. Evaluation of template matching for tumor motion management with cine-MR images in lung cancer patients. *Med Phys* 2014; **41**: 052304. doi: [10.1118/1.4870978](https://doi.org/10.1118/1.4870978)
 83. Yun J, Wachowicz K, Mackenzie M, Rathee S, Robinson D, Fallone BG. First demonstration of intrafractional tumor-tracked irradiation using 2D phantom MR images on a prototype linac-MR. *Med Phys* 2013; **40**: 051718. doi: [10.1118/1.4802735](https://doi.org/10.1118/1.4802735)
 84. Stankovic U, van Herk M, Ploeger LS, Sonke JJ. Improved image quality of cone beam CT scans for radiotherapy image guidance using fiber-interspaced antiscatter grid. *Med Phys* 2014; **41**: 061910. doi: [10.1118/1.4875978](https://doi.org/10.1118/1.4875978)
 85. Knopf A, Nill S, Yohannes I, Graeff C, Dowdell S, Kurz C, et al. Challenges of radiotherapy: report on the 4D treatment planning workshop 2013. *Phys Med* 2014; **30**: 809–15. doi: [10.1016/j.ejmp.2014.07.341](https://doi.org/10.1016/j.ejmp.2014.07.341)