Gated Radiotherapy Development and its Expansion

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ABSTRACT

One of the most important challenges in treatment of patients with cancerous tumors of chest and abdominal areas is organ movement. The delivery of treatment radiation doses to tumor tissue is a challenging matter while protecting healthy and radio sensitive tissues. Since the movement of organs due to respiration causes a discrepancy in the middle of planned and delivered dose distributions. The moderation in the fatalistic effect of intra-fractional target travel on the radiation therapy correctness is necessary for cutting-edge methods of motion remote monitoring and cancerous growth irradiancy. Tracking respiratory milling and implementation of breath-hold techniques by respiratory gating systems have been used for compensation of respiratory motion negative effects. Therefore, these systems help us to deliver precise treatments and also protect healthy and critical organs. It seems aspiration should be kept under observation all over treatment period employing tracking seed markers (e.g. fiducials), skin surface scanners (e.g. camera and laser monitoring systems) and aspiration detectors (e.g. spirometers). However, these systems are not readily available for most radiotherapy centers around the word. It is believed that providing and expanding the required equipment, gated radiotherapy will be a routine technique for treatment of chest and abdominal tumors in all clinical radiotherapy centers in the world by considering benefits of respiratory gating techniques in increasing efficiency of patient treatment in the near future.

This review explains the different technologies and systems as well as some strategies available for motion management in radiotherapy centers.

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Keywords

Breast Neoplasms; Radiotherapy, Conformal; Radiotherapy; Respiratory Gated Radiotherapy; Tumor Tracking

Introduction

Respiration is the process of exchanging oxygen with carbon dioxide in the lungs. The contraction and relaxation of the muscles around the lungs lead to periodic motion of the lungs in the some phases, including breathing, inhalation and exhalation [1]. It has been shown that the pattern of respiratory motion is patient dependent [2] and breathing travel models could change between fractions and also into a fraction [3]; thus, there is not any common respiratory manner that can be considered for a particular patient before observing [4].

Furthermore, contraction and relaxation of respiratory muscles, along with changes in lung volume, will cause the movement in some internal organs in abdominal and chest areas. The numerous studies aim to investigate movement of internal organs, due to the breathing procedure. A research carried out by Langen et al. has investigated the movements of lung, diaphragm, rectum, liver, bladder, prostate and pancreas owing to breathing [5]. These studies show that many factors, including tumor location, tumor pathology and general health of patients can affect the motion of internal organs and also there is not any specific general patterns, for movement of internal organs arising from respiration, for all purposes [6]. According to these studies, internal organs have the largest displacement, as a result of respiratory procedure, in superior-inferior orientation. Moreover, there is a much smaller displacement in lateral and anterior-posterior orientations. Average, standard deviation and the maximum displacements in these directions are provided for a number of organs in Table 1 [6].

Furthermore, Liu et al. have shown that in 40% of patients who are battling with lung cancer, tumor experience a motion some greater than 5 mm. They have also find out that lung tumors of around %12 of lung cancer patients move further than 10 mm [7]. Nevertheless, some organs such as liver, kidneys, pancreas and spleen which are located in the upper abdomen move considerably as a consequence of aspiration, commonly greater than 10 mm [5, 8].

Movement managing is suggested based on patient-characteristic, for tumor motion more than 5 mm in every orientation [4]; in addition, remarkable efforts are made to determine patient–particular cancerous cells excursion applying tumor location [9, 10], implanted fiducial markers [11, 12], the organ in which tumor is located [13], or explore other portions of the body assumed to be correlated to cancerous growth excursion,(i.e., abdomen surface and diaphragm) [14-16]. All efforts aim to increase local control of tumor [7, 9].

The effects of internal organ motion caused by respiratory procedure can be viewed by three categories of diagnostic imaging, treatment planning as well as delivery.

Diagnostic imaging

Blurring and fading are made at diagnostic imaging due to any kind of body motion within the field of view. Breathing caused movements could lead up artifacts at magnetic resonance imaging, cone-beam computed tomography, positron emission tomography and computed tomography images. Since the time of image acquisition per slice is commonly less than 1 second and this time is a fraction of one respiratory period. Although it seems that a single slice is not influenced by breathing movement, sequential sections happen in various phases of breathing period lead to faults in the visible figure, position, size, and volume of body organs [9, 17, 18]. For instance, in nuclear

Table 1: Average, standard deviation and the maximum of the peak to peak displacement of some internal organs as a result of respiratory procedure

Organ	Displacement (mm)						
	Average			Standard deviation			Maximum displacement in the direction of SI
	SI	AP	L	SI	AP	L	
Lung	11.8	4.7	3.2	12.6	2.3	2.1	50
Liver	25.6	---	---	14.5	---	---	55
Kidney	30.0	---	---	23.2	---	---	86
Pancreas	40.3	---	---	24.9	---	---	80
Diaphragm	35.7	---	---	29.5	---	---	99

SI: superior-inferior, AP: anterior-posterior, L: lateral medicine imaging, the image shows cumulative activity at time of image acquisition [19], and even a small movement could cause a significant blur in comparison with the intrinsic resolution of the nuclear scanner. Therefore, advancement in the technology to elevate special resolution of nuclear medicine imaging systems is not reasonable until a proper motion correction technique for improvement of resolution can be used. Similarly, it should be considered that respiratory motion can lead to artifact and uncertainties in acquired images depending on different elements such as frequency and amplitude of organs movement. Moreover, these upshots in diagnostic images navigate to skepticism in localization of tumors as well as radiosensitive organs. It can also have an impact on election of planning borders and tackling of inhomogeneities. Cancerous growth territorialisation in image guided radiation therapy (IGRT) is impressed. Consequently, respiratory movement can reduce the accuracy of treatment planning as well as treatment delivery. Breathing caused movements should be confronted in all stages of treatment planning and delivery [20].

Treatment Planning

External radiation therapy aims to delivery prescribed dose to cancerous growth so that the normal cells surrounding the tumor have the minimum absorbed dose. However, owing to the complex structure of tumors and the surrounding tissues, scattering of the primary beams as well as organ motions, attaining to this aim is difficult. Figure 1 shows a treatment planned theoretical image of a tumor and its surrounding tissues. In this image, Biological Tumor Volume (BTV) will be delineated by images of Positron Emission Tomography (PET) or single photon emission computed tomography and Gross Tumor Volume (GTV)

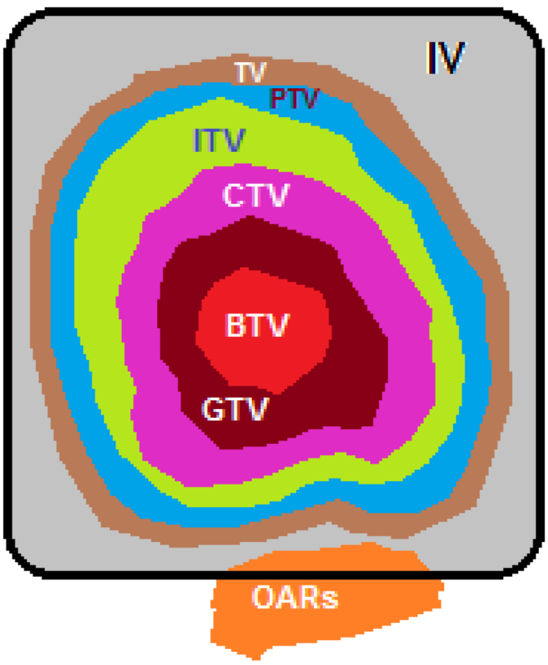

Figure 1: Schematic image of treatment planning volumes in external beamradiation therapy. Biological Tumor Volume (BTV), Gross Tumor Volume (GTV), Clinical Target Volume (CTV), Internal Target Volume (ITV), Planning Target Volume (PTV), Treated Volume (TV), Irradiated Volume (IV) and Organ at Risk (OARs).

will be specified by computed tomography or magnetic resonance imaging with high spatial resolution. At the next, a medical oncologist will delineate the Clinical Target Volume (CTV) as well as Planning Target Volume (PTV) based on microscopic tumor spread, organ motions as well as systematic and random errors related to setup of the patient. The concept of internal target volume (ITV) was introduced in report 62 of ICRU (International Commission on Radiation Units and Measurements) for tumor movement consideration [21]. ITV is determined as the clinical target volume (CTV) plus an extra border count geometric doubts of respiration, heart beating as well as movement of the bowel. Moreover, it calculates tumor size and shape alterations. For ITV determination of a tumor located in the chest wall, firstly, GTV delineates in different respiratory bins including the four-dimensional computed tomography, MR or PET imaging. Secondly, GTV expands to CTV for consideration of microscopic disease and finally ITV defines for covering CTV movements [21].On the other hand, in the lack of movement recompense, borders must be greater (10-20 mm) to minimize the target lost opportunity due to the movement [22].

Although, adding an extra margin to CTV for determination of PTV reduces the error caused by the tumor motion, this policy increases the risk of higher dose delivery to normal tissues and organ at risk (OAR) tissues. Therefore, many researchers have surveyed different methods and techniques with the aims of patient motion correction, PTV minimization, more protection of organs at risk and maximization of dose delivery to tumor tissues [23, 24].

Treatment Delivery

However, evaluating the impacts of breathing movement is essential for treatment planning, it might not be adequate for treatment delivery. Breathing could change in amplitude and period from time to time; shifting baseline, position shift of a curve evaluated upon multiple cycles (consisting breathing, organ or tumor tract), can be happened and phase relevancy from one anatomical site to another can change. While measuring breathing movement and factors can act on it for every patient, the expanse of incertitude is crucial. For example, baseline shifts are especially problematic [25-27] and 2 mm baseline alteration is anticipated to be sufficiently rectified by a 5 mm border for movement [28]. In spite of the fact that breathing is commonly uneven, the termination of exhalation phase is rather constant and minor affected by the uneven behavior. In addition, people usually spend more time on close end exhalation than close other phases [10, 26, 29]. Thus, the CT50 or end exhalation phase is frequently applied for contouring, planning and assessment. Nevertheless, at the end of expiration, the volume of the lung is minimum and therefore, the portion of lung obtaining a certain dose will be larger.

Lastly, involuntary movement and displacement of the tumor as well as its surrounding healthy tissues during dose delivery (intra-fraction motion) and between different treatment sessions (inter-fraction motion) can lead to alteration of dose distribution. Therefore, monitoring and, if possible, controlling the amplitude of these involuntary movements have been considered and analyzed in a number of radiotherapy studies [30, 31].

Material and Methods

Tracking Target movement

As already noted, compensation of the effects arising from the organ motion due to respiration has a particular importance in diagnostic imaging and radiotherapy treatments. However, we can find appropriate techniques for compensation of the adverse effects caused by organ motion, there is a need to track and monitor the movements. Methods of monitoring and gating of the organ motion can be evaluated and studied in the two categories of internal target tracking and gating based on as well as external surface tracking and gating based on.

Internal target tracking and Gating based on

Many studies have been carried out for tracking and monitoring of internal organ movements, during image acquisition in diagnostic imaging as well as dose delivery in external beam radiotherapy. Some of the most important gating methods based on internal target tracking are explained further.

Fluoroscopy

One of the most efficient tracking methods is planting a fiducial marker within or near the target tissue and then monitoring this marker via fluoroscopy images. For implementation of this technique, an extensive diversity of fiducial markers for various parts of the body and clinical applications have been designed and manufactured, but implantation of these markers inside the body is invasive method and associated with a possible risk of putridity [32, 33]. In addition, it should be considered that the entry of fiducial markers by bronchofiberscopy is safe and feasible for peripheral pulmonary tumors and difficult for central pulmonary tumors [34, 35]. Similarly, piercing the chest wall to implant the fiducial marker may lead to pneumothorax in some cases [34, 35].

One of the most important evolutions for tracking internal body tumors was the invention of Mitsubishi / Hokkaido Real-Time Tumor-Tracking (RTRT) system using simultaneous tracking of implanted gold markers inside the tumor via fluoroscopy images [11, 12, 35-38]. The RTRT system was designed and built in 1998 and also installed at the Hospital of Hokkaido University in Japan. This system uses four image intensifying amplifiers and four X-ray tubes mounted on the roof of Linac room and upon the floor of Linac room, respectively, in order to obtain fluoroscopy images from different angles for determining the three-dimensional positions of implanted fiducial markers inside the patient's body. Afterwards, only when the fiducial marker is on the predetermined gate, a command of exposing will be given to the linear accelerator [39, 40]. The strong point of RTRT internal gating systems is precision. It also provides a real time determination of tumor location during radiotherapy treatment while getting coupled with Image Guided Radiotherapy (IGRT) localization [41]. However these gating systems are criticized by many researchers. According to the research of Imura et al. [42], the relationship between location of implanted fiducial marker in the bronchial branches and tumor site can have experienced considerable changes after two weeks of implantation. It is noteworthy that tracking and monitoring an inner body tumor is very difficult without using fiducial markers and only via fluoroscopy images and in many cases is not possible [42]. Additionally, this system uses a fluoroscopy modality for imaging and tracking tumor location and this imposes an extra dose on the patient. Moreover, planting of fiducial markers is not possible for some tumor locations such as pulmonary tumors because of pneumothorax risk [12]. Therefore, owing to these concerns, few radiotherapy centers in the world are using the RTRT system in order to perform the respiratory gating technique [12]. Figure 2 shows the concept of real-time tumor-tracking in radiotherapy.

4D CT

Another procedure toward internal body movement watching is motion correlated with CT or 4D CT. A 4D CT data set contains many 3 dimensional images demonstrating a different bin of the breathing period. Binning modes applied are either phase binning- relating every 3D CT image with a fraction or phase of respiratory cycle- or magnitude binning—relating every 3D CT image with a portion of the whole respiratory magnitude. Every 3D image of 4D CT image group has a specific phase or deduction of magnitude. Mostly, the group of 4D CT image contains 10 various 3D CTs.

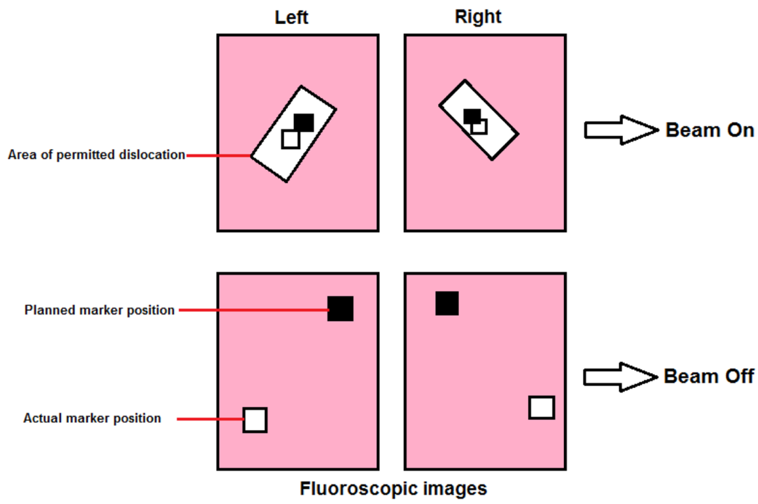

Figure 2: The sense of real-time tumor-tracking in radiation therapy. The projected location of the planned and real 3 dimensional coordinates of the marker could be observed on the corresponding fluoroscopic image. When the planned and actual positions of the marker occur simultaneously within the allowed displacement, the therapy beam is on. While the actual location of the marker is out the allowed displacement area, the treatment beam is off.

Asymmetrical breathing builds the attainment of high-quality 4D CT images so difficult [43]. Binning way of CT images based on breathing signal could have an impact on the image quality 4D CT.

Phantom study of Abdelnour et al. has shown that "consistency error" (which they define as a measure of the ability to correctly bin over repeated cycles: average binning error ± standard deviation within one bin) is ranged from 11% ± 14% to 20% ± 24% for amplitude binning and from 18% ± 20% to 30% ± 35% for phase binning [44]. This study concluded that amplitude binning, bins the images more accurately, but it is more sensitive to irregular respiration, specially to magnitude irregularities that can cause gaps on the images [44].

EPID

Another strategy for tracking inner body tumors in radiotherapy treatment rooms is the use of an Electronic Portable Imaging Device (EPID). Although the use of EPID prevents from imposing additional imaging doses to the patient, the resolution of the derived images by EPID is much lower than the images acquired by fluoroscopy systems due to the use of high energy for image acquisition in EPID [45]. Currently, research and investigation on this method has been in progress.

Fiducal electromagnetic transponders

Implantation of an Electromagnetic Transponder (EMT) inside the body, in order to track internal tumors, has been examined in several studies. In this method, an electromagnetic transponder, in order to receive a radiofrequency signal and send a different signal, is implanted inside the body. Simultaneously, an antenna is utilized outside the body for tracking the location of the transponder [46, 47]. These techniques are able to measure the tumor position in real-time in the course of treatment and improve patient positioning.

TULOC system, that is successfully examined in PSI for the proton treatment of mobile tumors has been using this method [48]. It utilizes a periodic magnetic field to transfer data between a field generator and a tiny implantable transducer located near the moving cancer lesion. TULOC system uses six differential coils as a field generator and a tiny induction winding covered with slim pad of combinatorial substances as an implantable sensor [48]. Depending on the sensor orientation, the angular accuracy of the TULOC system is 0.5-1° and the spatial accuracy of it is 1-2 mm [48]. It should also be considered that, although this method prevents from imposing extra doses due to the imaging procedure to patients, this method does not provide any information about the anatomy around the transponder. Therefore, three-dimensional information, such as images of cone beam CT, should be used to perform conformal radiotherapy treatments, in some Image Guided Radiotherapy (IGRT) systems.

Lastly, using electromagnetic tracking systems is underway especially in particle treatment centers, but patient's sensor insertion via biopsy needle or catheter is an invasive procedure and can cause side effects.

ExacTrac® Adaptive Gating system

The ExacTrac® Adaptive Gating system includes X-ray imaging system for detection and correction of tumor position alteration in real-time. The system has also an optical infrared tracking system for respiratory gating. In the X-ray imaging system, two detectors have been installed on the ceiling and two X-ray tubes have been housed within the floor of linear accelerator room, and the angel among the two X-ray tube-detector mates is about 90°. Stereoscopic X-ray can be taken at the gating window for confirmation of tumor position both before and during treatment procedure. For gating radiotherapy by ExacTrac® Adaptive, fiducial marker implantation is necessary.

4 dimensional CBCT imaging

A linear accelerator integrated with a cone beam computed tomography (CBCT) scanner can also be a strong gadget for movement monitoring of organs as well as tumors on the therapy couch. Breathing associated with CBCT consists of retrospectively assorting images in layout area yielding subdivision of layout images that each of them correlates with a given respiratory phase. These subdivisions are next reconstructed to figure a collection of 4D CBCT images. Provided fiducials are seeded within target and CBCT localizes targets more accurately. Next, planar images could localize the target and provide essential information about probable deformation and neighbor organs at risk [49]. Purdie et al. made the alteration of a lung target against the time between primary and repeated CBCT. They figured out that after passing 34 minutes, the movement becomes bigger [50]. Higgins et al. evaluated diverse inter-fraction imaging protocols, providing CBCT imaging on a daily basis was essential. They inferred setup margin of 3-4 mm for implementation of daily CBCT as well as 5-9 mm for less often CBCT accomplishment than each fraction [51].

4 dimensional PET/CT imaging

4D PET/CT scans could use for adding breathing correlated functional images to 4D CT images. After acquisition of 4D CT images, a 4D PET scan is obtained in gating modality. Breathing period is separated into phase bins of adequate time according to breathing signal, and every signal of the PET is associated with its affiliated phase. 4D PET/CT modality is demonstrated as a possible procedure for correction of respiratory movement artifacts in PET images containing an increase in measured SUV, and improves accuracy of PET to CT co-registration, and also reduces smearing [23, 52, 53].

4 dimensional MR imaging

4D MR imaging is another way for imaging of organ movements located in the abdomen [54]. Cai et al. compared 2D cine images of a phantom with 4D MR images and figured out that the perfect accordance is within 1 mm [55]. 4D MRI is also utilized for determination of movement for some other treatment locations such as the lung [56], liver [57], and abdomen [58, 59]. Hu et al. utilized from an external bellow to track breathing and provoke image acquisitions at predefined magnitude of breathing procedure [54]. Moreover, Breathing signal is linked to each image so that it can be sorted into the suitable breathing phase resulting in a 3D MR image for every breathing phase [54].

Ultrasonic tumor localization

Amongst non-ionizing and non-invasive movement tracking systems, ultrasound-relying systems definitely merit consideration. They are basically exploited for inter-fractional assessment of prostate position [60-62]. In addition, researchers have been working on accomplishment of this technique for liver cancer monitoring along with breathing movement [63]. Real-time volumetric imaging of targets and its surrounding soft tissues can be performed during radiotherapy treatment by means of remotely operated ultrasound system. The system, unified with Linac, is formerly constructed and tested prosperously [61]. Ultrasound-relying device called BAT is a commercially constructed system for dealing with patient status alterations and prostate movability resulted from organ movement [62].

External surface tracking and Gating based on

Monitoring respiration is necessary for determining its impacts on cancerous growth as well as critical organ movements. Free-respiration is not stable in amplitude and period and makes anticipating breathing movement difficult and also limits utility of respiratory assessments [64]. As mentioned in Section 2-1-1, Planted fiducials could monitor cancerous growth and critical organ movements; but, these invasive methods have intrinsic hazards and could not be used in various situations [22]. A method amending respiratory reproducibility could modify tracking and assessment of breathing. Applying external surrogates for following respiration avoids intrinsic hazards of implanting fiducials. Navigating, while tracking chest wall or lung tidal volume, has been illustrated to modify the reproducibility of breathing procedures [65, 66]. Numerous studies have been conducted to develop new equipment for monitoring the respiratory cycle and body movement during diagnostic imaging and external radiotherapy [24, 67, 68]. Pneumatic devices and a device, for tracking the vertical position of the external body surface via infrared reflective markers, have been designed to track respiratory motions [69]. Moreover, some investigators have focused on developing tracking systems without any markers such as the three-dimensional imaging system for body surface area imaging (Galaxy, LAP Laser, Luneburg, Germany) [70] and 4 dimensional laser cameras [71]. This equipment produces a three-dimensional network (3D mesh) from the patient's chest wall as a function of time for diagnostic and therapeutic applications. Despite the fact that many items of this equipment are capable of producing a correct respiratory pattern, its use is not common in radiotherapy clinics.

Various external sensors such as combination of air-bag and strain-gauge sensors or the use of radar systems or infrared sensors have been also surveyed and studied, from 1989 to 2017, in order to gauge respiratory motion monitoring of patients [72-78]. In the meantime, Kubo et al. in the California University reported the first study in 1995, on implementation of external respiratory gating, using the obtained signal from the external body surface of patients, which had been used in the Varian 2100C linear accelerator [79]. In 2000, they also reported an innovation of a new respiratory gating system used a video camera for tracking infrared reflective markers located upon the abdomen of patient [80]. This system, with the name of Real-Time Positioning Management (RPM) system, was later commercialized by the Varian Company and used and also evaluated in many radiotherapy centers [81-87]. At the same time, similar studies were conducted in radiotherapy centers using Elekta AB linear accelerator for treatment of patients. Traveling waveguides used in Elekta linear accelerators were found not to be as efficient and suitable for creating narrow respiratory gated windows as standing waveguides of Varian linear accelerators, thus breath-hold techniques by use of spirometry devices were examined to implement respiratory gating via the Elekta linear accelerators. Therefore, through the use of breath-hold techniques, an Elekta linear accelerator could be continuously on exposure mode for longer time [88, 89].

In addition to studies concentrated on therapeutic dose delivery by a static beam from 2001 to 2016, some studies have been done to track the motion of tumors by dynamic beams. The goal of this method is real-time tracking and exposing of the tumor location by therapeutic beam. However, studies conducted by Hoisak et al. [90] in 2004, Nøttrup et al. [16] in 2007 and Sawant et al. [91] in 2010, show that dynamic real-time tumor tracking and exposing need a motion management strategy which is complicated and require implementation of very strict quality control and quality assurance protocols [16, 91-94]. In 2005, a dynamic tumor tracking technique, which was functional on a Cyberknife robotic arm, was commercialized [95, 96]. In addition, gantry-based linear accelerators with dynamic multi-leaf collimators (MLCs) are now in use for dynamic tumor tracking implementation [94, 97, 98]. In spite of these remarkable advancements in dynamic delivery of therapeutic doses [98], such as Dynamic Multi Leaf Collimators (DMLCs), robotic accelerators and robotic couches, all of these technologies suffer from a time lag in conformity of moving tumor location with therapeutic beam. As a result of this time lag, there is a lapse between adaptations of planned and delivered dose and this adaptation can be affected adversely by increasing the system time lag and latency [99-103]. Therefore, implementation of dynamic tumor tracking techniques due to the technological restrictions as well as unpredictable and complex respiratory motions, which have been shown for lung tumors, are more challenging than accomplishment of breath-hold and respiratory gating techniques [16, 90].

The most common and practical respiratory gating techniques and systems use external body surface tracking in order to monitor respiratory motion [104]. The non-invasive nature of these techniques, with their feasibility for implementation on a wide variety of radiotherapy patients, are main advantages of external respiratory gating systems. RPM (Varian Real-time Position Management, Varian Medical System) and AZ-733 V (Anzai Medical) are two of the most commercially utilized respiratory gating systems in radiotherapy centers, which use tracking of external body surface motion to obtain respiratory cycle signal and perform respiratory gating techniques [105, 106]. The RPM system includes an infrared camera, a computer and a marker block and two infrared reflecting dots. In this system, the marker block places on the abdominal surface of the patient, and the position of the infrared marker are determined on the basis of the images acquired by the infrared camera. Finally, the RPM system measures the movement of infrared marker with frequency of 25 Hz and shows it as a respiratory signal after processing [106].

The AZ-733V system includes a control personal computer, a sensor port, pressure sensor and a belt. The pressure sensor is within the pocket of the belt worn by the patient. The system indicates pressure alterations supposed as the respiratory signals. Frequency of the AZ-733V system is 40 Hz [106].

Another system is Synchrony™ Respiratory Tracking System (Accuray Oncology, Sunnyvale, CA) associates external markers with rectangular stereoscopic images of implanted fiducials close or in the target mass to build a pattern of the target movement [22]. The pattern is then applied to move the CyberKnife® robotic linear accelerator to monitor and track the target, and intermittently extra X-ray images are obtained for confirmation and/or update the target movement pattern [22, 107].

3 dimensional imaging systems based on

video cameras are also accessible for acquiring 3D plane images during radiation therapy. For instance, AlignRT utilizes three cameras composed with a projected light scheme to obtain 3 dimensional plane images, whilst C-Rad system employs a line scanning method with alone camera as well as a laser device [108]. Furthermore, a study inspected performing several inner surrogates, such as air content, lung density, and body zone for sorting of 4D CT and reported strict settlement with external surrogates registered via RPM [109].

In Breath-Hold (BH) technique, the patient is under exposure only in an interval time while they hold their breath. In addition, if breath-holding has been done at the end of inspiration cycle, it is called Deep-Inspiration Breath-Hold (DIBH). BH and DIBH techniques are used to establish constant and reproducible status of the external surface body position, during simulation and treatment [110]. One of the most important advantages of the implementation of BH techniques is a considerable decrease in internal organ movements arising during respiration. Therefore, unwanted delivered dose to healthy and sensitive tissues can be diminished by using these techniques [6]. Currently, the most important clinical application of BH technique in radiotherapy centersis for lung cancer treatment and some studies have conducted implementation of BH technique using respiratory motion monitoring systems with and without using these systems [111, 112]. Furthermore, a reproducible CT scan in breath -hold status could be obtained for treatment planning and it could be repeated on a daily basis during radiation therapy. Several systems are accessible for monitoring respiratory procedure to aid breath-hold reproducibility. These systems are substantial for exact treatment of SBRT or SRS utilizing breath-hold techniques. These tracking systems consist of spirometers [79], reflective markers on the chest tracking by cameras [113, 114], mechanical devices tracking the torso [65], thermal sensors near nostrils [79], laser and camera devices which straightly monitor the body surface (e.g. AlignRT® and C-Rad Sentinel™) [22, 115], fluoroscopic images of implanted fiducials [38], strain gauges attached to the body surface [79] and implanted transponders [22].

Another device to diminish breathing-inferred tumor movement throughout radiation therapy is active breathing control (ABC) system [116]. It is exploited to confine breathing movement reproducibly and repeatedly for an interval time which could be easily sustained by patients. Respiratory is provisionally postponed in a repeatable cycle of the breathing period. Facility's operator utilizes a computer-controlled valve to close and open the air flow of the patient at a predefined point in the breathing period resulting a supervised breath hold [117]. A clip upon the nose is utilized to ban nasal respiratory and warrant that patients aspire via mouthpiece. The system of ABC generally digitizes respiratory volumes all over respiratory period. In this method, visual control of the respiratory period is probable. Both the inhalation and exhalation routes of patients' airstream could be provisionally banned at a predefined breathing volume and flow direction. The CT or Linac machine is turned on only while respiratory is provisionally stopped. Dawson noticed that during ABC breath holds, no movements of hepatic microcoils or diaphragm was detected on fluoroscopy [118]. Wong et al stated that in ABC scans, reproducibility of the lung and liver volumes were about within 6% and 1%, respectively. They also showed that scan artifacts related with free respiratory movement were not remarked in scans with ABC [89]. Gagel presented a considerable decline of breathing movement in the lower, middle, and upper areas of the chest while ABC was employed [116]. For 36 patients with indecent cancerous growth of the chest subjected in their evaluation, the mean dislocation ranged from 0.24 mm (chest wall) to 5.25 mm (diaphragm) and from 0.24 mm (chest wall/tracheal bifurcation) to 3.5 mm (diaphragm) for normal inspiration and expiration and shallow breathing, respectively [116].

In addition of ABC and BH techniques, DIBH technique is considered and used for left breast cancer radiotherapy. Performing DIBH technique leads to an increase in lung volume and as a result the left breast and cardiac tissue are being far apart; therefore, the delivered dose to the cardiac tissue witnesses a reduction by partial or complete exclusion of cardiac tissue from the treatment field. Furthermore, implementation of DIBH technique with an increase in lung volume will lead to reducing lung density; thus, relative delivered dose to lung will be diminished [119]. One of the most significant difficulties in radiation therapy planning patients with left side breast cancer is increasing of delivered dose to cardiac tissue, especially when Internal Mammary Chain (IMC) is located inside the target volume. Furthermore, recent studies have shown an increase in survival fraction among patients where their IMC lymph nodes are within the treatment fields [120, 121]. Therefore, there has been much effort involved in exposing IMC lymph nodes along with protection of cardiac tissue by implementation of respiratory gating. In the meantime, some investigations have shown that implementation of DIBH technique on left sided breast cancer patients treated with tangential fields without any compromise in target volume coverage would lead to decreasing cardiac dose [122, 123].

A spirometer is the most common device for monitoring of a patient's respiratory cycle to perform DIBH technique in an active way. In performing active DIBH technique, the entry and exit of air to the patient's lungs is performed under computer control. Therefore, implementation of this technique is not based on the patient's ability for breath-holding [73]. Meanwhile, some other methods such as monitoring the position of lateral tattoos [124], using a real-time skin to surface distance system to monitor the anterior surface of the patient's body [124] and using magnetic transducers connected to the chest of patients [72] have been surveyed in various studies to implement the voluntary DIBH technique. Nevertheless, the weakness of the voluntary DIBH technique is relying on the patient's ability for independent breath holding [125].

Many studies carried out on respiratory gating and implementation of DIBH technique. In 2005, the study conducted by Vander Laan et al. shows that employment of wide tangential fields, in free breathing conditions, is the reason for increasing cardiac and lung doses. Moreover, by implementation of DIBH techniques, it is possible to utilize the potential benefits using narrower tangential techniques along with minimization of the cardiac dose [126]. Stranzl and Zurl in 2008 showed that performing DIBH technique, during breast cancer radiotherapy, brings considerable volume of cardiac tissue out of high dose areas [127]. In addition, Stranzl et al. in 2009 have shown that implementation of DIBH technique, when using wide tangential fields for treatment of IMC lymph nodes, is beneficial for decreasing heart tissue dose. Rochet et al. in 2014 have mentioned that DIBH technique should be operative as a routine technique for all left breast cancer patients, since implementation of DIBH is associated with potentially reducing of cardiac dose [128]. Moreover, Walston et al. in 2015 and Tanguturi et al. in 2016 showed that implementation of DIBH technique on left breast cancer patients reduces the maximum and average absorbed dose of the cardiac tissue, considerably [87, 129].

Finally, it should be noticed that several factors must be considered based on electing respiratory depth and phase at which to have patient's breathe holding. As early mentioned, the end of exhalation phase is the most likely reproducible part [10, 66, 116, 130]. In addition, Nakamura et al. have shown that a 5 mm internal margin is essential to consider for alterations in GTV (pancreas) position with repeated, video-coached breath holds at the end of expiration [131]. However, not all patients can sustain repeatedly holding their breath particularly at the end of exhalation [132]. The end of inhalation phase is not as repeatable as the end of exhalation phase, but volume of the lungs are larger at deep inhalations modifying the DVH of lung [84]. While acquisition of CT simulation, breath hold volumes might vary from volumes of free breathing, even at the same phases [4, 133]. It is necessary that CT simulation be obtained at the same method as dose delivery will be accomplished.

Conclusion

In radiotherapy treatment of tumor tissues located in the thorax and abdominal regions, respiration is the most important cause of difference between planned doses and delivered. Tracking of respiratory motion by respiratory gating systems is one of the most efficient and cheapest methods used to compensate respiratory motions. Movement model could be anticipated through breathing-associated computed tomography (4D-CT) images carried out former to the dose delivery. Nevertheless, the feasible alterations in patient's respiration require real-time remote monitoring of tumor site while irradiancy. It could be done with fluoroscopic imaging from seeded fiducial markers or with electromagnetic identification of transponders (beacons) planted in the tumor neighborhood. Monitoring of surface body (thoraco-abdominal surface) motion permits to estimate cancerous growth movement, but establishment of external-internal association is necessary. However, such scanners could be utilized for gating, they also notify therapists from respiratory disorders containing coughs and sneezes and allow them to interfere in the therapy as needful. Furthermore, new systems utilizing particle rays for volumetric or planar imaging are under progression. Difficulty of motion target irradiation is attempted to be dissolved by some ways, including gating, rescanning, gated rescanning or tumor tracking. These ways have been still incomplete and a lot of work has to be done to improve them.

At the same time, patients suffering from breast cancer experience a considerable decline in heart delivered dose by performing DIBH technique. Furthermore, it seems that BH and DIBH techniques are the optimal methods to perform respiratory gating for patients and departments, as it involves no significant increases in workload, cost or education. Finally, to consider the clinical performance benefits of gated radiotherapy, it is predictable that these systems will be used for treatment of all thorax and abdominal area tumors, in all radiotherapy centers in the near future, provided that there is access to adequate equipment.

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Conflict of Interest

None

References

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