Review Article

# The battle against respiration-induced organ motion in external beam radiotherapy

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## ABSTRACT

شهدت العقود الأخيرة من القرن الماضي تحسينات كبيرة في تقنية العلاج الإشعاعي الخارجي ، نتج عنها تحسين في طرق التصوير و تخطيط العلاج بالكمبيوتر و إضافة البعد الثالث و الرابع . مع ذلك مازالت هناك تحديات بسبب حركة الجسم الداخلية الناتجة تلقائيا بسبب الجهاز التنفسي و التي تغير في موقع الورم و الهدف مما يقلل من نسبة نجاح العلاج. سلطت العديد من الدراسات الحديثة الضوء على حركة الورم والتأثير الناجم عن التنفس خاصة على الجرعة التراكمية. بذل الكثير من الجهد للوصول إلى طرق وعمليات إكلينيكية للتغلب على هذا التغير الزماني والمكاني الناجم عن حركة التنفس في جلسات العلاج الإشعاعي و لتصحيح الخطأ الحسابي. العديد من الأبحاث المنشورة تناولت جمع و إبراز اخر التطورات في هذا المجال بشكل غير منظم أو بمعلومات محدودة. في الوقت الحالي هناك حلول و أبحاث إما قيد الدارسة الإكلينيكية أو تمت تطبيقها على نطاق محدود. هذه الورقة العلمية تهدف لتقدم لمحة موجزة عن هذا المجال سريع النمو بشكل أكثر دقة وشمولية.

The latter 2 decades of the last century have witnessed significant improvements in external beam radiotherapy (EBRT), moved primarily by the advances in imaging modalities and computer-based treatment planning. These advancements lead to introducing the addition of a fourth-dimension, time, to the three-dimensional geometry in EBRT. The new era in EBRT presents challenges and opportunities to compensate for the effect of respiratory-induced target motion and improve treatment output. A number of these methods have been investigated, some of them already clinically approved and some still under development. Thus, there has been an increasing amount of literature in the area of respiratory motion compensation in EBRT. One criticism in most of the literature is that, it is either unorganized, or provides limited information. A few literature reviews provide a comprehensive overview regarding this fast growing area of study. The literature review here will provide an up to date summary of these publications.


*Saudi Med J 2014; Vol. 35 (7): 651-662*

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Radiotherapy in cancer treatment has become a major tool in the battle against cancer. Its significance is marked in several studies that estimated that more than 50% of all cancer incidences receive radiotherapy as a treatment method.[1] External beam radiotherapy (EBRT) is one of the common forms of radiotherapy treatment. In EBRT, cancer cells forming a malignant mass are targeted with precise fields of highly ionizing radiation from an external source. The main goal of treatment planning for radiotherapy is to facilitate delivery of a lethal radiation dose to the tumor while avoiding or minimizing radiation-related toxicity to adjacent healthy tissue and organs. The latter 2 decades of the last century saw significant improvements in EBRT, moved primarily by the advances in imaging modalities and computer-based treatment planning. These advancements lead to improvement in conventional radiotherapy techniques to deliver highly conformed focused radiation while sparing normal adjacent tissue in 3-dimensional conformal radiotherapy (3D-CRT). Following the introduction of the multi-leaf collimator (MLC), EBRT moved to a new era of intensity-modulated radiotherapy.[2] Further development by

**Disclosure**. Authors have no conflict of interests, and the work was not supported or funded by any drug company.

integrating medical imaging modalities, such as x-ray, computed tomography (CT), or magnetic resonance imaging (MRI) with a linear accelerator (LINAC) led to a more advanced treatment procedure known as image-guided radiotherapy (IGRT). This treatment procedure motivates a need for tracking the internal tumor motion, caused by respiration during treatment, and readjusting the beam. Currently, researchers are investigating the adaptation of the beam to follow the tumor during treatment, moving towards introducing 4-dimensional treatment methods. As technology and methodology in EBRT have evolved and produced ever more detailed planning schemes, the impact of tumor motion on dose delivered to target and non-target tissues becomes ever-more prominent. The impact of respiration-induced tumor motion on the cumulative dose delivered to a clinical target volume (CTV) in EBRT has been highlighted in many studies.[3,4] Therefore, much effort has been made to compensate for respiration-induced organ motion in EBRT. A number of methods have been investigated, some of them already clinically approved, and some still under either clinical trials or in earlier stages of development.

In recent years, considerable material has been published on respiratory motion compensation in EBRT. One criticism of much of the literature is that, it is either unorganized, or provides limited information. A few literature reviews, such as one published by Keall et al,[3] Webb,[2,5] and the latest book in adaptive motion compensation in radiotherapy by Murphy,[6] provide a strong and comprehensive overview regarding this fast growing area of study. The literature review here will provide a compact summary of these publications and update the information with the most recent studies. Another review paper by Riboldi and colleagues[7] summarized the efforts required for an application of real-time tumor tracking in particle therapy. The paper compared and assessed competing strategies for time-resolved target localization, and related clinical outcomes in x-ray radiation oncology.[7] In 2012, there has been an increasing amount of literature on organ motion compensation. The review paper conducted by Korreman[8] focused on 4D organ models to compensate for respiratory motion during therapy. In addition, Tanner et al[9] published a review paper, in which they described the management of motion in photon radiation therapy.

The literature review will start by defining the breathing mechanics and the respiration-induced organ motion. Then it will demonstrate a compact summary of the approaches and methods used, either to observe and track, or to compensate for these motions in EBRT.

***Respiratory motion. Breathing mechanics.*** In a cellular level, creating energy involves using oxygen to oxidize carbohydrates, such as sugars, fats, or protein. This process produces some chemical by-products such as carbon dioxide ($CO_2$), which is carried by the bloodstream to the lungs, where it is exchanged for more oxygen. The process of exchanging the carbon dioxide with oxygen can be defined as breathing. The process of breathing occurs via a cyclic motion of 2 phases or processes, inhalation/inspiration, and exhalation/expiration. These 2 processes are driven by the contraction or relaxation of muscles around the lungs. A main muscle that contributes to the breathing process is the diaphragm, which is an internal skeletal muscle layer that runs across the bottom of the rib cage. **Figure 1A** shows an anatomical structure and action of the muscles around the ribcage and lungs, while **Figure 1B** shows the changes of the thoracic cavity size during

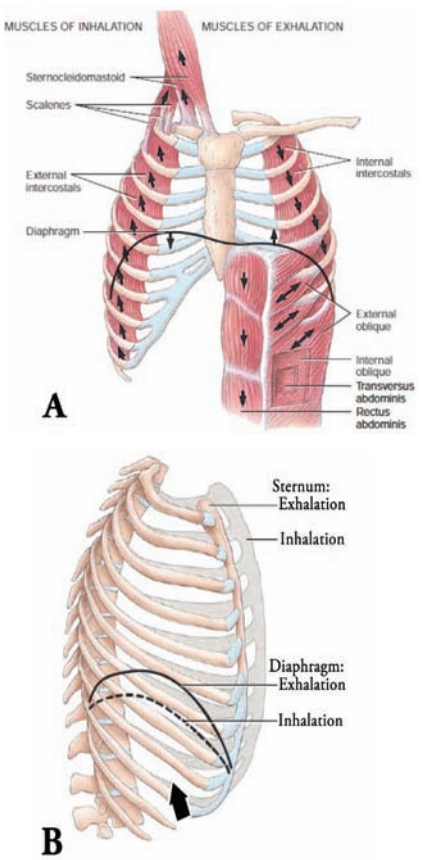


**Figure 1 -** Images showing: **A**) an anatomical structure and action of the muscles around the rib cage and lungs; **B**) changes of the thoracic cavity size during inhalation and exhalation.[10] Permission obtained from Wiley & Sons. Tortora GJ, Derrickson BH. Principles of Anatomy and Physiology. In: Muscles of inhalation and exhalation and their actions. 12th ed. Hoboken (NJ): John Wiley & Sons; 2006. p. 891.

inhalation and exhalation.[10] Contraction of the muscles of inhalation, the diaphragm, and intercostal muscles, causes an increase in the size of the thoracic cavity and elevates the ribs and sternum. The air will then flow into the lungs as a result of a pressure difference, outside (high) and inside (low) the lung. In normal situations when both muscles freely relax, the lungs will recoil to their original volume due the elastic fibers inside them.[10] This will push the air outside the lungs and cause exhalation. When the human body is under stress, or in need of high rates of oxygen, this process will speed up by using the exhalation muscles (the intercostal muscles and the abdominal muscles) to increase exhalation speed. A pattern of thoracic 3 breathing, called costal breathing is described by the thoracic upward and outward movement due to contraction of the external intercostal muscles. Abdominal breathing, called diaphragmatic breathing is described by the abdomen surface movement due to the contraction and descent of the diaphragm.

On average, the respiratory rate, the number of breathing cycles in a set amount of time, typically 60 seconds for a healthy adult is approximately 12-18 breaths per minute.[10] However, the average respiratory rate varies significantly between studies. Moreover, the movement of the diaphragm and ribcage during breathing will cause some movement in the internal organs. The next section will present a general overview about the respiratory motion and the organs affected.

***Respiration-induced organ motion.*** There are a significant number of publications about internal organ motion, with 2 of particular note, by the American Association of Physics in Medicine (AAPM),[2] and Langen et al.[11] Both studies presented expansive coverage not only of one or 2 organs, but almost all organs affected by respiratory motion. In 2001, Langen et al[11] published a collection of 66 studies about respiratory motion for lung, liver, kidney, diaphragm, rectum, bladder, prostate, and pancreas. In 2006, the AAPM publication showed tables for 50 studies for all the organs mentioned in the Langen study apart from the rectum, bladder, and prostate. The AAPM publication repeated some of the work already mentioned in the Langen paper, and added some new material published after the Langen study. To summarize the outputs of these 2 studies and avoid having excessive tables of numbers and references, the mean and standard deviation of the peak-to-peak motion of organs across all studies are summarized in **Table 1**.[2] The table shows a mean ± standard deviation of approximately 11.8 ± 2.6 mm for lung tumors, and 25.6 ± 14.5 mm for the liver in the superior inferior (SI) direction. One of the major disadvantages of these 2 comprehensive studies is the lack of consistency in measurement methods and conditions. Most of the studies used in these 2 publications are organ-based studies, and based on cohorts of 10-30 subjects.[4] These studies presented major organs/organ motion in the SI direction, and slightly less motion in the anterior posterior (AP) and lateral (L) direction. Additionally, they showed that there are no general patterns of internal organ motion during respiration, and that many factors could affect internal organ motion, such as general health, tumor location, and pathology. Therefore, it is difficult to make an assumption about a particular subject prior to observation or treatment.[2]

**Table 1 -** Mean and standard deviation of the peak-to-peak motion of organs across all studies (in mm).

| Organ | Displacement (mm) | | | | | | Maximum displacement in SI |
|---|---|---|---|---|---|---|---|
| | Mean | | | Standard deviation | | | Magnitude |
| | SI | AP | L | SI | AP | L | (mm) |
| 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 |

The last column shows the reference of the maximum displacement observed.[2,11] SI - superior inferior, AP - anterior posterior, L - lateral

***Respiratory motion effects.*** The previous section focused on presenting evidence that the temporal spatial position of an internal organ is affected by respiratory motion. A detailed description of the effect of organ respiratory motion is presented in this section. The effects of organs' respiratory motion were highlighted in many studies summarized below. Therefore, these studies will be divided into 3 main categories based on the applications affected by organ motion during respiration. These categories are diagnostic imaging, treatment planning, and treatment delivery.

***Diagnostic imaging.*** In nuclear medicine (NM) imaging, the image represents the integral of the accumulated activity over the acquisition period, which in single-photon emission computed tomography (SPECT) lasts 5-30 minutes, and in positron emission tomography (PET) is 5-15 minutes.[12] In such an image, any object that moves with respect to the imaging field of view will appear blurred or smeared along the direction of relative motion, as illustrated in **Figure 2**.[13] Even small amounts of motion can cause significant blurring of images in comparison to the intrinsic resolution

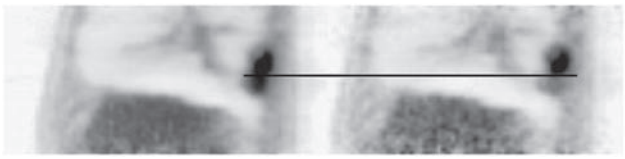

**Figure 2 -** Comparison of uncorrected blurred lung tumor motion in positron emission tomography (PET) image (left) and corrected PET image illustrating the effect of motion on the apparent size of the tumor.[13] Originally published in the Journal of Nuclear Medicine.[13] Bundschuh RA, Martínez-Moeller A, Essler M, Martínez MJ, Nekolla SG, Ziegler SI, et al. Post-acquisition detection of tumor motion in the lung and upper abdomen using list-mode PET data: a feasibility study. J *Nucl Med* 2007; 48: 758-763.

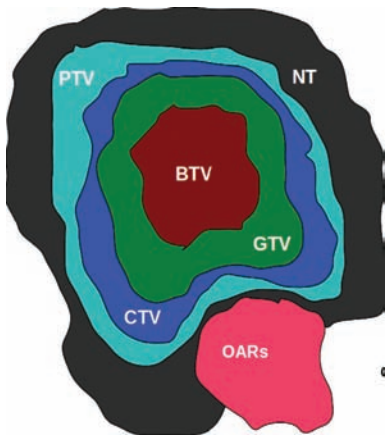


**Figure 3 -** Theoretical image of external beam radiotherapy (EBRT) planning volumes. PTV - planning target volume, NT - normal tissue, BTV - biological tumor volume, GTV - gross tumor volume, CTV - gross tumor volume, OAR's - organ at risk

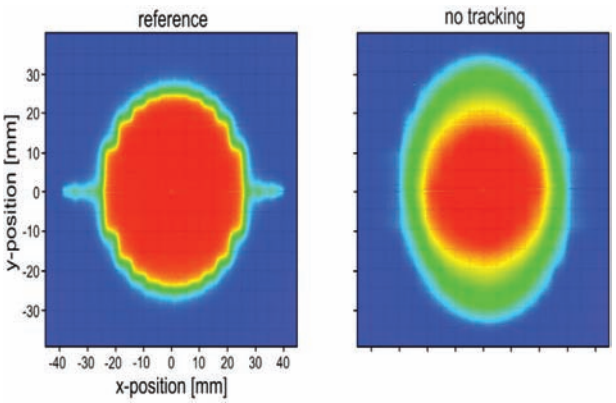


**Figure 4 -** Dose distributions of circular field applied to target moving in 2 directions.[17] Permission obtained from Elsevier Limited. Krauss A, Nill S, Tacke M, Oelfke U. Electromagnetic real-time tumor position monitoring and dynamic multileaf collimator tracking using a Siemens 160 MLC: geometric and dosimetric accuracy of an integrated system. *Int J Radiat Oncol Biol Phys* 2011; 79: 579-587.

of nuclear scanners. Therefore, further technological enhancement in the intrinsic spatial resolution of NM imaging systems cannot be justified until an adequate motion correction method is considered, in order to recover the true spatial resolution of the scanner.

***Treatment planning.*** The aim of radiotherapy is to deliver a prescribed dose of radiation to a tumor without irradiating the surrounding normal tissues. However, due to complicated surrounding structures, motion, and scattered radiation, it is hard not to irradiate the healthy tissue. **Figure 3** shows a theoretical image of EBRT planning volumes, where the biological tumor volume (BTV) is defined using PET or SPECT, and a gross tumor volume (GTV) is defined using high spatial resolution CT or MRI. Then, to account for microscopic tumor spread, a clinician defines the clinical target volume (CTV). Finally, a physicist defines the planning target volume (PTV) to incorporate margins allowing for tumor motion and set-up errors. However, the physicist should take into account the NT (normal tissue) and the organ at risk (OAR), volumes of tissues or organs that are highly radio-sensitive, and therefore, must be saved from receiving a radiation dose when defining the PTV.

The International Commission on Radiation Units and Measurements (ICRU) Report 6214 shows the PTV obtained by adding some margin to the CTV to account for intra/inter-fraction motion and set-up error. Although, this additional margin will reduce the impact of tumor motion, it will also increase the risk of delivering a high dose to NT or OARs. Therefore, researchers have focused on minimizing the size of the additional margin added to the CTV using different methods.[15,16] The aim of these studies is to minimize the PTV and radiation toxicity risk, and facilitate dose escalation to achieve a higher tumor control probability.[3] These methods will be illustrated in more detail in the next section

***Treatment delivery.*** As stated previously, the aim of radiotherapy is to deliver a prescribed dose of radiation to a tumor without significantly irradiating the surrounding normal tissues. However, due to complicated surrounding structures, motion, and scattered radiation, it is almost-impossible not to irradiate some healthy tissue. Therefore, clinicians and physicists together generate a PTV, as mentioned in the previous section. However, the inter/intra-fraction motion (differences in anatomy and patient position observed between treatment fractions in fractionated radiotherapy, and during treatment time) of the target area during treatments causes an averaging, blurring, or shifting of the static dose distribution along the path

of the motion. These effects have been highlighted in many studies.[17-19] **Figure 4** shows an example plot of the blurring of a static reference dose distribution.[17] The figure shows 2 sub-figures for a circular target dose distribution in 2 cases, static and moving target from left to right. This study shows that the isodose area that receives a radiation dose of equal intensity (red area in the figure line) decreased from 13.8 mm to 8.1 mm, and the area (green) between and isodose lines increased from 11.7 to 24.6.

***Tracking respiratory motion.*** The previous section has shown the need to find a method for compensating for respiratory motion during a diagnostic imaging, or a therapeutic treatment. However, before finding a method for motion compensation, there is a need to track this motion. Thus, this section will present a detailed description of some of the respiratory motion tracking techniques or systems. This section is divided into 2 subsections: methods of tracking the external surface, and methods of tracking the internal target.

***External surface tracking.*** In recent years, there has been a significant research focus on developing new tools to monitor, and track respiratory and body motion during diagnostic image acquisition and EBRT.[15,20,21] A number of external instruments have been used to track respiratory motion, such as, pneumatic devices and infra-red (IR) tracking of the vertical position of external surface by 2 respective markers.[22] The Real-Time Position Management (RPM) system from Varian Medical Systems of Palo Alto, California, United States of America[1] is widely used in clinical environments. The RPM system monitors the motion of an object placed on the patient's abdomen/thoracic. However, these methods do not adequately describe the variation in the chest wall configuration, or differentiate between thoracic or abdominal breathing. Therefore, researchers focused on using more than one marker over the chest to acquire more detailed information about the respiratory motion.[23,24] Other researchers[15,25] have used stereo camera tracking systems with markers in various configurations arranged on the subject's anterior surface. Three optical markers attached to a wearable vest are used in Cyberknife Synchrony (Accuray Inc., Sunnyvale, California, USA) which is a respiratory motion tracking system.[26] Some researchers focus on developing a marker-less tracking system, such as a four-dimensional (4D) laser camera,[27] a 3D-surface imaging system (Galaxy, LAP Laser, Lüneburg, Germany),[28] and AlignRT (developed for radiotherapy patient alignment by Vision RT Ltd, London, United Kingdom).[29] These systems generate a 3D mesh of the chest wall of the patient as a function of time. Despite the fact that some of these systems can provide an accurate result of the patient's body or respiratory motion, most of these tools are either expensive (£10k–£100k), or more. The advantage of the marker-less system is that it is non-invasive and non-ionizing, thus facilitating high throughput without the need for marker-based patient set-up time.

***Tracking internal target.*** Studies have used CT to compensate for tumor motion; slow CT,[30] inhale and exhale breath hold CT,[31] and 4D CT.[32] In the slow CT method, the CT scanner is operated in a slow mode to acquire multiple respiration phases per slice. In an inhale and exhale breath hold CT, the maximum intensity projection (MIP) is used to define the entire range of tumor motion. The major disadvantage of these 2 methods is that the motion blurring will lead to lower resolution and higher error in the tumor and normal organ contour.[2] Moreover, they delivered higher doses compared with conventional CT scanning. The third method is 4D CT, which constitutes conventional CT 3-dimensional (3D) images with the additional dimension of time. This is a promising solution for obtaining high-quality data for internal organs or tumor motion. However, using a CT scanner to track respiratory motion is more applicable during the treatment planning stage but not during EBRT. Other studies suggested using PET to define the entire range of tumor motion due to the fact that PET capturing time is long.[2] However, using PET in EBRT requires more investigation.[33,34]

Thus, several researchers are focused on optimizing a method to track internal organs motion during diagnostic image acquisition or EBRT. An x-ray fluoroscopy with an implanted fiducial marker in, or near the tumor[35,36] was used to measure internal target motion. Implantable fiducial markers provide a highly effective method of tracking internal tumors or organs. There is a wide variety of fiducial markers for different organs and clinical application, such as a 2 mm diameter gold sphere. Another tracking system based on using an implanted fiducial marker is the Electromagnetic Transponder (EMT), which used an antenna to localize an implanted passive Beacon transponder inside the patient.[37,38] One of the major advantages of the EMT system is using non-ionizing radiation to track the implanted markers. However, using a fiducial marker in, or near a lung tumor is limited due to the increased risk of pneumothorax, and it being an invasive method. Moreover, the markers sometimes slightly move during acquisition, or between the planning and treatment stages. Therefore, some researchers studied methods

using x-ray fluoroscopy alone without an implanted fiducial marker,[39,40] or combining fluoroscopic images with CT scan.[41] One of the main advantages of using x-ray fluoroscopy is its availability in most of the new generation of EBRT treatment systems. However, increasing the x-ray fluoroscopy dose or sampling rate is still clinically problematic. In addition, tracking an internal tumor using x-ray fluoroscopy without an internal marker is a challenge, and not possible in all cases.[4]

Electronic portal imaging device (EPID) is technique use the LINAC MV treatment beam, which avoids an additional imaging dose to the patient. However, the image resolution is lower than the x-ray fluoroscopy. This method is still under investigation.[4] Another technique to track internal tumor motion is based on using multiple implanted positron emission markers, which are detected by a positron detector. This approach is still under investigation.[42] Other researchers have studied the feasibility of using ultrasound to track tumors or internal organs' respiratory motion.[43,44] Using ultrasound to measure internal target motion is a promising approach, but needs further investigation before being implemented in an actual treatment trial procedure. However, a study carried out by Artignan et al[45] showed that the pressure applied by the ultrasound probe to the external surface may lead to some deformation or shift of the internal target, this was also highlighted by Webb in 2006.[4] Magnetic resonance (MRI) was also used to measure internal organs' motion.[46-48] Using MRI to track internal target motion is a promising approach. The major advantages of this approach are being non-invasive, using non-ionizing radiation, and providing a high soft tissue contrast. However, using MRI during EBRT is still under investigation.[6] Moreover, a cone beam computed tomography (CBCT) scanner integrated with a linear accelerator is another tool for image-guided radiotherapy. The CBCT images can be obtained from linac-based kilovoltage imagers. These image sets can be used for Adaptive Radiotherapy (ART). However, motion artifacts in CBCT, deteriorates the image quality, and reduces the soft tissue contrast. In spite of this drawback, many studies have investigated the use of respiration-correlated CBCT to correct for the respiratory motion.[49,50]

In summary, all the previous studies track internal organs motion either directly by tracking the tumor itself, or indirectly by tracking the host organs with an implanted fiducial marker in or near the tumor, or a surrogate organ, such as the diaphragm. However, some studies have focused on using an external thoracic/abdomen surface as a surrogate for the internal target motion to avoid excessive doses, or invasive procedures.[22,51,52]

***Handling respiratory motion in EBRT.*** The previous sections have shown several studies and analysis on whether to investigate the effect of respiratory motion, or to observe and track this motion internally and externally in diagnostic imaging and therapeutic imaging. This section will give a general overview of the methods and systems used to handle/compensate for respiratory motion in EBRT. Handling respiratory motion in EBRT is a broad area of research. There are different ways of categorizing these methods, whether by the systems used,[53] or by the techniques implemented.[2,4] This section will divide the methods of compensating for respiratory motion in EBRT according to the techniques used. However, the system used by any of these studies will be detailed within each approach. In general, there are 3 different approaches to compensate for respiratory motion in EBRT: gating, breath hold, and real-time tracking. The following subsections offer some overview of each approach.

***Gating.*** Gating is a process of irradiating a target during certain phases of the respiratory cycle, such as at maximum exhalation. The width and position of the phase of the respiratory cycle that is irradiated are manually determined, and learned by monitoring the respiratory motion externally or internally. Thus, there are several studies to optimize gating methods, such as whether gating is based on inhale or exhale respiratory signal, and whether to use respiratory signal phase, or amplitude for gating. In gating-based treatment, the radiation beam is activated when the phase or displacement of the respiration signal reaches a predefined window or gate. The ratio between the overall time and the time the target is irradiated is defined as a duty cycle, where the value of the duty cycle indicates the accuracy of the gating techniques investigated. One of the disadvantages of a gated treatment is that the treatment time could be increased by up to twice that of conventional treatment.[2]

***Gating based on external surface motion.*** One the most widely used methods is gating based on external surface motion.[54] Different instruments to track external surface motion have been used as mentioned earlier. One of the most widely used systems for gating, based on external respiratory signal is Varian Real-time Position Management (RPM) system (Varian Medical Systems, Palo Alto, CA). Another system based on external respiratory signal gating is ExacTrac Gating/

Novalis Gating by BrainLab (Heimstetten, Germany) although this system uses x-ray imaging to support the gating decision. Being a non-invasive technique and applicable for almost all patients are the major advantages of gating based on external surface motion. However, using external surface motion as a surrogate for internal organs or tumor motion is a challenge.

***Gating based on internal surrogate motion.*** Another method for gating respiratory motion is using x-ray fluoroscopy to track the implanted fiducial marker in or near the tumor.[55] A gantry-based system, where the treatment couch can move while radiation is delivered from any angle, using up to 4 room-mounted x-ray detectors developed jointly by Hokkaido University and Mitsubishi Real-Time Respiratory Tracking (RTRT) system (Sapporo, Japan),[56] is a common example for gating systems.

As mentioned earlier, implantable fiducial markers provide a highly effective method of tracking internal tumors or organs. However, using a fiducial marker in or near the lung tumor is limited due to the increased risk of pneumothorax and being an invasive method. Therefore, some researchers studied a method of using x-ray fluoroscopy alone without an implanted fiducial marker.[39,54]

***Breath hold (BH).*** Breath hold methods can be defined as a method of irradiating the tumor only during a period of time of BH. The major challenge in the BH approach is that it requires more understanding of the ability of the patient to hold his/her breathe, and reproduce the same level of breath hold again and again. There are several studies of methods that use BH as an approach for compensating respiratory motion in external beam radio therapy. One advantage of breath hold methods is that they significantly reduce internal target motion and facilitate protecting critical normal tissues by changing internal anatomy structure.[2] For example, cardiac and lung toxicity can be significantly reduced in breast cancer treatment if treated during maximum inhalation BH, as it allows the diaphragm to pull the heart posteriorly and inferiorly away from the breast.[57,58] In general, BH methods have been used in lung cancer treatment; however, it may have some application in the treatment of different organs.

***Deep-inspiration breath-hold (DIBH).*** A DIBH is a method of coaching the patient to provide a reproducible deep inhale breath-hold during simulation and treatment.[59] Spirometer-monitored is the most common and widely used system for DIBH, such as the VMAX Spectra 20C (VIASYS Healthcare Inc, Yorba Linda, CA) and the SpiroDyn'RX (Muret, France). A patient will be connected to a breathing tube and spirometer while a nose clip is attached to prevent nasal breathing. **Figure 5** shows transversal CT-slices with dose distribution illustrations for breast cancer treatment. The patient's ability to produce DIBH during simulation and treatment is one of the major challenges of this method. A study has shown that approximately 60% of the lung cancer patients cannot do DIBH.[59]

***Active-breathing control (ABC).*** In ABC at a certain time, as a patient exhales, the breathing device will measure the air volume, and will prevent the patient from exhaling any further once he/she reaches the desired lung volume (around 75% of lung volume).[60] The breath-hold duration is patient dependent, on average around 15 to 30 seconds. Some currently

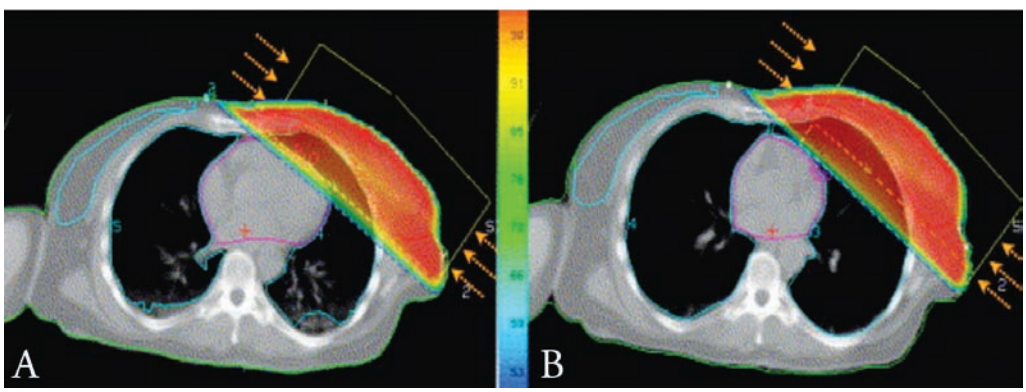


**Figure 5 -** Transversal CT-slices with dose distribution illustrations for breast cancer treatment: **A**) end-expiration gating; and **B**) deep inspiration breath-hold.[57] Permission obtained from Elsevier Limited. Korreman SS, Pedersen AN, Nottrup TJ, Specht L, Nystrom H. Breathing adapted radiotherapy for breast cancer: comparison of free breathing gating with the breath-hold technique. *Radiother Oncol* 2005; 76: 311-318.

available commercial systems are Active Breathing Coordinator by Elekta (Norcross, GA) and Vmax Spectra 20C, VIASYS (Linda, CA). Similar to DIBH, depending on a patient's ability to produce BH during simulation and treatment is one of the disadvantages of ABC.[2]

In addition to DIBH and ABC methods, some researchers have investigated a self-held BH approach either with,[61] or without[62] a respiratory monitor. In a self-held BH, the patient holds his/her breath at some point in the breathing cycle. However, one major disadvantage of these 2 methods is that they rely heavily on the ability of the patient to hold his/her breath independently.[6]

Forced shallow breathing (FSB). This method of motion compensation is achieved by using abdominal compression to induce forced shallow breathing.[63,64] The general concept of this strategy is to reduce the diaphragm motion and limit the respiratory motion by applying pressure to the abdomen.

A study by Eccles et al[63] showed that FSB methods achieved a reduction of a respiratory motion of a liver tumor to 9.4 mm (range; 1.6-23.4) and 5.0 mm (range; 0-19.3) from 11.7 mm (range; 4.8-23.3) and 5.6 mm (range; 1.5-15.5) in the caudal-cranial, and AP directions. However, accuracy, reproducibility, and patient discomfort are some of the disadvantage of this approach.[6]

***Dynamic adaptive motion.*** New technological advancements in both treatment and diagnostic modalities allow a dynamic dose delivery to the tumor during respiration. The basic concept behind a dynamic motion adaptive approach is that the radiation beam shape or isocenter, in the center of the target/tumor volume, is synchronized with the tumor respiratory motion. Thus, theoretically by synchronizing the motion of both target and beam together, a static correlation between the 2 will be developed. There are several approaches to create a static correlation between the radiation isocenter and tumor respiratory motion. This can be carried out by either moving the beam source, the couch, or shaping the beam. As mentioned earlier, to be able to track the tumor during the treatment time, several approaches have been investigated and 4 have been widely used: on-line imaging of the tumor, fiducial markers implanted in or near the tumor, such as using x-ray fluoroscopy, using external surface as a surrogate, or using active or passive implanted markers with a non-radiographic tracking system. A dynamic adaptation of the beam shape during treatment can be carried out using a Dynamic Multi-leaf Collimator (DMLC), or called Synchronized moving aperture radiation therapy (SMART). A Multi-Leaf Collimator (MLC) is used on linear accelerators to facilitate a conformal shaping of radiotherapy treatment beams.

Several studies investigated the adaptive treatment method using a DMLC, either under an assumption of a rigid body motion[17,38] or elastic tissue movement.[65] However, these studies assumed that the respiratory motion is regular and periodic. A phantom study carried out by Ravkilde et al[38] showed that one advantage of using DMLC is that it can provide sub-mm geometrical errors. Another example of adaptive treatment is moving the LINAC with a robotic arm.[66,67] The synchrony respiratory tracking system integrated with the CyberKnife robotic linear accelerator (Accuracy Incorporated, Sunnyvale, CA) allowed monitoring the tumor position and repositioning of the radiation beam. Mounting the LINAC on a 6-joint robotic arm allowed greater freedom of movement around the patient. The motion of the robotic arm is directed by 2 kilo-voltage x-ray scanners, and/or infra-red Synchrony camera, which monitor external respiratory motion via light-emitting diodes. The effectiveness of CyberKnife with tumor tracking for treating primary and recurrent lung cancer has been reported. One of the main advantages of CyberKnife is that it provides effective treatment for lung tumors with tolerable toxicity with tighter margins. However, further studies are still required to identify patients who would derive the most benefit.[68,69]

Mounting a LINAC on a gimbaled x-ray head with an MLC installed on a ring-shaped gantry is another approach for adaptive treatment introduced by Takayama et al[70] in 2009. In this approach, the x-ray head rotates along the 2 orthogonal gimbals (pan and tilt rotations) allowing the radiation beam to follow the tumor respiratory motion using x-ray fluoroscopy.

Recent advancements resulted in the development of a dual-modality verification system, consisting of an orthogonal kilovoltage system and a megavoltage imaging device, for tumor tracking on a gimbaled linac system to treat moving targets with precision. The Vero system (BrainLab AG, Feldkirchen, Germany) has been brought to clinical practice in 2013. It has proven its functionality and showed high accuracy during validation on phantoms. In a clinical study by Depuydt et al,[71] an initial assessment showed that the tracking error was approximately 0.45±0.95 mm for the TILT direction, and 0.25±0.55 mm in the PAN direction. A completely different approach is with the use of a robotic couch.[72,73] Theoretically, sub-millimeter motion accuracy can be achieved in 3D by synchronizing the

couch movement to the respiratory motion. However, this approach is still under investigation, and did not reach clinical trials.

Tomotherapy arose to solve common problems in radiation therapy. It is a technique introduced by Goddu et al,[74] where rather than irradiating the entire tumor volume, the radiation is delivered slice-by-slice in a helical mode. The system has a built-in CT scanner to track the internal target during the treatment. It results in highly distributed dose treatment and sharp dose gradients. The use of helical tomotherapy has shown encouraging dosimetric results and improvement in patient positioning. It allows the use of smaller margins around targets and organs of risk.[75] However, it requires dosimetric validation of patient-specific dosimetric quality assurance.[76]

The effect of breathing on treatment quality during helical tomotherapy was evaluated by several authors.[77,78] Although their sample size was small, Stepin et al[78] found that when patients are coached on regular breathing during treatment, motion due to breathing had no effect. In addition, the motion and volume changes of tumors during tomotherapy could be minimized when patients are in prone position. Still, tumor motion due to breathing is a barrier to the treatment quality and requires solutions that are still not available for tomotherapy.[77,79] As technology and methodology in EBRT have evolved and produced ever more detailed planning schemes, the impact of tumor motion on dose delivered to target and non-target tissues becomes ever-more prominent. The common requirement across all of these studies is the ability to predict, and then readjust the beam dynamically during the treatment time based on the spatial and temporal motion of the tumor as a result of respiration. Therefore, understanding, characterizing, and predicting respiratory motion is of major interest in current and future work in this area. Respiratory motion models are widely used in many applications such as dose calculation in external beam radiotherapy,[80] internal organ and external surface correlation,[45] respiratory motion predication,[51,80,81] and gating algorithm or building respiratory motion phantom.[19,82]

Despite impressive advances in treatment delivering technologies, for example, DMLC, robotic LINAC, gimbals, or even a robotic couch technique, these systems suffer from a very high latency. The system latency can be defined as the lag between locating the tumor and repositioning the beam. System latency has been quantified in several studies: the response time of the DMLC ranges from 160±2 ms[83] to more than 500 ms.[17,84] The latency of the robotic treatment system is approximately 192.5 ms[85] where in a LINAC-based gating system ranges from 90 ms to 170±30.[86] In gimbals-based radiation therapy the system latency was approximately 47.7 ms for panning and tilting.[87] Several studies highlighted the dosimetric effect[88-92] of the system latency in external beam dose delivery, showing that the agreement between the delivered and planned dose was adversely affected as system latency increased. In the search for more computationally efficient methods with minimal error, several attempts have been made to overcome system latency using different respiratory motion predictors.[92] Moreover, predicting the behavior of the external surface motion is not sufficient in itself, but it must be correlated with internal target motion. Several studies focused on using the external thoracic/abdominal surface as a surrogate, fully (as a main method of correlating the motion of the external surface with the internal tumor) or partially (to overcome the low sampling rate of imaging modalities using or minimizing excessive dose from the medical imaging modality used during the treatment) for the internal target motion to avoid excessive dose, or the need for invasive methods.[51,52]

In conclusion, there have been several attempts and technology solutions for motion management throughout the years. In the quest for real time tumor tracking, precision for an optimal solution is still ongoing.

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