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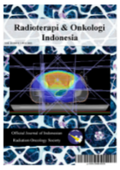

Respiratory Motion Management in Radiation Therapy of The Moving Organ

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Abstract

The goal of radiotherapy is to eradicate the tumor but still consider the surrounding normal organs. However, This is not easy to achieve because there are many factors that influence the process of external radiation. These factors are broadly divided into 2, namely intra-fraction motion and inter-fraction motion. It contributes to acute and late effect. These acute and late effects can be an obstacle in attempting to increase the dose in the tumor. this literature review will discuss the problems and developments of radiation techniques in relation to intra-fraction problems due to respiratory movements.

Keywords : Radiotherapy, Tumor, Inter-fraction motion, Intra-fraction motion

Introduction

Radiotherapy is one of the treatments for cancer in addition to surgery, chemotherapy, immunotherapy, and hormonal therapy.[1] Radiation therapy involves many factors in the course of radiation, namely inter-fraction movement and intra-fraction movement. The inter-fraction motion will vary from one fraction to the next due to daily variability of patient positioning, patient setup error, or due to changes in tumor volume. While the intra-fraction motion is the variation that occurs during the radiation patient in 1 fraction. Intra-fraction variation can be caused by intentional or unintentional movement of the patient during therapy such as due to respiratory movements, swallowing movements, tongue movements, or movements induced when organs in relaxation position.[2,3] Both of them can contribute to early and late effect.[4] Its effect can limit radiation dose to tumor. This literature review focuses more on intra-fractional variability caused by respiratory movement. A more in-depth discussion of the problems and developments of radiation techniques will be carried out in relation to the problem of intra-fraction due to respiratory movements.

Organ Movement due to respiration

The mechanism of respiration can make organs in the abdomen and thorax such as the lungs, liver, pancreas, esophagus, and breasts experience movement. It can be significant factor influencing the geometric and dosimetric uncertainty in the radiation planning process. In general, the movement of organs has many variations. In organs located in the abdomen, significant movement occurs in the superior-inferior direction, while in the anterior-posterior and lateral directions the shift is not more than 2 mm. For organs such as the lungs, tumor movement shows a lot of variation and is not limited to superior-inferior as shown in figure 1.

The Issue of Respiratory Motion During Radiotherapy

Image acquisition limitations

Commonly, the problem is artifacts that appear as a result of image acquisition as shown in Figure 2 which compares images taken with Computed Tomography (CT) Scans using the respiratory gating method which is a method of image acquisition by tracking the normal respiratory cycle, which allows the patient to be irradiated specifically in one segment of the respiratory cycle and the free-breathing method. The

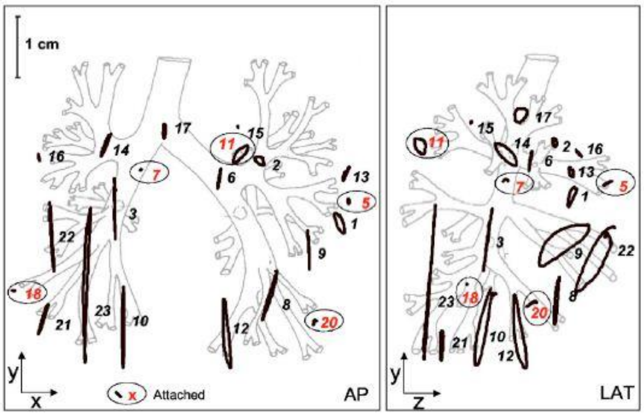


Figure 1. Tumor trajectories measured with implanted marker and real time fluoroscopy.[5]

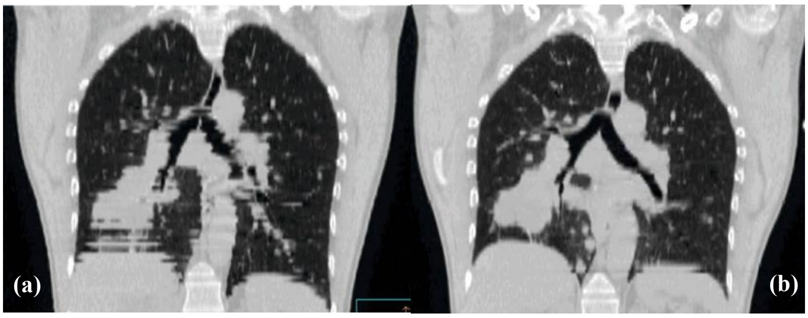


Figure 2. Coronal view CT scan during free breathing (a) and respiratory gated (b)

artifact can give impact in the accuracy of delineation and the dose calculation.[6]

Treatment Planning Limitation

During treatment planning, the given margin is usually large enough to ensure that all target areas receive radiation. The ICRU 62 report added the concept of internal target volume (ITV) from ICRU 50 to compensate for changes in organ motion and clinical target volume (CTV). As shown in Figure 3.[7] In conditions where ITV is not administered, such as in ICRU 50, where the setup margin and internal margin are combined in PTV, the treatment planning becomes suboptimal due to the large area of radiation that causes a large number of normal tissues to receive high doses. However, if the margin given is not large enough, it will result in part of the CTV not getting an adequate dose.[8]

Radiation Delivery Limitation

During radiation delivery, various kinds of movements can result in uncertainty of the setup process and organ movement. The uncertainty of the setup process is caused by both intentional and unintentional patient movements during radiation. Movement of this organ can occur intra-fraction and inter-fraction. Intra-fractional organ movement occurs mainly due to respiratory movements and affects tumors in the thorax and abdomen. The movement of intra-fractional organs during radiation delivery will cause deviations between the planned dose distribution or static dose distribution with the dose distribution given in the form of dose blurring and interplay effects as shown in Figure 4.[9]

Dose blurring itself is a condition that occurs due to the movement of tumors and internal organs during radiation delivery, which causes the dose limit at the edge of the light to be blurred. Apart from dose

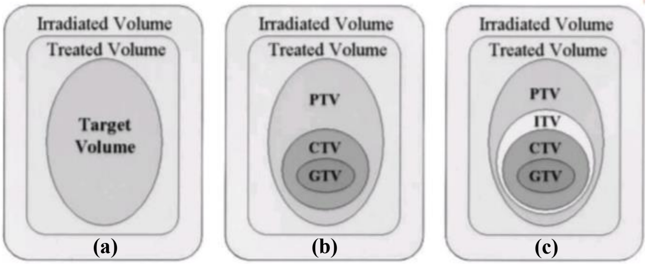


Figure 3. Schematic showing the difference between (a) ICRU 29, (b) ICRU 50 and (c) ICRU 62.[7]

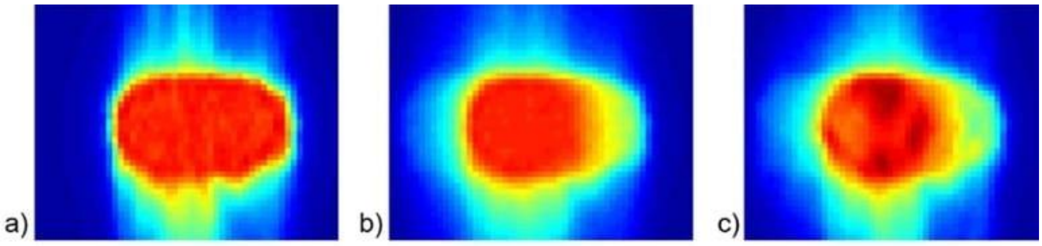


Figure 4. Static dose distribution (a), dose blurring distribution (b), and dose distribution involving interplay effect and dose blurring (c).[9]

Figure 5. Patient on treatment position using anzai belt as external respiratory signal.

blurring, interplay effects can also occur if radiation delivery using the intensity modulated radiotherapy (IMRT) technique due to the simultaneous movement of the tumor and the time of radiation administration by the movement of the multi-leaf collimator (MLC) and rotation of the gantry, which causes a large number of hot spots and cold spots in the dose distribution. The dose heterogeneity occurred because at the time of simultaneous movement by the tumor against the actively moving MLC, there were areas that should have received more doses but were covered by MLC and on the other hand, there were areas that should have received low doses but were not covered by MLC.[10]

Methods To Account For Respiratory Motion in Radiotherapy

Motion-encompassing Methods

Tumor movement caused by respiratory movements is a problem that arises in the process of image acquisition, treatment planning, and radiation delivery, so it is important to estimate more accurately the average position and range of motion that occurs during image acquisition and radiation delivery. There are 3 techniques that allow image acquisition with CT that can cover the entire range of tumor motion due to respiratory motion, namely slow CT, inspiratory and expiratory breath-hold CT, and 4-dimensional CT.[6]

1. Slow CT Scanning

Slow CT is a technique with the lowest workload compared to other techniques that have a function to cover movement. This technique performs a scan with a slow gantry rotational speed that can record multiple respiration phases per slice to capture tumor movement during each slice acquisition. The advantage with this technique is that the patient during the acquisition can breathe normally. In addition, this technique does not require special additional tools. This technique is considered to be able to overcome the problem of non-gated CT images where the tumor image is produced in the wrong position due to being taken in a certain respiratory cycle so that it contributes to the occurrence of systematic errors in radiation planning and radiation delivery.[11]

2. Inhalation and Exhalation breath-hold CT

This process requires twice amount of time compared to a typical CT simulation. This technique relies on the patient's ability to hold their breath, which is a reproducible process. By taking these 2 images set, it needs to be fused and the delineation process usually takes more time than usual. The advantage of this technique over slow CT is that the blurring caused by movement without the breath hold method is significantly reduced. Dosage calculations performed on each patient may differ depending on the condition taking into account the distance between the target organ and critical organ structures, but in general CT taken during the expiration phase tends to interpret the lung volume as smaller than it should be, resulting in overestimation of the lung volume which received a certain dose.[6,12] The disadvantage of this technique is that it unable to cover tumor motion trajectories (hysteresis).[5]

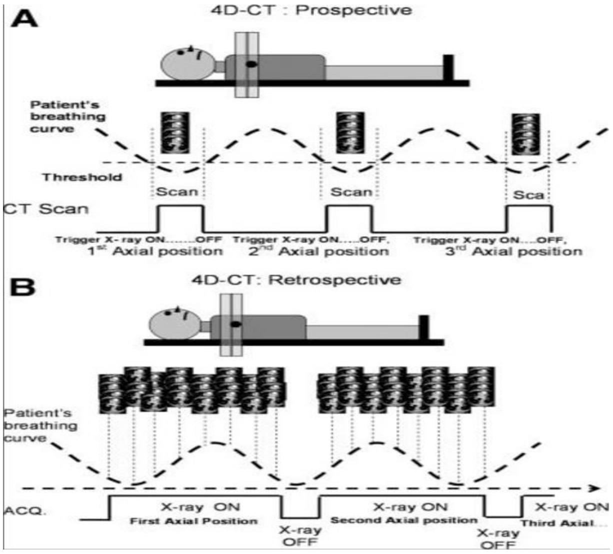
3. Four-Dimensional CT

Four-dimensional CT is an imaging tool that can be used to overcome the problem of taking pictures related to breath movements. This 4D CT can be used to reconstruct images generated by 4D CT in the inspiratory, expiratory and slow phases of CT when synchronized with an external respiration signal as a surrogate marker of respiration.[13] There are many types of external respiratory signals, such as Variant RPM, Elekta Active Breath Control, Novalis Brainlab Exac Trac, Phillips Bellows System, and Anzai Belt.

Image acquisition can be done prospectively or retrospectively. In the prospective acquisition method, the imaging technique used aims to obtain data on one phase of the respiratory cycle or a portion of the respiratory cycle. The x-ray tube will take images when the patient's breathing curve crosses the specified threshold. This acquisition process allows specific images to be taken.[14] In retrospective acquisition method, CT will continue to take images without stopping as the respiratory cycle is recorded by the external respiratory accessory. The images are then separated or grouped according to their phase.[15] The resulting signal then can be reconstructed based on either phase-based gating or amplitude-based gating using the software provided by the CT system. In the amplitude-based gating method, the percentile amplitude of the respiratory signal and the inspiratory or expiratory direction of the tidal breath are used to combine the signals and then the CT data is given the respiratory percentile for each amplitude value in waveform. For the phase-based gating method, a tag or marker is placed on the CT data at the end point of inspiration by the respiratory monitoring system. Rarely does the marker match the peak of the amplitude. The respiratory phase is then presented on a scale of 0% - 90% with 0% being the part that has a marker.[16]

Respiratory Gating Methods

Respiratory gating method is a method in which the implementation of radiation both at the time of image acquisition or radiation administration is in a part of the patient's respiratory cycle which is refer to as a gate. In taking CT images with this method, it can correct blurry images, while during radiation therapy, this method can minimize the radiation target area that moves due to breathing movements. The position and width of a gate in the respiratory cycle is determined based on the results of monitoring respiratory movements using external respiratory signal aids or by installing internal fiducial markers. Since the radiation given is not continuous, the procedure with this gate lasts longer than without the gate.[6] This respiratory gating method has advantages compared to taking images with CT scans in general because the average position on a regular CT scan cannot represent the



Figures 6. Illustration of prospective (A) and retrospective (B) acquisition of images.[15]

actual position during inspiration and expiration. This makes the respiratory gating technique more accurate and reproducible.[22] The technique using respiratory gating is divided into 2 categories, namely phase-based gating and amplitude-based gating. In phase-based gating, radiation is given at a certain phase of the respiratory cycle, while in amplitude-based gating, radiation is given if a certain amplitude value is achieved regardless of the phase of the respiratory cycle. Amplitude-based gating is said to be better at suppressing artifacts due to respiratory movements. Irregular breathing patterns are also a more significant problem in producing good dosimetry in phase-based gating compared to amplitude-based gating.[17,18]

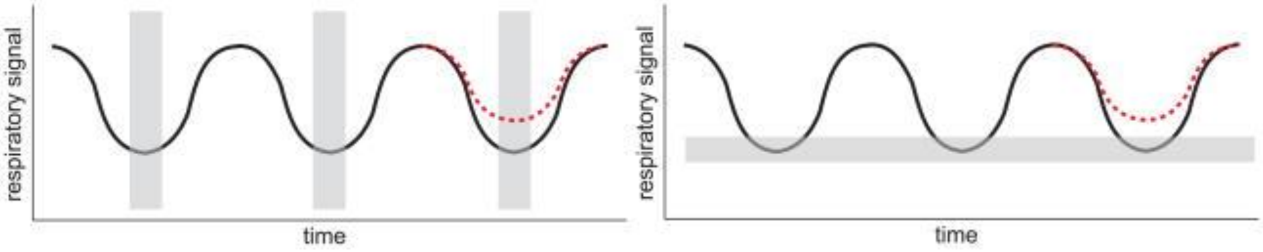
1. Gating using an external respiration signal

   This gate method utilizes external respiratory signals to assist the process of image acquisition and radiation therapy in areas affected by respiratory movement. In the radiotherapy department, RSCM currently has an Anzai Belt, which assists in the gating method using an external respiratory signal that can be irradiated by phase-based gating or amplitude-based gating. In phase-based gating, radiation will be given if it is at the desired phase in the patient's respiratory cycle, while for amplitude-based gating, radiation will be given if it reaches the specified amplitude as shown in Figure 7.[19]

2. Gating using internal fiducial marker

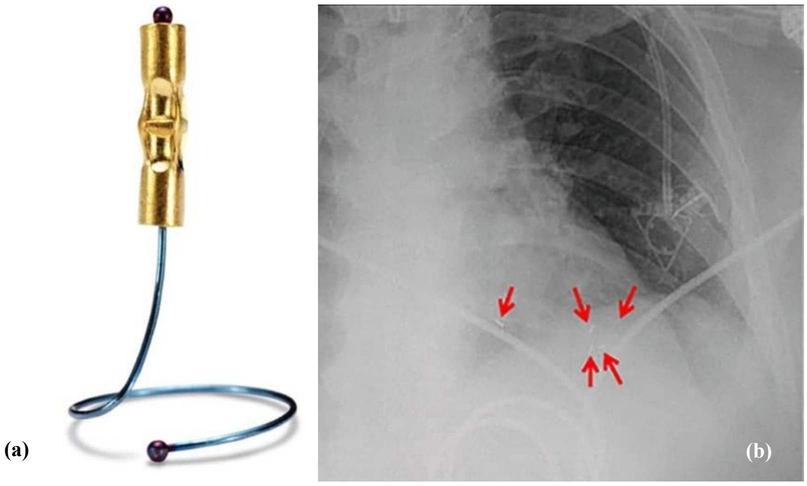
   A fiducial marker is an object placed near or inside a tumor that can help provide information that a given beam of radiation is in the same location. The fiducial used most often is the gold marker because it is easy to visualize and has a fairly high contrast level.[20] Fiducial placement can be done with fiberoptic bronchoscopy or percutaneously.[21] This fiducial marker is very helpful in visualizing the location of tumors that require high doses of radiation such as on stereotactic body radiotherapy (SBRT) in areas affected by movement such as tumors in the abdominal and thoracic regions. However, there is a potential for migration of the fiducial during therapy. Currently there are products that are able to reduce the potential for migration by adding a nitinol wire as shown in figure 8.[22]

The CT process is carried out by taking pictures when holding inspiratory breaths, holding expiratory breaths and when breathing normally. Radiation



(a) (a)

Figures 7. The respiratory cycle in phase-based gating (a) and amplitude-based gating (b).[19]



Figures 8. Gold fiducial marker with nitinol wire (a) and 5 fiducial implants around tumors that are difficult to visualize on radiographs (b).[22]

planning is done by taking pictures while holding inspiratory and expiratory breaths, then the best plan is determined by a radiation oncologist by considering the dose distribution and toxicity to normal surrounding organs such as the heart and lungs.[6]

Breath-Hold Methods

The breath hold method is a method that is often used in cases of breast cancer and lung cancer. This method aims to reduce toxicity to the heart because when the patient inhales during inspiration, the diaphragm pulls the heart posteriorly and inferiorly.[6] This technique also improves reproducibility by creating a static state during radiation therapy. This can prevent the interplay effect.[23] The deep inspiration breath hold (DIBH) method is a method in which the patient tries to perform maximal inspiration which can be repeated during therapy and simulation. This method is very beneficial for radiation therapy of tumors in the thoracic region because it can reduce tumor movement significantly and can protect normal organs such as the heart from exposure to radiation doses that are higher in toxicity.[24] The DIBH method can be implemented using a spirometer or non-spirometer. This spirometer can be used for both voluntary and involuntary breath holding techniques. The voluntary breath holding method is carried out with visual guidance from glasses that display the patient's breathing waves and the patient is instructed to hold his breath deeply to the specified point. The spirometer that supports this procedure is the SDX respiratory gating system by DYN'R. As for the method of holding your breath involuntarily, you can use an active breathing coordinator (ABC) unit made by ELEKTA. Using this method, the patient breathes normally through a spirometer then the operator determines the lung volumes and stages of the respiratory cycle to activate the system by which the balloon valve holds the airway. In this process the

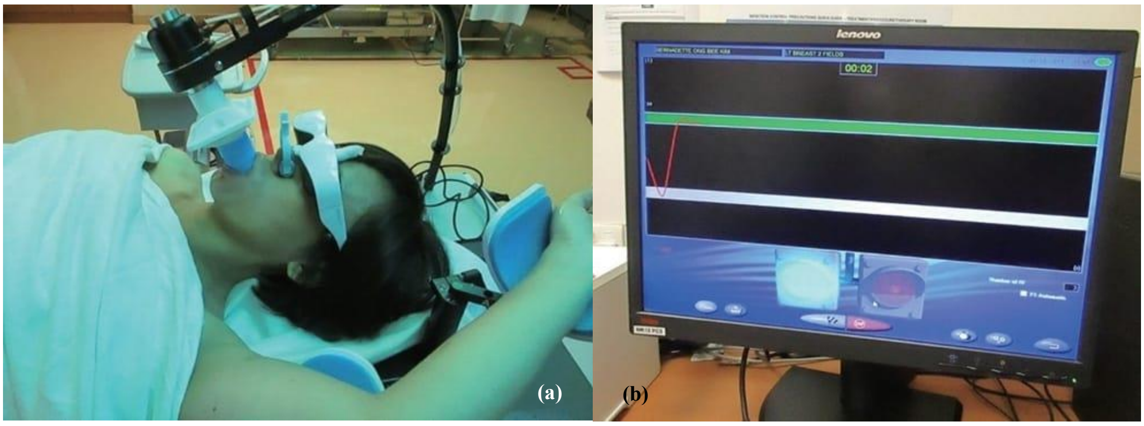


Figure 9. Figure (a) shows a patient who underwent DIBH preparation using a spirometer and spirometer gate system (b) where the green color indicates the breath holding region during radiation therapy .[23]

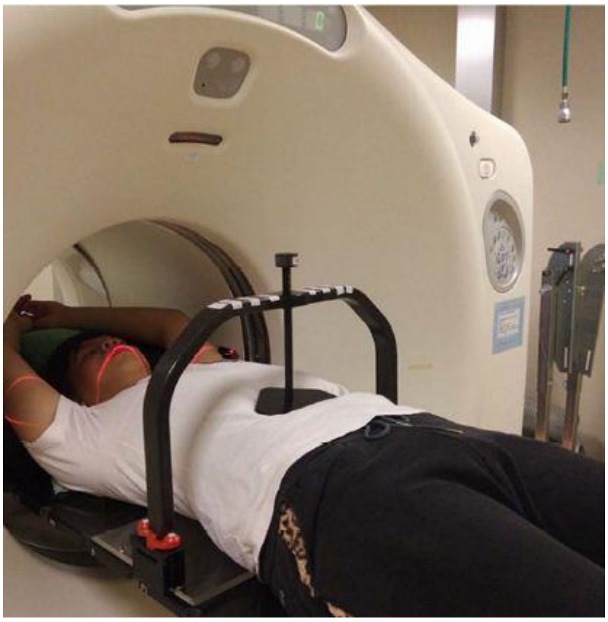


Figure 10. Patient setup in CT simulator using abdominal compression device.

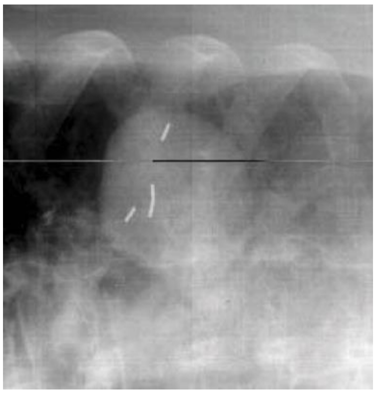


Figure 11. Lung tumor with four gold fiduciaries implanted in it to improve the measurement of tumor position.[6]

patient is instructed to reach a specified lung volume and usually requires two preparatory breaths. Previously it was necessary to do training with verbal instructions to ensure the patient could hold a deep breath which in practice could be repeated during simulations and during therapy. The patient breathes through the mouthpiece which is connected to the spirometer. The patient's nose is closed with a clip and then the therapist trains the patient to do deep inspiration, deep expiration, and holding the breath then the computer program displays and records the volume of air that comes in and out as a function of time. The patient then underwent 3 image acquisitions, namely with normal breathing, deep inspiration monitored with a spirometer, regular inspiration monitored with a spirometer. Acquisition of CT during normal breathing is an alternative if the patient cannot be treated with the DIBH technique. At the time of therapy, the radiotherapist will perform radiation when the position of holding your breath during deep inspiration is within the specified range. Meanwhile, without spirometry, the breath holding method is carried out using external respiratory signals such as using the RPM variant or the Anzai belt.[23]

Forced Shallow Breathing with Abdominal Compression

This technique uses a stereotactic frame with attached plates that press against the abdomen. The applied pressure serves to limit the movement of the diaphragm but still allows limited normal breathing. This technique is most often used for cases of early-stage lung cancer and liver cancer without mediastinal involvement. During the simulation, the patient was immobilized using a rigid frame with a vacuum pillow. Tumor movement in the superior-inferior direction was assessed using a fluoroscopy simulator. If the movement exceeds 5 mm, the attached plate is used to press the abdomen under the ribs forming a triangle. Usually, the pressure applied is the maximum pressure the patient can tolerate for the duration of the given radiation session. It is important to verify each fraction of the tumor position because reproducibility using abdominal compression is quite difficult.[25]

Real Time Tumor Tracking Methods

Tumor tracking is a process that involves administering radiation to a tumor with a small margin while the tumor or target is moving. This mainly accommodates the movement of the tumor due to the movement of the breath. The advantage of this technique is that it can reduce margins or eliminate margins under ideal conditions. This method requires 4 things to achieve these conditions, namely being able to identify the position of the tumor in real-time, being able to compensate for the time delay in responding to changes in tumor position, repositioning the radiation direction, adjusting dosimetry to changes in lung volume and the location of other important structures during the respiratory cycle.[6]

1. Determining tumor position

   Determining the position of the tumor at the time of radiation therapy can be done using fluoroscopy to see the position of the tumor itself or to view fiduciary markers implanted in the tumor, infer tumor position based on surrogate respiratory movement signals, or track without the aid of radiographic imaging of signals from implanted devices. Inside the tumour. For direct tumor location determination, fluoroscopy can be used in some cases (eg, lung cancer), as shown in Figure 10. However, most lung tumors and other tumors cannot be visualized properly and require additional markers to help locate the tumor. These fiducial markers usually need more than one to determine whether the movement follows the tumor, measurement of translation and rotation and migration of markers is concluded by observing the distance between the two markers.[6]

2. Compensating for time delays in the beam-positioning response

   The response of the system to the position of the beam direction to the tumor position signal is not rapid and there is a delay between the introduction of fiduciary markers with the aid of fluoroscopy images and the onset of radiation. This lag on Cyberknife tools can be up to 200 milliseconds. This makes the position of the tumor must be predicted in advance so that the direction of the beam can match the actual tumor position at the time of radiation. The problem is that the respiratory cycle is typical and has significant fluctuations in displacement between cycles. However, these fluctuations are not purely random, so it is still possible to predict certain breath cycles based on previously observed characteristics.[6,40]

3. Repositioning the beam

   There are 2 methods that can be used to reposition the beam direction to match the radiation target. The first method uses a dynamic multileaf collimator (DMLC) which continuously changes the position of the MLC according to changes in the target position.

   The second method is to use the CyberKnife robot with an image-guided radiosurgery system that can move the linear accelerator (linac) freely in six directions. In the second approach, the CyberKnife robot is connected to an image imaging system that monitors the position of the tumor and the direction of the radiation delivered by the linac. Both of these methods are in response to identification of tumor position, compensation for the time delay that occurs and dosimetry correction for breathing.[6,42]

4. Correcting the dosimetry for breathing effects

   CT image used to perform dosimetry calculations must take image in a static configuration while during the breathing process there are continuous anatomical changes in the lungs. This can change the relative position of the tumor, normal organs, and surrounding critical organs. The approach that is often used is to give large margin in PTV so that the CTV will get a high dose even though the target is moving. However, this does not solve the problem in cases where the target location is close to critical organs. The second approach is to consider the effect of movement on the dose distribution during the radiation planning process. This can provide accurate information on the dose given to the target as well as the distribution of the dose to the surrounding normal organs. Organ movement will cause blurring in the dose distribution that occurs intra-fraction but the per fraction dose distribution is not affected however the accumulated dose will be blurring, which then causes the penumbra to become wider so that the dose is not conformal. The amount of the blurring dose is determined by the amplitude and characteristics of the organ movement.[27]

Conclusion

Intra-fractional movements that are influenced by respiratory movements make problems in organs that are affected by respiratory movements. It causes limitations in image acquisition, treatment planning, and radiation delivery. As a result, the planned radiation dose differs from the actual dose received by tumor and surrounding normal tissue. In this case respiratory control management has an important role to increase the accuracy to the target organ which can be done by various methods such as motion encompassing method, respiratory gating method, breath hold method, forced shallow breathing with abdominal compression, and real time tumor tracking method. Basically, all techniques can be used for all cases that are affected by respiratory movement. The use of a technique is influenced by modality and existing human resources. The method that can be used by most of radiotherapy centre is the motion encompassing method, especially slow ct. the weakness is the low image resolution due to motion blurring. The real-time tumor tracking method is the most advanced method available in respiratory motion management. Only few centres can perform real-time tumor tracking method.

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