Review Article

Motion management in gastrointestinal cancers

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Abstract: The presence of tumor and organ motions complicates the planning and delivery of radiotherapy for gastrointestinal cancers. Without proper accounting of the movements, target volume could be under-dosed and the nearby normal critical organs could be over-dosed. This situation is further exacerbated by the close proximity of abdominal tumors to many normal organs at risk (OARs). A number of strategies have been developed to deal with tumor and organ motions in radiotherapy. This article presents a review of the techniques used in the evaluation, quantification, and management of tumor and organ motions for radiotherapy of gastrointestinal cancers.

Keywords: Gastrointestinal cancers; motion management; motion control; radiotherapy; respiratory motion

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Introduction

Radiotherapy for gastrointestinal cancers has traditionally been confronted with two major physical challenges: (I) the proximity of the tumor(s) to many vital normal organs such as duodenum, stomach, small intestine, kidneys, or spinal cord in the abdomen and (II) the mobility of both the tumor and its surrounding organs at risk (OARs). The advent of intensity modulated radiation therapy (IMRT) has provided an effective tool to deal with the first challenge. With IMRT, highly conformal 3-dimensional (3D) dose distributions can be generated for large irregular target volumes with sharp dose fall-offs to reduce the radiation exposure to the nearby OARs (1). The confidence in delivering such conformal dose distributions has been improved dramatically with the use of onboard soft-tissue based imaging guidance. Indeed, it has led to increased use of hypofractionated stereotactic body radiation therapy (SBRT) for selected tumors in lung, spine, liver, and pancreas in recent years (2-4). To fully achieve the potential of IMRT and SBRT for gastrointestinal cancers, one must deal with the second challenge posed by tumor and organ motions during radiotherapy.

Tumor (and organ) motion in the abdomen can be triggered by respiration and/or by changes in the filling status or the internal anatomic arrangement of gastrointestinal organs. Unlike respiration-induced motions, the changes in organ arrangement or filling status lack regularity and could lead to large tissue deformations. The presence of tumor/organ motions complicates the planning and delivery of radiotherapy (5). Without proper accounting of these motions, target volume could be under-dosed (e.g., when it moves out of a planned conformal therapeutic dose region) and the nearby OARs could be over-dosed (e.g., when they move into the tumoricidal high dose region). This is further exacerbated by the close proximity of the tumor and normal OARs in the abdomen. It has been observed in many studies that tumor motion can result in degradation of radiation treatment effectiveness and accuracy (6-8).

A number of strategies have been developed for dealing with tumor/organ motions in radiotherapy, ranging from passive approaches such as expanding the high-dose volume to encompass a moving target to active managements such as using an abdominal compression device to limit the range of motion or dynamic tracking to follow a moving tumor/organ for motion-compensated dose delivery (5). In this article, we review the techniques used in the evaluation, quantification, and management of tumor/organ motions in radiotherapy for gastrointestinal cancers in the abdomen. Specifically, the review focuses on intrafractional motions in

fractionated radiotherapy for distal esophageal, pancreatic and liver tumors, and SBRT for liver and pancreatic tumors. Organ motion could also affect interfractional tumor or OAR positions, a large portion of which (e.g., rigid-body displacements) can be managed effectively by imaged-guided patient setup and tumor localization in the daily treatments (which will not be reviewed here). Nonetheless, one should carefully evaluate the effects of large interfractional tissue deformations that cannot be fully accounted for by daily patient setup and tumor localization so that it can be properly taken into account, for example, via adaptive re-planning. Section 'Motion magnitude' below reviews the magnitude of tumor/organ motions in the abdomen. Motion management strategies for gastrointestinal cancers are reviewed in section 'Motion management'. The dosimetric impact of motion management is summarized in section 'Dosimetric implications'.

Motion magnitude

Tumor and organ motions in the abdomen are driven by several factors. Chief among them is the ever-present respiration. All tumors and most normal organs in the abdomen are subject to respiration-induced motions, which occur in all three spatial directions with generally greater magnitude along the cranial-caudal (CC) direction. For some organs, the inspiration and expiration motion patterns can differ from each other making a pathway known as hysteresis. The complex physiological process of breathing can also introduce an element of irregularity in cyclic nature of respiration. As a result, the pattern of respiration-induced motions can vary in the absence of active control (e.g., breathing with visual feedback for reproducible breathing cycle/magnitude). In general, the magnitude of respiration-induced tumor/organ motions is dependent on the location and the degree of fixation of the tumor/organ to other anatomic structures; it could vary from patient to patient and with time even for the same patient.

Tumor or organ motion in the abdomen can also be triggered by changes in the anatomic arrangement or in the filling status of adjacent gastrointestinal organs. Unlike respiration-induced motions, the changes in organ arrangement or filling status are mostly irregular with variable time dependence. The magnitude of motion caused by these physiological changes is generally difficult to predict. The probability of having a large change in tumor/organ position is likely greater over a longer time span (e.g., between treatment fractions) than over a short period of time (e.g., during single-fraction dose delivery). Image-guided patient setup/localization would be able to take into account a large portion of this type of motion. However, large tissue deformations caused by this type of motion would require online adaptive re-planning to fully taken it into account. For example, Ahunbay *et al.* (9) have investigated various online strategies to account for inter-fractional variations for pancreatic cancer and reported that online re-planning strategies can improve the target coverage and reduce OAR doses compared to conventional image-guided radiation therapy (IGRT).

Most of the studies on intrafractional tumor/organ motions in the abdomen have focused on the respiration-induced motions. Imaging modalities used to assess respiration-induced tumor/organ motions included conventional and 4D computed tomography (CT) (10,11), ultrasound (12), cine magnetic resonance imaging (MRI) (13), nuclear medicine imaging (14) and X-ray fluoroscopy (15). Some studies used surrogates such as the diaphragm [e.g., (12,15,16)] or the fiducial markers implanted in the tumor site while most studies examined the movement of tumor or OARs directly. The magnitudes of tumor motion reported for liver, pancreatic, and esophageal cancers are summarized below.

Motion magnitude of liver tumors

The movement of liver tumors has been measured using MRI, 4DCT/CBCT, as well as real-time tracking of fiducials implanted in the vicinity of tumor. Shimizu *et al.* (17) measured liver tumor motion in all three directions with MRI and found that they can move up to 21 mm in CC direction, 8 mm in anterior-posterior (AP) direction and 9 mm in right-left (RL) lateral direction. Park *et al.* (18) investigated inter-fraction and intra-fraction liver tumor motion using 4DCT and CBCT. Gold fiducial markers (2 mm ×5 mm) were implanted around the GTV in twenty liver SBRT patients and were tracked with X-ray projections of CBCT. Motion characteristics observed with 4DCT were compared with CBCT results. They found the liver tumors moves as much as 17.9 mm in CC, 5.3 mm in AP and 3 mm in RL direction. Nishioka *et al.* (19) used real time tumor tracking system (RTRT) to monitor the movement of fiducial gold markers implanted in the vicinity of liver tumors. They reported liver tumor movement of 15.98 mm in CC, 7.23 mm in AP and 4.19 mm in RL direction.

These results, summarized in *Table 1*, are generally consistent with each other. In general, the magnitude of

Table 1 Magnitude of motion for liver tumors

Reference	Technique	Magnitude of motion		
		CC (mm)	AP (mm)	RL (mm)
(17)	High-speed MRI	21.0	8.0	9.0
(18)	4DCT (w fiducials)	17.9±5.1	5.1±3.1	3.0±2.0
	CBCT (w fiducials)	16.5±5.7	5.3±3.1	2.8±1.6
(20)	4DCT	9.7±5.0	NA	NA
(19)	RTRT (w fiducials)	15.98±6.02	7.23±2.96	4.19±2.46

CC, cranial-caudal; AP, anterior-posterior; RL, right-left; MRI, magnetic resonance imaging; NA, not available.

Table 2 Magnitude of motion for pancreas tumors

Reference	Technique	Magnitude of motion		
		CC (mm)	AP (mm)	RL (mm)
(13)	Cine MRI	20±10	8±3 (A) 6±2 (P)	na
(22)	4DCT	5.5±2.3	3±1.7	3±1.8
(20)	4DCT	5±1	NA	NA
(21)	3D & 4DCT	5.9±2.8	NA	NA

CC, cranial-caudal; AP, anterior-posterior; RL, right-left; MRI, magnetic resonance imaging; NA, not available.

movement in CC direction was two to three times larger than the movements in the AP and RL directions. The magnitude measured by MRI was greater than those measured by 4DCT/CBCT or by real-time tracking of surrogate fiducials, especially along the lateral direction.

Motion magnitude of pancreatic tumors

The movement of pancreatic tumor has been reported by several groups (13,20-22). In 2009, Feng *et al.* (13), investigated pancreatic tumor motion using Cine MRI imaging. They found that the tumor borders moved much more than expected: 20 mm in CC and 8 mm in AP direction. They noticed that tumor position correlated poorly with diaphragm and abdominal wall position and cautioned that these surrogates should be used with care for pancreatic tumor motion management (13).

Tai *et al.* reported a study of pancreatic tumor and organ motion using conventional 3D and 4DCT scans for 15 pancreatic cancer patients (including ten randomly selected patients and five patients selected from a subgroup of patients with large tumor respiratory motions) (21). Gross tumor volume was delineated on the 50% and 0% phase CT sets, and the OARs were drawn on the 3D CT images. Deformable registration was used to populate contours over the CT sets at other respiratory phases. For the 10 randomly selected patients, peak-to-peak motion amplitudes along the CC direction were 5.9±2.8 mm for the target. The peak-to-peak motion amplitudes for liver, left kidney, and right kidney along the CC direction were 7.9±3.2, 7.1±3.1, and 5.7±3.2 mm, respectively.

4DCT was also used by Hallman *et al.* to quantify the magnitude of respiration-induced motion for liver and pancreatic cancer patients (20). Contours were drawn at one phase and were propagated to other phases by deformable registration. 3D organ models were generated from the contours at each phase. They found, on average, the center of mass motion in CC direction was 9.7±5 mm (range, 3-18 mm) and 5±1 mm (range, 3-7 mm) for liver clinical target volume (CTV) and pancreatic CTVs, respectively.

Goldstein *et al.* investigated the motion of locally advanced pancreatic adenocarcinoma for 30 patients using 4DCT (22). Treatment planning software was used to contour the GTV, bilateral kidneys, and biliary stent. Excursions were calculated according to the centroid of the contoured volumes. They reported mean and standard deviation of GTV excursion was 5.5±2.3 mm in CC direction and about 3 mm in AP and RL directions. The mean and standard deviation of left and right kidneys was 6.5±2.7 and 7.7±3.0 mm, respectively, along the CC direction.

Table 2 summarizes their findings. It is interesting to note that the tumor excursions measured with 4DCT were consistent among different studies. The average magnitude

Table 3 Magnitude of motion for esophagus tumors

Reference	Technique	Magnitude of motion		
		CC (mm)	AP (mm)	RL (mm)
(23)	Cine-MRI	13.3±5.2	4.9±2.5	2.7±1.2
(24)	4DCT	8.7±4.7	3.8±2.3	3.9±2.7
(25)	4DCT	8.9±0.8	3.0±0.5	1.2±0.2
(26)	4DCT	8.0±4.5	2.8±2.0	2.2±2.3

CC, cranial-caudal; AP, anterior-posterior; RL, right-left; MRI, magnetic resonance imaging.

in CC direction ranged from 5 to 5.9 mm. However, the magnitude of excursion measured with cine MRI was significantly greater than those measured with 4DCTs: approximately a factor of four in CC direction and a factor of two in the other directions. Similar disparity between the results measured with cine MRI and 4DCT was noted for liver tumor as well (see section 'Motion magnitude of liver tumors'). Further study on the dependence of imaging modalities is needed.

Motion magnitude of esophageal tumors

Respiration-induced motion of esophageal tumors has been reported by several authors (23-27). Lever *et al.* (23) used cine-MRI to visualize tumor movement directly throughout multiple breathing cycles. The study included 36 patients with tumors located in the upper [8], middle [7], and lower [20] esophagus. The mean and standard deviation of peak-to-peak displacements in the CC, AP, and RL directions were 13.3±5.2, 4.9±2.5, and 2.7±1.2 mm, respectively. The range of motion was 2.7-24.5, 1.6-11.3, and 0.9-6.1 mm in CC, AP and RL directions, respectively. Tumors in lower esophagus, the focus of this review, showed more movement than did higher tumors in the CC and AP directions. They also noted that intrafraction tumor movement was highly variable between patients.

Zhao *et al.* quantified the internal motion for primary tumors located near the gastroesophageal junction using 4DCT for 25 patients (24). GTV was contoured on the exhale-phase images set and a deformable image registration method was used to automatically propagate the contours to other phases of the 4DCT images. Target motion was quantified by measuring the displacement of the GTV centroid and the variations in the target boundary and volume. The mean and standard deviation of peak-to-peak GTV centroid motion was 8.7±4.7, 3.8±2.3, and 3.9±2.7 mm in the CC, AP, and RL directions, respectively.

Yaremko *et al.* investigated the motion characteristics of distal esophagus cancer using 4DCT for 31 patients (25). Deformable image registration was used to map the full expiratory motion GTV to the full-inspiratory CT image. They reported that all 31 patients exhibited mean centroid displacement interiorly with 8.9±0.8 mm; equally in left and right direction with mean absolute value displacement of 1.2±0.2 mm. Most patient (29/31) had it moved anteriorly with 3.0±0.5 mm. The magnitude of average centroid vector-sum displacement was 10.0±0.9 mm with direction being predominately inferior, anterior, and to the right. They also noted that the esophageal GTV displacements increased with descent along the esophageal axis toward and beyond the diaphragm. The abdominal esophageal components showed significantly greater displacements compared with thoracic esophagus in CC (by 2.5 mm) and AP (by 1 mm) directions on average.

Patel *et al.* used respiration-synchronized 4DCT scans of 31 patients to quantify the motion of primary tumors located in the proximal, mid, or distal thoracic esophagus, as well as any involved celiac-region lymph nodes (26). Measurements of respiratory tumor motion were obtained for 1 proximal, 4 mid, and 25 distal esophageal tumors, as well as 12 involved celiac-region lymph nodes. The mean and standard deviation of peak-to-peak displacements of all primary tumors in the CC, AP, and LR dimensions were 8±4.5, 2.8±2, and 2.2±2.3 mm, respectively. Distal tumors were found to have significantly greater CC (8.9 *vs.* 3.5 mm mean peak-to-peak displacement) and AP (3.3 *vs.* 0.3 mm mean peak-to-peak displacement) motion than proximal or mid-esophageal tumors. The mean and standard deviation of SI, AP, and LR peak-to-peak displacements of the celiac-region lymph nodes were 9.2±5.6, 4.6±2.7, and 1.9±2.6 mm, respectively.

These data is summarized in *Table 3*. The data obtained by 4DCT is remarkably consistent among three different studies. As observed earlier, the magnitude of motion measured by cine MRI was greater (by approximately 5 mm) in the CC direction compared to those measured

with 4DCT. Although this discrepancy was not as big as seen in the case of pancreatic tumor, the fact it shows the same trend underscores the need to understand why 4DCT seems underestimate the magnitude of motion compared to cine MRI.

Motion management

Several strategies have been reported for managing tumor/organ motions in radiation therapy (5,28). These strategies generally fall into three broad categories: those aims to accommodate the tumor motions using large irradiation volumes (motion encompassing); those aims to control or reduce the magnitude of tumor/organ motion (motion control); and those aims to track the tumor/organ motion with moving radiation fields (motion tracking) or gated irradiation (gating). Often, these strategies can be combined, e.g., motion reduction plus motion encompassing, to achieve a prescribed dosimetric goal.

Motion encompassing strategy is passive: one assesses the motion and designs the radiotherapy fields to cover most, if not all, possible positions of the moving target by adding an internal margin to the CTV. This strategy is easy on the patient but typically irradiates a larger volume of healthy tissue (especially when a population-based margin is used) compared to other strategies. Motion reduction strategies involve active motion management using, e.g., shallow breathing, breath-hold (BH), or abdominal compression to control or reduce the magnitude of motion. These strategies require the cooperation of the patient but it has the potential to use a smaller internal margin for adequate target irradiation and thereby reduce normal tissue irradiation. Gating and motion tracking involve active manipulation of the radiation source to follow a moving target by controlling either the beam on/off time (gating) or the beam shaping/positioning (e.g., using dynamic multileaf collimators or a linear accelerator mounted on a robotic arm as in the case of Cyberknife). This strategy is also easy on the patient and has the potential to significantly reduce normal tissue irradiation. However, it does require more sophisticated technology for accurate and robust tracking of a moving target and for synchronized radiation delivery. Other than beam gating and use of the Cyberknife, dynamic tracking for motion-compensated dose delivery is not yet available for routine use in the clinic.

More systematic description of these strategies for managing respiration-induced motions can be found in the report of the American Association of Physicists in Medicine (AAPM) task group 76 "Managing respiratory motions in radiation oncology" (5). A Japanese group representing the Japan Conformal External Beam Radiotherapy Group, the Japanese Society for Therapeutic Radiology and Oncology, the Japan Society of Medical Physics, and the Japanese Society of Radiological Technology has also recently published Japanese guidelines for respiratory motion management in radiation therapy (28).

Motion-encompassing methods

Motion-encompassing methods aim to design a conformal dose distribution to cover all possible movements of GTV/CTV with a defined probability. This is accomplished by (I) expanding CTV with an appropriate margin (internal margin) to account for the tumor movements that are independent of patient setup uncertainties, creating the so called internal target volume (ITV); (II) further expanding the ITV with a setup margin to take into account the uncertainties associated with daily patient setup/tumor localization, resulting in the final planning target volume (PTV); and (III) plan the treatment to cover PTV (29,30). Construction of setup margin from systematic and random setup errors is well established (29-31). So the key task of motion-encompassing methods for tumor/organ motion is to determine the internal margin or ITV [and planning risk volume (PRV) for normal organs].

Techniques that have been used to determine ITV/PRV include slow CT, BH CT, X-ray fluoroscopy, 4DCT, and cine MRI. Intuitively, slowing down the CT image acquisition time would yield a CT more representative of a moving target/organ over a period of time. When the acquisition time at each table position is long enough to cover the entire cycle of motion (e.g., a complete cycle of respiration), the resulting CT would provide the average volume traversed by the moving target/organ. However, slowing down the acquisition time can cause image blur and motion artifacts which may increase the target delineation error. This method has been used for lung tumors that were not involved with either the mediastinum or the chest wall and is not recommended for abdominal tumor sites (5).

BH CT

Motion blurring can be reduced by using BH CT scans. Inhalation and exhalation BH CT scans can be fused to obtain the motion encompassing tumor volume. Respiration of the patient should be monitored during these scans to verify the reproducibility and constancy of the BH. The

utility of BH CT scans for motion assessment and free-breathing treatment of pancreatic and liver cancer patients has been investigated recently for patients treated with SBRT using volumetric modulated arc therapy (VMAT) (32). In this study, two to five radio-opaque fiducial markers were implanted in the target at least 72 hours before CT simulation. Free breathing (FB) and inhalation breadth hold/exhalation breadth hold (IBH/EBH) CT scans were acquired for each patient. The tumor was identified on the FB scan and the coordinates of fiducial markers on breadth hold scans were used to calculate the motion of target. An ITV was generated from the GTV by considering the average displacement of fiducial markers. A setup margin of 3 mm was added to the ITV to obtain the PTV. All patients planned with the ITV approach met SBRT constraints. During the course of treatment, CBCT and kV orthogonal images were taken and analyzed for setup before patient treatments. Images were registered using skeletal land marks and fiducial markers. They noted that registration using fiducial markers was superior to the registration using skeleton landmarks in accurately representing the tumor position. The setup margin of 3 mm was adequate to keep the tumor inside the PTV during treatment. It was concluded that breath hold CT scans can be used to quantify tumor motion and to generate an ITV from the GTV (32).

Respiration-correlated (or 4D) CT

Respiration-correlated CT or 4DCT has become a preferred and commonly used method to assess the extent of tumor/organ movements in the abdomen [see e.g., (18,20-22,24-26,33)]. With 4DCT, a 3D CT representation of the patient can be reconstructed for any selected phase in the respiratory cycle. Tumor motion and ITV can be easily assessed by examining the tumor/organ locations on images of different breathing phases or on the movie loops of phase images. Ideally, each patient should have a 4DCT scan so that an individualized ITV can be determined. 4DCT can also be used to assess the variation of the ITV within a specific population of patients and to determine a population-based internal margin. For example, in the study discussed earlier in section 'Motion magnitude' on locally advanced pancreatic adenocarcinoma, the authors contoured the GTV, bilateral kidneys, and biliary stent on different phase images of the 4DCT (22). By studying the excursions of these structures during respiration the authors were able to determine an asymmetric internal margin (1.0, 0.7, and 0.6 cm along the respective CC, AP, and RL directions) that may be used for patients in this population group if a 4DCT scan is not available. It should be noted that to use a population based internal margin, one must first validate that their patient matches the characteristics of studied patient population and use the same treatment technique.

Cine MRI

MRI offers superior soft-tissue contrast compared to X-ray based CT. This is especially advantageous for imaging tumor and normal organs in the abdomen. Cine-MRI involves acquisition of a series 2D image at a user-selected imaging plane with high temporal resolution. It is an effective modality for noninvasive visualization of the movement of tumor and normal organs. It has been used by several investigators in assessing intrafractional tumor motions for liver, pancreatic, and esophageal cancers (13,17,23). However, cine-MRI based on a single imaging plane does not represent the exact 3D displacement of the tumor. Judicious selection of imaging plane and/or using multiple imaging planes may be needed for a more realistic assessment of the 3D tumor/motion. The full potential of MRI's superior soft-tissue contrast could be realized in 4D-MRI, which is being actively investigated (34).

Motion control or suppression methods

Motion control or suppression methods seek to maintain or reduce the magnitude of tumor/organ motion, thereby reducing the CTV-PTV margin needed in motion encompassing methods. Methods include voluntary or forced shallow breathing and BH. The residual organ motions can then be taken into account by using appropriate (often much smaller) internal margin. For patients with large breathing excursions, this strategy can lead to a significant reduction in the PTV margin, and thereby reducing radiation exposure to nearby OARs and normal tissues. The key for successful implementation of this strategy lies at careful patient selection (not all patients are suitable candidates) and at reproducing the level of shallow breathing or BH at each treatment fraction.

Active breathing control (ABC)

The feasibility of using ABC to temporarily immobilize the patient's breathing has been investigated by many authors (3,35-37). In this method, an ABC apparatus is used to actively hold the patient's breadth at certain level. Simulation, treatment planning and delivery are performed

at identical ABC conditions with minimal margin for breathing motion. It has been shown that reproducible and substantial internal organ displacement can be achieved using a moderate deep inhalation BH with this method at patient's comfort level. Liver radiotherapy with long time breath-holding at end-inhale was reported as an effective method to reduce liver motion, PTV and dose to normal tissues (36).

Self-held breath hold

In this method, patient voluntarily holds his/her breadth and the CT or treatment beam is turned on during the breadth hold interval. This method depends on the patient's ability to produce a reproducible breath hold for at least 10 seconds, therefore patient selection is very important. It is also important to verify that the patient's internal anatomy has minimum motion during the breadth hold. Residual anatomical motion during the breadth hold, uncertainty in breadth hold reproducibility and set up uncertainty should be taken into account in designing ITV or PTV. Ideally, self-held breath hold treatment should be delivered with active respiratory monitoring. Treatment machines used for this method should have special interlocks which can turn off the treatment delivery when the level of breath hold falls outside the predetermined tolerance window using patient-controlled beam-off switch or integrated breathing monitoring system (e.g., the RPM system from Varian Medical Systems). Although the technical requirements are similar to FB gated delivery (to be discussed in the section 'Respiratory gating methods'), this method is more efficient because the radiation is delivered continuously during the breath hold. Deep inspiration breath hold (DIBH), used in the treatment of breast cancer for the left breast (38) and of lung cancer (39), is also a form of self-held breath hold technique. While the primary purpose of DIBH for breast and lung cancers was to reduce dose to normal organs (heart and lung), it can also be used for motion management in abdominal cancers. To the best of our knowledge, no clinical study has evaluated the use of DIBH for tumor/organ motion management in the abdomen.

Forced shallow breathing with abdominal compression

This is a simple and often used approach in tumor/organ motion control. Several abdominal compression devices are commercially available for clinical use. A typical compression device consists of a compression arch that can be attached to the treatment couch top (or a custom base plate) over a patient's abdomen and a compression plate that is connected to the arch via a screw and pressed against the abdomen. The position of the arch can be adjusted in the longitudinal and vertical direction to adapt it to the patient's anatomy. The pressure plate is typically positioned 2 to 3 cm below the triangular rib cage border. By adjusting the screw up and down, the pressure applied to the abdomen can be regulated. The applied pressure reduces magnitude of diaphragmatic motion and improves target localization especially in abdomen. Another option for abdominal compression involves the use of a compression belt, instead of the rigid compression arch. The belt is strapped around the patient with an attached air bag, positioned over the abdomen, that can be inflated to create desired pressure on the abdomen. The effectiveness of using abdominal compression depends on the ability to accurately reproduce the location of the compression plate and the applied pressure between simulation and daily treatments. For lung tumors, the use of abdominal compression can reduce the mean range of target motion from 12.3 mm (range, 8-20 mm) to 7.0 mm (range, 2-11 mm) (40). In SBRT for liver tumor, it has been shown that forced shallow breathing with abdominal compression can effectively reduce the liver tumor motion significantly in all directions and the compression level established at the simulation could be safely reproduced at the time of treatment delivery (41).

Respiratory gating methods

Respiratory gating methods aim to irradiate the target volume only when it moves into a predefined position in the respiratory cycle. It has the potential to significantly reduce the CTV-PTV margin needed in the motion encompassing methods. Unlike in the self-held breath hold methods discussed in section 'Self-held breath hold', patients here would maintain normal breathing while radiation is triggered when the respiratory signal falls within a predefined range of the breathing cycle. Respiratory gating methods are easy on patients; the burden of breath holding by patients is shifted to the treatment machine which must turn the radiation on and off at required positions in the respiratory cycle. However, because radiation is on during only a selected segment (30-50%) of the respiratory cycle, gating usually takes longer time to deliver the same prescribed dose (low duty cycle).

In principle, respiratory gating can be performed with either external or internal surrogates of respiratory motion. Examples of external surrogates include chest wall surface, infrared markers placed on the abdominal surface, and lung

air volume exchange measured by a spirometer. Internal surrogates could be real-time imaging of the moving target or fiducial markers implanted in the target volume. Internal surrogates would provide most direct and accurate information of tumor/organ position for beam gating. However, due to limitations of current onboard imaging capabilities and the invasiveness of implanting fiducial markers, this technique has not been widely used. Most of the respiratory gating treatments have been performed using external surrogates. Typically, the respiratory signal is derived from respiration-induced movement of chest wall (via optical surfacing imaging or infrared markers placed on the abdomen surface). Treatment planning CT acquisition and treatment delivery are performed within a preset respiratory window based on either the breathing phase or amplitude. The gating window is typically centered on end-exhalation as it is most stable. For liver and pancreatic cancers, 4DCT study found that gating near end-exhale (with a 20% phase window) reduces the range of motion by a factor of approximately 10 (20).

Gating with external surrogates requires (I) reproducible breathing patterns; and (II) accurate representation of the time-dependent tumor/organ position by the surrogates tracked by the gating system for tumor/organ motion. Natural breathing always contains certain degrees of irregularity. It has been shown that visual and/or audio coaching help improve the reproducibility of breathing patterns (42). The relationship between the surrogate respiratory cycle and tumor/organ position requires careful evaluation at simulation, especially for amplitude-based gating. Periodic confirmation of the constancy of this relationship may be needed over the treatment course. The region of interest or marker location selected for external surrogate should be stable and easily repeatable at daily treatments. Recent research has shown that combined use of external and internal surrogates can improve the accurate of respiratory gating. In particular, Shirato *et al.* have reported on the use of a real-time tumor-tracking device to gate the treatment for liver SBRT based on fluoroscopic tracking of an implanted fiducial marker near the tumor (43,44).

Real-time motion tracking methods

Ideally, radiation delivery can be designed to follow a moving target if the tumor/organ movement can be tracked continuously in real-time. This would eliminate the need for a tumor-motion margin, thereby reduces normal tissue irradiation. It would also eliminate the need to turn off radiation periodically (with gating methods) or allow the patient to breath (with BH methods), resulting in the most efficient dose delivery (100% duty cycle).

Real-time motion tracking methods require accurate and robust identification of the target position in real-time. Direct tracking of the target volume itself or internal surrogates (e.g., fiducial markers implanted at the target site) would be ideal. When external surrogates are used, the correlation between the positions of the surrogate and the target must be confirmed and maintained throughout the respiratory cycles. In addition, the relationship of the surrounding anatomy with the tumor must be verified to make sure the normal tissue protection is as planned. Because the time delay from target position detection to reposition the radiation beam, this approach also requires a reliable model to predict target position ahead of time to account for the time delay in beam adjustment. The third major requirement of this approach is dynamic beam adjustment based on the detected target motion. Active research are ongoing exploring the possibility of using dynamic MLC, couch motion, gantry motion, combined MLC and couch motion, or dynamic movement of the entire Linac (as in the case of Cyberknife).

At present, the Cyberknife system is the only commercially available treatment device that can perform dynamically tracked dose delivery based on the motion of internal surrogates (radiographic markers implanted in the target volume). It has been used to deliver SBRT treatments for liver (45,46) and pancreatic (47) cancers, in addition to lung cancers. Preliminary studies indicate motion tracked dose delivery using Cyberknife is safe and effective. A phase I dose escalation study using Cyberknife stereotactic radiosurgery for liver cancers has been indicated safe administration of single fraction 18-22 Gy dose to the PTVs of 11-42 cc (46). Real-time motion-tracked dose delivery using dynamic MLC has not been used for gastrointestinal cancer. A first clinical application of dynamic MLC tracking for prostate cancer has been reported recently (http://medicalphysicsweb.org/cws/article/opinion/55518).

Dosimetric implications

The presence of tumor and organ motion can have a profound impact on the planning and delivery of radiotherapy. Conventional treatment planning is typically performed on a static CT scan while the tumor and/or normal organs can move during the dose delivery. Inter-fraction set up variations, intra-fraction tumor/organ

motions, and potential interplay between dynamic dose delivery and a moving target can lead to differences between the calculated dose distribution on the static CT and the radiation dose actually received by the tumor and normal organs (5). Without proper accounting of these motions, target volume could be under-dosed and the nearby OARs could be over-dosed.

As discussed in section 'Motion management', a number of strategies are available for motion management in radiotherapy for gastrointestinal cancers; each could have a different dosimetric impact on tumor coverage and normal organ sparing. For example, motion-encompassing methods aim to design adequate CTV-to-PTV margin to cover expected target motions. This approach usually leads to more irradiation of normal tissues to high doses. It also does not account for the variation in dose delivery to OARs. Motion management strategies such as motion suppression, gating, and real-time motion tracking will result in smaller CTV-to-PTV margins and thereby reduce the dose to normal tissues. The dosimetric impact of different motion management strategies should be assessed with regard to their effects on target dose coverage, normal tissue protection, and the ease and robustness of clinical implementation. While formal analysis of intra- and inter-fraction uncertainties on fractionated treatments has been reported [e.g., (8,48)], to the best of our knowledge, there is no single study that has systematically compared the dosimetric impact of all available motion management strategies for gastrointestinal cancers. Examples of dosimetric analysis for individual motion management techniques are presented below.

Dosimetric impact on liver tumor

Dosimetric effect of respiration-induced organ motions on intrahepatic tumors has been studied by several investigators. Rosu *et al.* (49) examined the dose distribution of 40 liver cancer patients previously treated on a conformal therapy dose escalation protocol. Initial 3D dose calculations were performed on static CT scans taken with voluntary BH at normal exhalation phase. In the analysis, more realistic predictions of the actual delivered dose to intrahepatic lesions were obtained by a geometric convolution approach that accounts for random setup variations and breathing-induced organ motion. They found there was no significant change in minimum CTV dose, indicating adequate CTV-PTV margin. However, clinically relevant and statistically significant increases (decreases) in liver normal tissue complication probability (NTCP) from values computed for the static cases occurred for tumors located toward the bottom (top) of the liver. The change in liver NTCP (from a nominal 20%) ranged from +12.0% to –11.7% [average magnitude change 3.9% (sigma =3.3%)]. Changes in prescription dose required to restore the original 20% NTCP ranged from –3.7 to +7.9 Gy [average magnitude change 1.9 Gy (sigma =1.9 Gy)]. It was concluded that the PTV concept was adequate for CTV coverage, but the doses to normal liver were incorrectly modeled without including patient-related set up and respiratory induced uncertainties.

The effect of breathing motion on dose accumulation for liver tumors has also been investigated recently using deformable image registration by Velec *et al.* (50). Twenty one free-breathing stereotactic liver cancer patients were included in the study and their initial dose calculation was performed on static exhale CT. Deformable image registration was used to deform each exhale CT to inhale CT. Dose was calculated on exhale CT and inhale CT for all patients. Dose distribution was accumulated over the whole breathing cycle using deformable image registration. Compared to static plans, significant dose differences were observed to either the tumor or normal organs in the majority of patients as a result of breathing motion. These changes may not be accurately accounted for with rigid motion.

These studies indicated that normal liver dose can be reduced significantly by using the individualized margins for respiratory induced organ motion management (49). In a case study of SBRT for liver tumors, Molinelli *et al.* (51) found that a CTV-to-PTV margin reduction of 50% (2.5 mm laterally, 5 mm longitudinally) could lead to reductions of the D33% and D50% for normal liver by an average 22% (maximum 38%) and 26% (maximum 47%), respectively.

Dosimetric impact on pancreatic tumor

Radiation treatment for pancreatic cancers is complicated because of the frequent overlapping of the PTV and the OARs and intra-fraction organ motion. As discussed in section 'Motion magnitude', Cine MRI study found pancreatic tumor borders moved much more than expected; 20 mm in CC and 8 mm in AP direction (13). For 99% geometric coverage, margins of 20 mm inferiorly, 10 mm anteriorly, 7 mm superiorly, and 4 mm posteriorly are required (13). Gwynne *et al.* (52) investigated the effect of respiration-induced organ motions on radiation treatment

planning in pancreatic cancer patients. Three planning CT scans were acquired for each patient; quiet breathing, held expiration and held inspiration. Organ motion was quantified from displacement of a reproducible point within the pancreas in all directions. Two types of treatment plans were generated for each patient; standard plan and plan incorporating organ motion using individualized margins. It was found that the use of individualized margins reduced the mean PTV volume by 33.5% (P=0.0051). The percentage volume of kidney receiving >10 Gy, small bowel >45 Gy and liver >30 Gy were reduced by 63.7% (P=0.0051), 29.3% (P=0.0125) and 29.2% (P=0.0107), respectively, after using the individualized margins.

A recent dosimetric analysis of OARs during expiratory gating in SBRT for pancreatic cancer found that dose to the duodenum was higher when treating on the inspiratory than on the expiratory phase. The dosimetric analysis suggested that expiratory gating may be preferable to inspiratory BH and FB strategies for minimizing risk of toxicity (53).

Dosimetric impact on gastric cancer radiotherapy

Matoba *et al.* (54) investigated the dosimetric impact of respiration-induced target motion on gastric cancer. In this study, two types of treatment plans were created: one using 4DCT (plan A) and the other using regular helical CT with a uniform margin (plan B). For plan A, ITV was created using the images of all phases and PTV was defined as ITV plus 8 mm margin. For plan B, CTV was delineated on regular CT scan and PTV was created using a uniform margin of 20 mm in all directions to account for the organ motion and set up error. Dosimetric comparison was performed using dose volume histograms (DVH) for CTV, PTV and the OARs. For assessment of dose coverage of CTV, CBCT images were used to delineate the CTV during course of treatment and were registered with original plan A and plan B. The PTV volume was reduced from 1,291.4±111.6 to 867±120.9 cm^3 using 4DCT. The mean doses to the liver and heart were reduced significantly (P=0.02 and 0.03, respectively) when using 4DCT for margins. For kidneys, V20 was reduced (4.8±2.4)% for right kidney and (16.3±10.4)% for left kidney in plan A (4DCT). There was no significant difference in the dose coverage of the CTV between the plans. They concluded that the treatment planning using 4DCT for gastric was useful for reducing normal tissue toxicity.

Hu *et al.* (55) also investigated the impact of target motion on dose distribution for gastric cancer radiotherapy. They investigated the benefit of BH technique with online image-guided radiotherapy in the adjuvant gastric cancer radiotherapy. Surgical clips were used as surrogate to quantify target motion. Digital fluoroscopic images were obtained and the probability distribution functions (pdf) of the target motions were created for both the FB and BH treatment. Dosimetric comparison was performed among six randomly selected patients for two IMRT plans; FB IMRT plan without image guidance ($IMRT_{FB}$) and breadth hold IMRT plan with image guidance ($IMRT_{IGBH}$) using the same beam parameters. It was found that combining the daily image guidance and the breath hold technique can reduce the margin to 5-10 mm. Dosimetric comparison of the static $IMRT_{FB}$ and $IMRT_{IGBH}$ plans demonstrated no significant difference (P>0.05) in target coverage whereas the liver received lower dose in $IMRT_{IGBH}$ (P=0.01).

Concluding remarks

Curative radiotherapy for gastrointestinal cancers is difficult to implement because the tumors are usually embedded in or adjacent to mobile normal critical organs. Prior to the introduction of IMRT and onboard soft-tissue imaging, any radiation dose that could be safely delivered to these tumors without inflicting severe normal tissue complications was generally insufficient to fully control the disease leading to poor treatment outcomes. Tremendous advances have been made over the last two decades in target visualization, localization, radiation dose sculpting, and motion management. These advances have greatly improved our ability to deliver highly conformal dose to the tumor while reducing dose to adjacent normal organs.

In this article, we attempted to provide a snapshot of the current status of motion management in gastrointestinal cancers. It was gratifying to note that there is a great awareness on the need to manage motion for gastrointestinal cancers as reflected in the large number of published studies on this topic for the three primary disease sites reviewed here, although it was simply not possible to include all relevant references due to the limitation on the number of cited references. There is still room to improve and to further develop motion detection and management strategies. For example, additional development in 4D-MRI is needed to fully exploit the superior soft-tissue imaging capability of MRI for motion assessment. As onboard MRI guidance began to enter clinical practice, there is also a need to investigate whether the additional soft-tissue information provided by MRI could be efficiently utilized for tumor

identification and motion management. Because MRI has no imaging dose, continuous real-time monitoring of tumor/organ motion is feasible which could result in robust tumor tracking and individualized motion management, for each patient. With proper tumor motion management curative radiotherapy could be confidently delivered to gastrointestinal tumors.

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