

Four-Dimensional Imaging and Radiation Therapy: A Review of Challenges and Advancements in Clinical Practices

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Article History	Abstract
Received: 26 March 2023 Revised: 12 July 2023 Accepted: 29 July 2023	<i>4-Dimensional Radiation therapy (4DRT) has been vastly developed in the past two decades. Motion management has become a vital part of high precision radiotherapy, wherein Stereotactic Body Radiation Therapy (SBRT) turns out to be a great boon for treating thoracic and abdominal tumours with confidence. In this review paper, we have analyzed the development of motion management strategies and the advancement of 4DRT. We have discussed the evolution of Internal target volume (ITV), 4D imaging techniques and the problems of breathing motion. In the second part, we have discussed various methods to tackle breathing motion. We also have reviewed the dosimetric aspects of 4D imaging and its clinical implications. In the last section, we have elaborated the 4D radiation therapy and recent advancements and practices.</i>
CC License CC-BY-NC-SA 4.0	Keywords: Motion management, thoracic tumours, breath-hold, 4-dimensional imaging, gating, respiratory tracking.

1. Introduction

This review gives a brief introduction of development of imaging techniques at various levels and its adaptation to radiation therapy. We have also discussed the 4D scanning techniques of Magnetic resonance imaging (MRI) and Positron emission tomography (PET) systems. In the next session, we have discussed the motion management systems and its challenges for 4D imaging which is utilized for radiation therapy. In the final section we have discussed the 4D image utilization for radiation treatment, dosimetry aspects of a moving target and its implications on the treatment delivery.

Need for motion management

Respiratory motion is unique for every patient but predictable.^[1] The characteristic of respiratory motion for every patient varies with amplitude between two fractions and during each treatment.^[2] Hence the respiratory behavior cannot be presumed for any patient prior to 4D imaging. Lung motion is associated with the size of the tumor, the location of the tumor and diaphragm motion.^[3-5] The tumor motion is highest in superior-inferior direction and smallest in the lateral and anterior-posterior direction.^[6] The largest range of tumor motion in the lung is 5cm, whereas the abdominal organs such as the kidney, liver typically have more than 1cm.

Concept of ITV in motion management

Voluntary and involuntary motion of patients during the imaging is the major problem to obtain high quality images. High precision radiotherapy such as intensity modulated radiation therapy (IMRT), image guided radiation therapy (IGRT), adaptive radiotherapy (ART) requires high-fidelity image sequences without or minimal artifacts.^[7] It is understood that the target is constantly moving and this has to be accounted for during treatment planning especially for cancers of the thorax and abdomen. An adequate, additional margin must be defined to the clinical target volume (CTV) in order to cover the target and spare the organs at risk (OARs) simultaneously. The International Commission on Radiation Units and Measurements (ICRU) 62 has introduced the concept of internal target volume (ITV).^[8] Concept of ITV generation is shown in figure 1. It accounts for geometric uncertainties of organ motions

which includes movement of bowel, heartbeat or respiration. It also accounts for changes in tumor size and shape. ITV is the union of gross tumor motion of the entire breathing cycle and this reduces the uncertainty during the treatment planning and delivery.

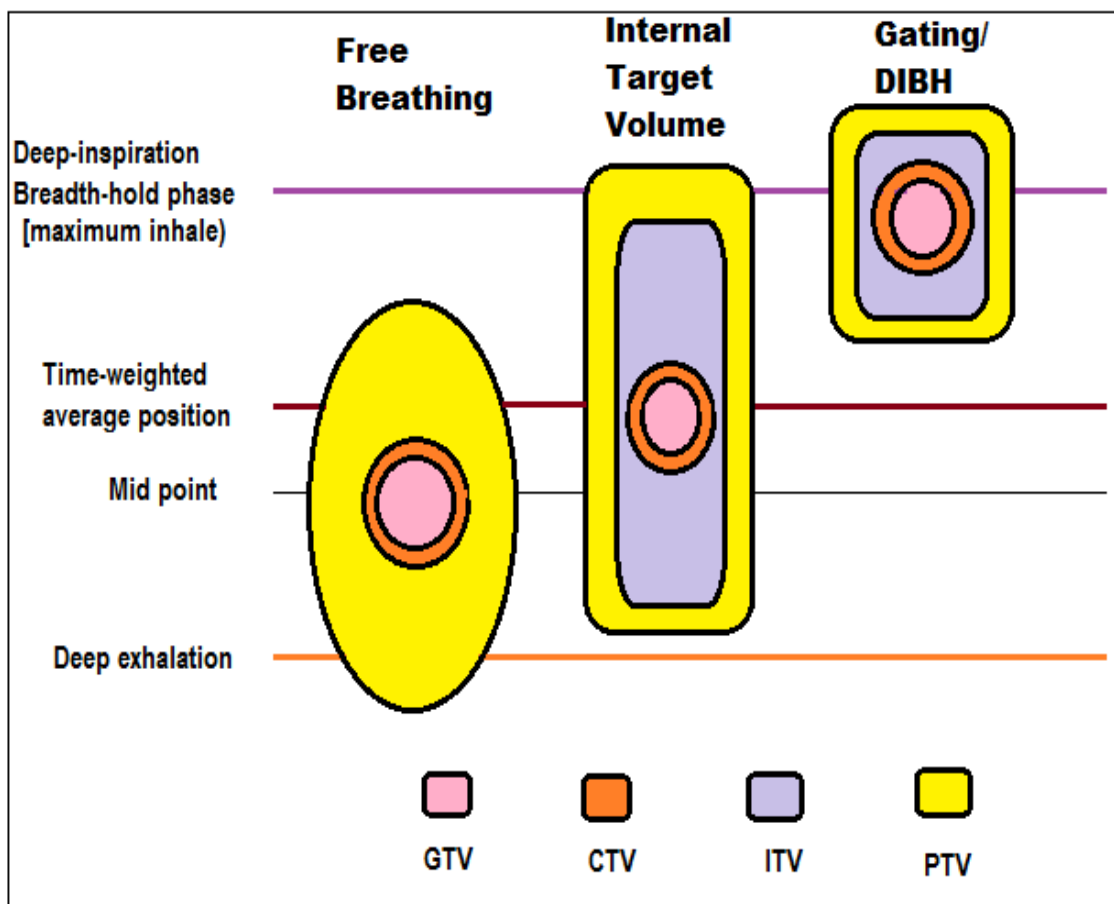


Figure. 1 Concept of ITV for motion management

4D Imaging Techniques

Significance of 4D imaging in motion management

The drawback of 3D conformal radiotherapy (3DCRT) is that more margin has to be given to adequately cover the target, thereby irradiating more normal tissues.^[9] This results in high toxicity and limits the overall dose to the target. Thus 4DRT, guided by 4D-imaging, precisely localizes the target in space and time to maximize dose to the target and minimize the dose to the normal structures.^[10] Advancement in cardiac imaging employed techniques to reduce the motion artifacts and this has been extended to 3DCT diagnostic image sets of the thorax and abdomen to tackle the respiration artifacts.^[11,12] Although this resolution of artifacts in diagnostic images is good, it is not quantitatively defined. Quantitative correction of image information is necessary for RT imaging which is incorporated into planning and delivery. Thus, 4D imaging has evolved specifically to capture this information for radiotherapy applications.^[13]

4DCT and Motion Management

Two types of 4D acquisition are available viz. Prospective and retrospective methods. In the prospective method, the images are acquired at a specific breathing cycle. The algorithm picks an appropriate breathing state, where suitable scans are acquired with minimal or negligible noise and reconstructed to yield a better 3D motion of the scanned area. In the retrospective method, several data sets are acquired at each breathing cycle. Thus, the breathing cycle has to be captured synchronously over the entire scan area. The entire breathing cycle is divided into 8-12 states, and each breathing state has a motion-free 3D volume data set. This type of 4D acquisition is more time consuming than the prospective scan but has improved quality. Each data set could be processed separately, or could be combined to yield a 4DCT.^[14-16] This gives a clear picture of movement of target or gross tumor at

different breathing states. Thus, a 4DCT is widely utilized to generate an ITV in radiotherapy, especially for stereotactic body radiation therapy (SBRT). A similar retrospective method is also employed in PET scans to yield a 4D PET.^[17]

Breathing Consistency:

Breathing motion for any patient is generally inconsistent and needs to be measured to give a meaningful waveform. It may vary with amplitude from time to time and measurement of respiratory motion is necessary for planning. Many studies have evaluated the variables in respiratory motion.^[18-20] The resting time at 'end expiration' is slightly higher compared to other phases of respiration and hence it is relatively stable. Thus, the end-expiration phase is less affected by the inconsistencies and useful for contouring and planning. However, the lung volume at this phase is very low compared to the deep-inspiration phase.^[21] When lung is accounted for during the end-expiration phase, the percentage of lung receiving any dose will be higher. In contrast, one of the studies for pancreatic cancer, the dose to the duodenum is less when planned at the end-expiration phase.^[22]

2. Materials and Methods

Large margins lead to unnecessary exposure of normal tissues near the target. The effects of tumor motion have to be limited to minimize normal tissue complications.^[23] There is also a possibility that the target volume may come out of the treatment margin when there are adverse respiratory changes (cough, sneeze etc.). Such changes can only be addressed when breathing is monitored.

Surrogates and Motion Tracking Methods

4D patient monitoring for radiation therapy requires external or internal markers to monitor the consistency of the breathing motion. These markers provide adequate information of time-amplitude in synchrony with the breathing motion.^[24-26] Common external markers employed for these purposes are:

1. Infrared markers placed on the thorax or abdomen
2. Spirometer to measure the lung volume
3. Thermometer based sensors to measure the external and internal air temperatures (nasal)
4. Pressure sensor in abdomen region to measure diaphragm pressure

Internal markers placed inside the body is labor some, time consuming and chances are there that we may lose or miss the information. Reports show that deformable image registration could be employed to segregate the inspiration and expiration scan stages with less than 5% error. But there are substantial image irregularities if the breathing motion is not uniform.^[27]

To minimize the respiration induced motion, some centers have employed abdominal compression. It required application of pressure in the lower abdomen region to restrict the motion of lung and liver lesions. With no compression, medium compression and high compression the mean tumor motions were 13.6mm, 8.3mm and 7.2mm respectively.^[28] Thus a significant motion control is observed in superior-inferior direction. In another study the liver motion is monitored and they observed that the liver motion is arrested within 5 mm in all directions.^[29,30] Another study by Eccles et al., 2011^[31] has concluded that significant decrease in motion for 40% of patients. Apart from liver lesions, abdominal compression also helps lower lobe lung lesions for motion restriction and it is statistically significant when compared without compression.^[32] Active breathing control (ABC) is another motion reducing method. In this method, the breathing is temporarily stopped for a comfortable period within which the radiation treatment is performed. Reproducibility is key to this method. A computer-controlled device is used to monitor the flow of air to the patient through the mouth and nasal breathing is stopped. Gagel et al have reported significant reduction of motion in the chest region when ABC is used.^[33] Reproducible lung (1%) and liver (6%) volumes were observed by Wong et al with ABC.^[34]

3. Results and Discussion

Breath Hold technique

In this technique, the patient is trained to hold the breath mostly at the end expiration phase or during deep inspiration. Thus, the patient is made to hold the breath voluntarily by arresting the tumor motion at a particular phase for a comfortable time. This breath-hold is performed uniformly during CT image acquisition, verification image acquisition and during treatment delivery. To maintain the consistency of the breath-hold, it is monitored using different methods. The most commonly used method is infrared based markers and a camera system to capture the motion of the marker in real-time. This marker

is placed either on the chest region or on the abdomen region to track the motion as shown in figure 2, thereby forming a wave pattern.^[35] Once the breathing waveform is obtained during the CT acquisition, this is used as a baseline value for subsequent treatments. Optimum window in the waveform is chosen for treatment delivery. Breath-hold can also be achieved using spirometers similar to ABC discussed previously. Other methods to track the breath-hold are mechanical devices on torso, thermal sensors near nostrils, tracking the implanted fiducials using fluoroscopy etc.^[36,37] These respiratory monitoring tools help to maintain the reproducibility of the breath-hold pattern and thus gives confidence for SBRT and SRS treatments.^[38] End expiration phase is considered most stable and reproducible, but patients may find it difficult to hold it repeatedly.^[39] To improve the lung DVH, end inspiration (deep inspiration) is useful especially for breast and lung treatments.^[40]

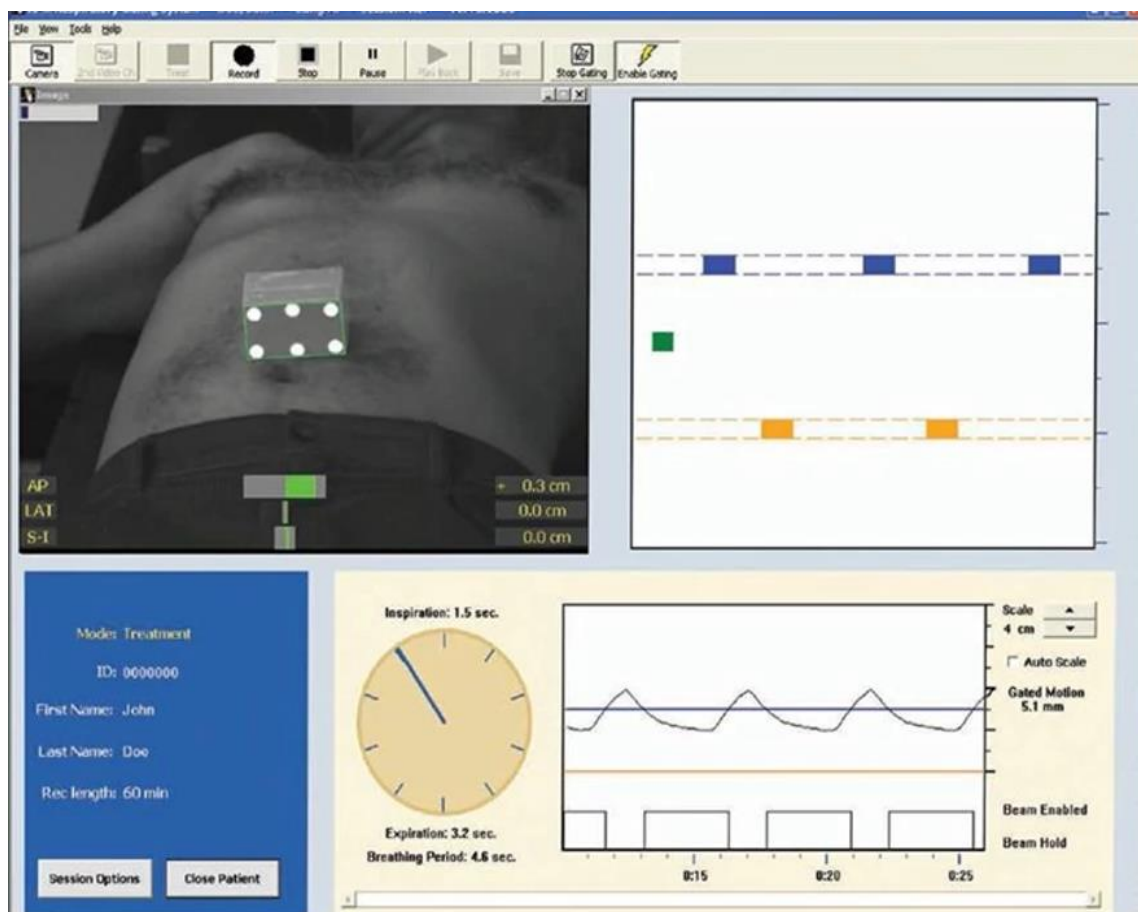


Figure. 2 Infra-red surrogate markers placed in upper abdomen for breath-hold treatment

Gating and tumor tracking

A few instances may not require a 4D information but gated 3D volume information of over one or optimum breathing state. For example, for radiation therapy of left-sided breast cancer 3DCT is required in a deep inspiration state for planning and dose reporting. Although this information is a subset of 4DCT, imaging only at a particular phase will save time and reduce the imaging dose to the patient.^[41] The process of gated imaging involves capturing the breathing cycle using external or internal markers and triggering the scan only during the required breathing state. Delineation of volumes and planning is done using this CT data set.^[42] Also, before the start of the radiation treatment, the verification image is acquired in this gating phase only. The selection of gating window levels could be broad or narrow. A broad window level makes the treatment faster where the beam will be on as long as the patient is holding the big window level, but there is uncertainty in the treatment delivery. If a narrow window level is selected the tumor could be targeted precisely, but the treatment time could be made longer. This is because the patient has to maintain the narrow breathing state for a long time which is practically difficult. Thus, an optimum window level must be selected and the patient has to be trained appropriately. Refer figure 3 for phase-wise gating technique. Also, a Gated CT may save time while

gated Cone beam computed tomography (CBCT) will require more time as the volumetric imaging requires a particular breathing window to acquire the images.^[43]

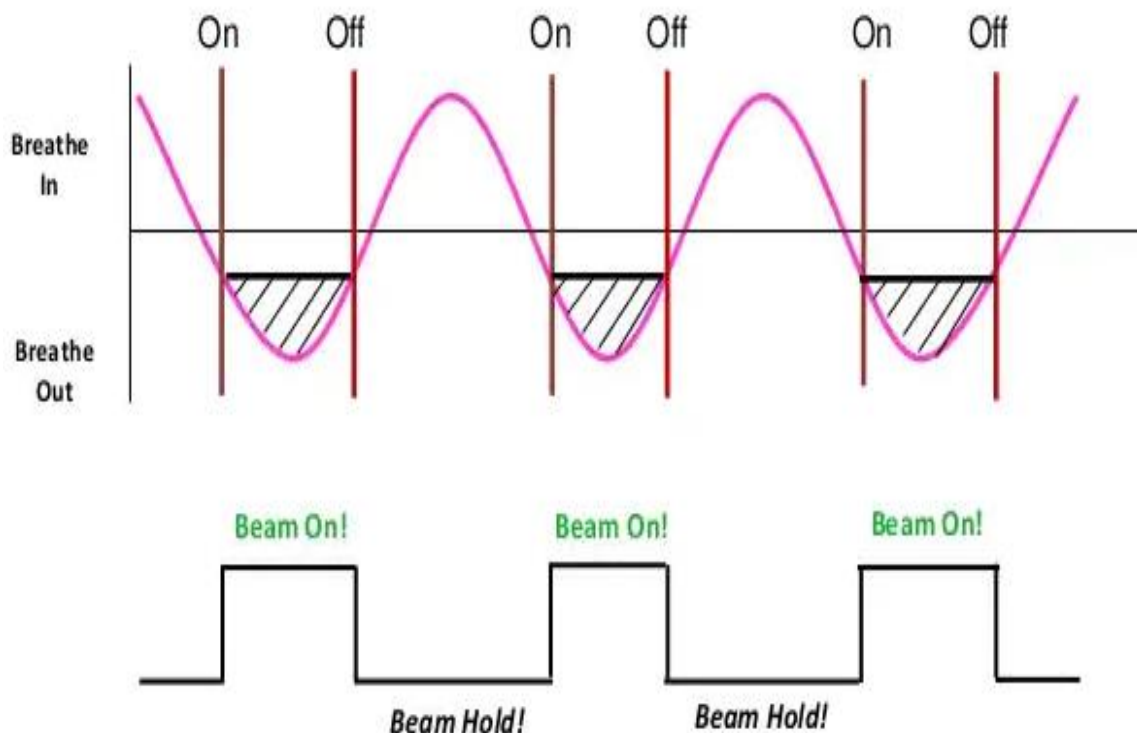


Figure. 3 Example for a phase-based gating technique

Tumor tracking utilizes dynamic multi-leaf collimators (DMLCs) to shape and align based on the movement of the tumor in real time. Thus, the apertures of DMLCs are continuously altered to shape the tumor in addition to the beam modulation. This is achieved for both static IMRT deliveries and volumetric modulated arc therapy (VMAT). Keall et al have reported an improvement in dose distribution with tumor tracking.^[44] They tracked the tumor position electromagnetically to shape the tumor using MLCs in real-time. Varian's Real-time positioning management (RPM) gating system helps us to track the tumor using MLCs in real time.^[45] Also, the gamma passing criteria is higher for plans with tumor tracking using DMLCs. Elekta, also uses motion compensated VMAT delivery using AgilityTM.^[46] Accuracy Oncology used SynchronyTM Respiratory tracking system. This creates a model of target motion using fiducials implanted in the tumor using orthogonal images. This model is then used to track the tumor during treatment using Cyberknife robotic linear accelerator.^[38,47]

Breathing pattern consistency is key to any type of motion management strategies. Thus, coaching a qualifying patient for relevant strategy helps us to achieve better results. Coaching the patient is very much required when an external surrogate placed between ziphoid notch to the abdomen.^[48] The internal markers such as implantation of fiducial(s) in tumors are invasive and coaching is not relevant. Correlation of abdominal wall and tumor position has improved with audio coaching as per Nakamura et al., 2009.^[49] Similar better results were achieved for Goosen et al., 2014 and Mageras et al., 2001 with coaching.^[50,51] Video coaching is also an effective way to achieve the reproducibility of the breathing motion. One study conducted by Onishiet al., 2010 found that the consistency of lung motion on an average was 2.0mm and 4.2mm with and without video coaching respectively.^[37] Thus either audio or video coaching for breathing helps to achieve reliable dose delivery.

4D Radiation therapy

Radiation therapy is primarily based on 3D volume which is basically acquired in one particular time. This 3D image set is static and does not account the intra-fractional motion within the patient. Conformal radiation therapy thus does not account for the errors from patient setup and organ motion. The GTV, and related organs change its size and shape due to the intrafractional motion. This information is available only on a 4DCT image. In addition to this the interfractional variation of patient setup is also not accounted for. This requires a real-time imaging and positional correction of daily treatment setup. Presently, On-board imaging (OBI) greatly reduces the interfraction variation but, the organ motion is still not accounted clinically. To compensate for this uncertainty, an additional margin has to be 'grown' which will account for both inter- and intra-fractional variations.

Treatment planning remains challenging for lung and lower abdomen regions for several reasons. Physics of radiation transport in low density areas, correction for heterogeneity, effect of motion on dose distribution, and physics of small field dosimetry for SBRT treatments in motion susceptible areas are some of the important challenges. There are several comprehensive reviews for planning and delivery for lung and upper abdomen regions.^[52-55] Lateral scattering is more pronounced for lung tumors as their tissue density is low. The central axis tumor dose tends to reduce as the energy increases since the secondary electrons travel more in low density regions.^[56] This problem is exaggerated when the tumor is subjected to motion. In case of small tumors, such as SBRT, there is loss of charged particle equilibrium laterally. Thus, selection of dose calculation algorithms for lung regions, especially for small tumors is challenging. It has been reported that the pencil beam algorithm is poor in dose prediction as it does not account for transport for secondary electrons. AAPM task group 101 recommends convolution-superposition or Monte-carlo based dose calculation algorithms for accurate dose prediction.^[57]

A maximum intensity projection (MIP) image can be generated from an image data set for each phase of the breathing cycle. Automatic tools are available to generate these MIP images as a 4DCT dataset is available.^[58] MIP represents the maximum intensity value for each dataset acquired in a particular phase. The summation of MIP images helps us to generate the GTV accurately and is mostly used for lung tumors only. Studies have shown that it is not effective for tumors near the diaphragm or in the upper abdomen.^[59] There is always a question of how many CT phases are required to generate accurate GTV motion. Studies have compared the GTV and ITV volumes using 2,4,8,10 seconds datasets acquired during the entire respiration cycle. Investigators have found that there is no statistical difference in generation of ITV when the respiration cycle is divided into 4 or 10.^[60] In another study for pancreatic cancer, just 3 phases of CT data is sufficient to accurately (95%) generate ITV when the motion is less than 8mm.

Conclusion

For lung and abdominal tumors, especially for SBRT treatments, a motion study must be performed using 4DCT, 4D PET and/or 4D MRI. Tumor and critical organ motion must be incorporated into the planning contours for all acquired phases. For lung and abdominal targets, end expiration phase can be used for gated treatments and mid-ventilation phase can be used if treated with free breathing. Any anatomic changes, intra-fraction motion and daily setup variation must be accounted for in PTV margin. Intra-fraction motion tends to increase when the treatment time exceeds 30 minutes and this can be mitigated with repetition of imaging during the treatment. Any residual tumor motion must be included with the ITV even after the employment of motion handling methods. Coaching the patient is essential for any type of motion management strategy. It improves the correlation of internal organ motion and the external marker. Amplitude gating is simple and more accurate than phase gating. Audio coaching is sufficient for amplitude gating.

Monte-carlo or convolution superposition algorithm is always preferred to pencil beam algorithms for low density tissues. Heterogeneity correction must be incorporated for dose calculation. Daily image guidance (CBCT, CT-on rails or 4D MRI) is required. Respiratory motion must always be monitored during the treatment and assist the physicians to intervene the treatment for breathing discrepancies. Thus, our work provides recommendations for performing SBRT treatment for lung and upper abdominal tumors and to incorporate them clinically.

Recommendation

Motion Management has been a big challenge in Radiotherapy, with many uncertainties in imaging, contouring, setup, and treatment. It is important to understand the advantages and limitations of various motion management techniques as they influence the treatment outcome, which is critical in the Thorax and Abdomen.

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