The management of respiratory motion in radiation oncology report of AAPM Task Group 76[a)]

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This document is the report of a task group of the AAPM and has been prepared primarily to advise medical physicists involved in the external-beam radiation therapy of patients with thoracic, abdominal, and pelvic tumors affected by respiratory motion. This report describes the magnitude of respiratory motion, discusses radiotherapy specific problems caused by respiratory motion, explains techniques that explicitly manage respiratory motion during radiotherapy and gives recommendations in the application of these techniques for patient care, including quality assurance (QA) guidelines for these devices and their use with conformal and intensity modulated radiotherapy. The technologies covered by this report are motion-encompassing methods, respiratory gated techniques, breath-hold techniques, forced shallow-breathing methods, and respiration-synchronized techniques. The main outcome of this report is a clinical process guide for managing respiratory motion. Included in this guide is the recommendation that tumor motion should be measured (when possible) for each patient for whom respiratory motion is a concern. If target motion is greater than 5 mm, a method of respiratory motion management is available, and if the patient can tolerate the procedure, respiratory motion management technology is appropriate. Respiratory motion management is also appropriate when the procedure will increase normal tissue sparing. Respiratory motion management involves further resources, education and the development of and adherence to QA procedures. [DOI: 10.1118/1.2349696]

The members of this Task Group wish to dedicate this work to Dr. Dale Kubo, a pioneer in the development and clinical implementation of respiratory motion management technology. Sadly, Dr. Kubo passed away during the formulation of this report.

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I. INTRODUCTION AND SCOPE

A. How to read this document

Readers are urged to review the general respiratory motion issues described in Secs. I–V D. Those interested in specific respiratory motion management techniques will find those described in subsections of Sec. VI, which comprises the bulk of the report. Readers interested in process-specific issues, such as patient selection, treatment or QA issues, will find those described in further subsections under each of the technique-specific subsections. The summary and recommendations are given in Sec. VII.

B. Introduction

Intrafraction motion is an issue that is becoming increasingly important in the era of image-guided radiotherapy. Intrafraction motion can be caused by the respiratory, skeletal muscular, cardiac, and gastrointestinal systems. Of these four systems, much research and development to date has been directed towards accounting for respiratory motion. The management of respiratory motion in radiation oncology is the subject of this task group report.

Respiratory motion affects all tumor sites in the thorax and abdomen though the disease of most prevalence and relevance for radiotherapy is lung cancer. Lung cancer accounts for 28% of all cancer deaths in the U.S. (American Cancer Society *Cancer Facts and Figures 2004*). An estimated 173,770 new cases were diagnosed in 2004, with an estimated 160,440 deaths. (American Cancer Society *Cancer Facts and Figures 2004*). The five-year survival rate for all

stages combined is 15%. (American Cancer Society *Cancer Facts and Figures 2004*). However, there is clinical evidence of a local control and survival advantage for higher dose levels.[1–9] Lung complications have been shown to correlate with mean lung dose (or similar surrogate, such as V_{20}).[10–15] The need for normal tissue sparing is of increasing importance due to the growing use of concomitant chemotherapy. Thus, there is clinical evidence that technologies that allow an increased dose to the tumor while sparing healthy tissue will improve the balance between complications and cure.

It is important to note that respiratory motion is just one potential source of error in radiotherapy. Other important errors such as large inter-physician GTV variations for lung cancer[16–19] and CTV variations for breast cancer[20,21] have been published. The dosimetric consequences of these variations are almost an order of magnitude larger than those caused by respiration-induced motion (see Sec. IV). Also, setup errors for lung[18,22–28] and breast[29–36] cancer are of the same or of a higher order than those of respiratory motion. Respiratory motion varies from day to day, and tumor and normal tissues can shrink, grow, and shift in response to radiation therapy and potentially to other concomitant therapies.

C. Scope

Methods that are used in the management of respiratory motion in radiation oncology and that are covered by this report include:

- Motion-encompassing methods;
- respiratory gated techniques;
- breath-hold techniques;
- forced shallow-breathing methods;
- respiration-synchronized techniques.

It is recognized that most facilities currently do not have access to methods that explicitly account for respiratory motion, and, thus, guidelines for treatments at these facilities are also included in the "Motion-encompassing methods" section. Note that respiratory management methods are not required for all patients.

The emphasis of this task group is on techniques that have been clinically implemented and used to treat patients. Less emphasis is placed on techniques that have been published and are under development, but have yet to be implemented in patient treatments. While there has been work on jet ventilation techniques[37–40] and other emerging technology, these methods will not be discussed further here.

Some of the imaging methods involved in the management of respiratory motion involve the application of additional ionizing radiation. The benefit of the additional imaging information should be weighed against the potential risks associated with the extra patient dose. Readers are referred to the report (currently being compiled) of AAPM Task Group 75 "Radiographic imaging doses in radiation therapy."

Charged-particle therapy delivery is not explicitly addressed, although many of the procedures are applicable to charged particle therapy, given the additional concern of the variation in particle range caused by respiratory motion.

II. GLOSSARY AND ABBREVIATIONS

This section will contain abbreviations of commonly used terms from the report as well as suggested terminology for instances when multiple words or phrases are used to describe the same object or function, such as:

4D	Four-dimensional
ABC	Active-breathing control
CTV	Clinical target volume[41,42]
Deep exhalation	Maximum expiratory level[43]
Deep inhalation	Maximum inspiratory level[43]
DIBH	Deep-inspiration breath hold
DRR	Digitally reconstructed radiograph
Duty cycle	The fraction of time a radiation beam is active during the delivery of a respiratory gated treatment field
Exhalation	Resting expiratory level[43]
FB	Free breathing
Gate	A device that (for this application) restricts image acquisition or treatment delivery to a particular part of the respiratory cycle
GTV	Gross tumor volume[41,42]
Hysteresis	The lagging of an effect (e.g., tumor motion) behind its cause (e.g., muscular contractions) resulting in the tumor taking a different path during inhalation and exhalation
Inhalation	Resting inspiratory level[43]
Interfraction	Occurring between treatment sessions
Intrafraction	Occurring within a treatment session
Phase	A particular stage in a periodic process (e.g., regular respiratory motion).
Physicist	A qualified medical physicist as defined by the AAPM (www.aapm.org/medical_physicist/fields.asp)
PTV	Planning target volume[41,42]
Range of motion	Displacement between inhalation and exhalation
RC	Respiratory correlated
Respiratory gated	The synchronization of imaging and radiation delivery with respiration, such that image acquisition/radiation delivery only occurs during a certain part of the respiratory cycle
Respiratory synchronized	The synchronization of radiation delivery with respiration via movement of the linear accelerator or the patient such that the radiation beam is following the tumor during treatment
Spirometer	A device that measures the volume of air entering and exiting the lungs

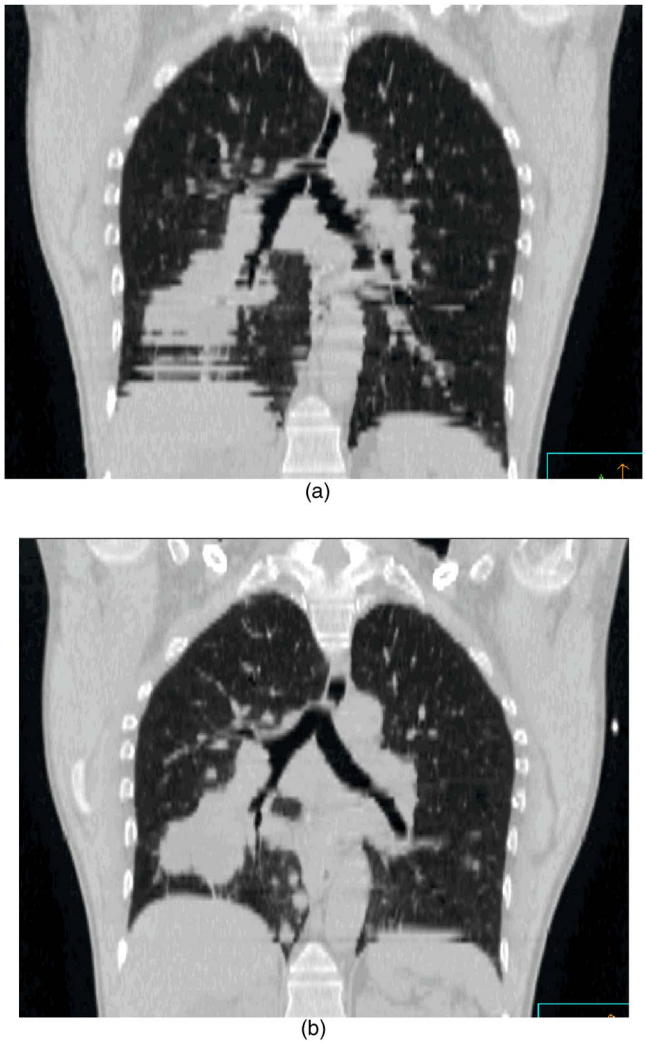

FIG. 1. Coronal views of CT scans of the same patient taken (a) during free breathing (FB) and (b) with respiratory gated scanning at exhalation. From Ref. 140.

III. PROBLEMS OF RESPIRATORY MOTION DURING RADIOTHERAPY

A. Image-acquisition limitations

If respiratory motion is not accounted for, as is the case when conventional radiotherapy techniques are applied in thoracic and abdominal sites, it causes artifacts during image acquisition. Motion artifacts are commonly seen with thoracic CT images. An example of the difference between a respiratory gated and a nongated CT scan for a patient is shown in Fig. 1. Artifacts from CT scans manifest themselves as target/normal tissue delineation errors and adversely affect dose-calculation accuracy. It is important to note that respiratory motion can generate artifacts for all imaging modalities, including positron emission tomography (PET) scanning.[44–47]

B. Treatment-planning limitations

During treatment planning, margins need to be large enough to ensure coverage of the target for most of the treatment delivery. Generally, for CT-planned lung cancer treatments, the gross tumor volume (GTV)[41,42] is outlined, and a margin is added to include the suspected microscopic spread[48] [which when added to the GTV creates the clinical target volume (CTV)]. Thus, using ICRU 62[42] nomenclature, to obtain the planning target volume (PTV) from the CTV involves margins to account for intrafraction motion, interfraction motion, and setup error. Accounting for respiratory motion by adding treatment margins to cover the limits of motion of the tumor is suboptimal, because this increases the radiation field size and consequently the volume of healthy tissues exposed to high doses. However, if the margins are not sufficiently large, part of the CTV will not receive adequate dose coverage. Because of the artifacts observed in CT images in which respiratory motion has not been accounted for, the magnitude of margin to allow for respiratory motion is difficult to quantify, particularly for individual patients in whom a wide range of tumor motion is observed.[49,50]

C. Radiation-delivery limitations

Radiation delivery in the presence of intrafraction organ motion causes an averaging or blurring of the static dose distribution over the path of the motion while inter-fraction motion causes a shift of the dose distribution. This displacement results in a deviation between the intended and delivered dose distributions. Assuming a static beam, the total positional error affecting the dose is the composite vector of internal (e.g., tumor-bone) and external (bone-treatment room) displacements. Thus, for conventional (non-intensity modulated radiation therapy) (IMRT) treatments, in which the dose gradient in the center of each field can be assumed to be fairly small, the effect is manifested by a blurring of the dose distribution by the anatomy moving near the beam edges, in effect increasing the beam penumbra. This effect is thought to be exacerbated during IMRT delivery, causing motion artifacts in dose distribution due to the interplay between motion of the leaves of a multileaf collimator (MLC) and the component of target motion perpendicular to the beam. Further discussion of IMRT effects is given in Sec. V C.

IV. MAGNITUDE AND MEASUREMENT OF RESPIRATORY MOTION

A. The mechanics of breathing

The primary function of the lung is to facilitate gas (O_2 and CO_2) exchange between blood and air, thus maintaining normal levels of gas pressure (partial pressure of oxygen, P_{O_2}, and partial pressure of carbon dioxide, P_{CO_2}) in the arterial blood. Respiration is an "involuntary" action; i.e., a person would continue to breathe despite being unconscious. However, within limits, individuals are capable of controlling the frequency and displacement magnitude of their respiration as well as breath holds. Unlike cardiac motion, the

respiratory motion is not rhythmic. The periodic cycle of respiration is regulated through chemoreceptors by the levels of CO_2, O_2, and pH in the arterial blood.

Anatomically, the lungs are held within the thoracic cavity, encased by the liquid-filled intrapleural space. Inhalation requires active participation of respiration muscles. During the inhalation part of quiet breathing, the increasing volume of the thoracic cavity draws air into the cavity. The most important muscle of inhalation is the diaphragm. As the diaphragm is contracted, it descends and the abdomen is forced inferiorly and anteriorly, increasing the superior-inferior (SI) dimension of the chest cavity. The intercostal muscles connect adjacent ribs and also participate in normal inhalation. They contract during inhalation, pulling the ribs superiorly and anteriorly, thereby increasing both the lateral and anterior–posterior (AP) diameters of the thorax. Exhalation is passive for quiet breathing. The lung and chest walls are elastic and return passively to their pre-inhalation positions at exhalation. Other ventilation muscles are involved only during active exhalation.

Transpulmonary pressure, the pressure difference between respired gas at the mouth and the pleural pressure around the lungs, is reduced during inhalation and is recovered during exhalation. During normal breathing, the deflating lung volume is larger than the inflating volume at the same transpulmonary pressure. This is called "hysteresis," attributable to the complex respiratory pressure volume relationship of the lung and chest wall.

Breathing pattern characterization measurements have been distinguished by posture (upright, prone, supine, lateral decubitus), breathing type (chest or abdominal), and depth of respiration (shallow, normal, deep). During normal respiration, the lung volume typically changes by 20% (from 3.3ℓ to 4.1ℓ on average in a 10-patient study[51]); at deep inhalation, the increase in lung volume is approximately three to four times that of normal breathing.[52]

B. Measuring respiratory motion

The lungs, esophagus, liver, pancreas, breast, prostate, and kidneys, among other organs, are known to move with breathing. We provide here a survey of published observations on organ motion due to respiration and other influences. The survey is not exhaustive, but is intended to provide guidelines for accommodating the motion during treatment. In many cases, the object being measured is the tumor or host organ itself, while in other cases it is an artificial marker implanted in or near the tumor, a surrogate organ such as the diaphragm.

Patients' breathing patterns can vary in magnitude, period and regularity during imaging and treatment sessions,[50,53–55] as demonstrated in Fig. 2. Systematic changes in the respiratory baseline also occur. Motion also varies markedly between patients, indicating that an individual approach to respiratory management is advised. Audio-visual biofeedback[54–56] has been demonstrated to improve respiratory reproducibility.

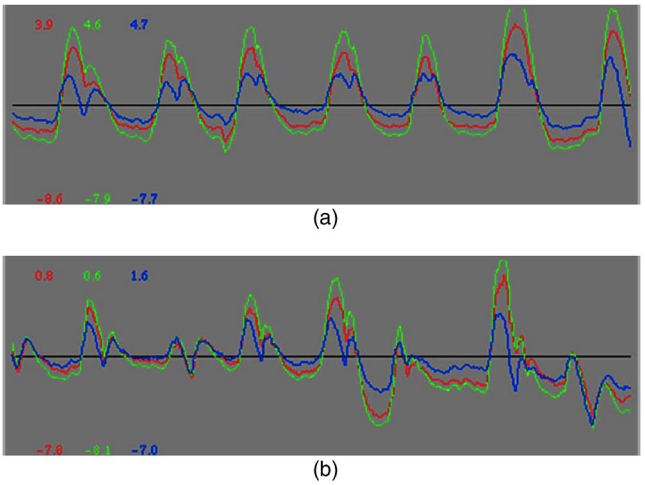

FIG. 2. Variations in respiratory patterns from the same patient taken a few minutes apart. The three curves in each plot correspond to infra-red reflector measured patient surface motion in the SI, AP, and ML directions, with each component arbitrarily normalized. In (a), the motion pattern is relatively reproducible in shape, displacement magnitude, and pattern. In (b), the trace is so irregular that it is difficult to distinguish any respiratory pattern. Figure courtesy of Dr. Sonja Dieterich.

C. Motion observables and observations

Organ motion has been detected via ultrasound,[57–59] CT,[60–63] magnetic resonance (MR),[64,65] nuclear medicine,[66,67] and fluoroscopy.[22,24,32,50,68–80] Respiratory motion studies have tracked the movement of the tumor,[24,49,60,61,74,79,80] the host organ,[57–59] radiographic fiducial markers embedded at the tumor site,[32,50,69,72,73,78] and surrogate organs, such as the diaphragm, which are assumed to correlate with the tumor.[53,63,71,76] These data are summarized in Tables I (lung) and II (abdomen).

Four-dimensional or respiratory correlated CT[81–88] using single-slice, multislice or cone-beam acquisition can provide three-dimensional (3D) data on tumor position at several points along the breathing cycle with a somewhat reduced temporal resolution, as compared with conventional CT, thus providing a compromise between the good time resolution of a fluoroscopic study and the detailed 3D information of a CT scan.

The investigators referenced in this section have published data based on anywhere from four[75,77] to fifty-one[67] subjects. Most of the published reports are based on cohorts of ten to thirty subjects. For the tumor sites discussed in this report, each set of published data has been condensed into a mean displacement and a full range of observed displacements.

Generally, abdominal organ motion is in the SI direction, with no more than a 2 mm displacement in the AP and lateral directions.[58,64] However, in some individuals, the kidneys show more complex patterns.[58] Lung tumor motions generally show a much greater variation in the trajectory of motion.

The amount a lung tumor moves during breathing varies widely. Stevens *et al.*[49] found that out of 22 lung tumor patients, ten subjects showed no tumor motion in the SI direc-

TABLE I. Lung tumor-motion data. The mean range of motion and the (minimum-maximum) ranges in millimeters for each cohort of subjects. The motion is in three dimensions (SI, AP, LR). AP: anterior-posterior; LR: left-right; SI: superior-inferior.

	Direction		
Observer	SI	AP	LR
Barnes: (Ref. 74) Lower lobe	18.5 (9–32)	-	-
Middle, upper lobe	7.5 (2–11)	-	-
Chen (Ref. 73)	(0–50)	-	-
Ekberg (Ref. 22)	3.9 (0–12)	2.4 (0–5)	2.4 (0–5)
Engelsman: (Ref. 24)			
Middle/upper lobe	(2–6)	-	-
Lower lobe	(2–9)	-	-
Erridge (Ref. 104)	12.5 (6–34)	9.4 (5–22)	7.3 (3–12)
Ross: (Ref. 60) Upper lobe	-	1 (0–5)	1 (0–3)
Middle lobe	-	0	9 (0–16)
Lower lobe	-	1 (0–4)	10.5 (0–13)
Grills (Ref. 80)	(2–30)	(0–10)	(0–6)
Hanley (Ref. 61)	12 (1–20)	5 (0–13)	1 (0–1)
Murphy (Ref. 77)	7 (2–15)	-	-
Plathow: (Ref. 65) Lower lobe	9.5 (4.5–16.4)	6.1 (2.5–9.8)	6.0 (2.9–9.8)
Middle lobe	7.2 (4.3–10.2)	4.3 (1.9–7.5)	4.3 (1.5–7.1)
Upper lobe	4.3 (2.6–7.1)	2.8 (1.2–5.1)	3.4 (1.3–5.3)
Seppenwoolde (Ref. 50)	5.8 (0–25)	2.5 (0–8)	1.5 (0–3)
Shimizu (Ref. 75)	-	6.4 (2–24)	-
Sixel (Ref. 79)	(0–13)	(0–5)	(0–4)
Stevens (Ref. 49)	4.5 (0–22)	-	-

tion. Of the remaining 12 subjects, the average SI displacement was anywhere from 3 to 22 mm (mean 8±4 mm). They found no correlation between the occurrence or magnitude of tumor motion and tumor size, location, or pulmonary function, suggesting that tumor motion should be assessed individually. Seppenwoolde *et al.*[50] measured 3D trajectories for 20 patients via dual real-time fluoroscopic imaging of a fiducial marker implanted in or near the tumor. They observed hysteresis in the trajectories of half the patients, amounting to a 1 to 5 mm separation of the trajectories during inhalation and exhalation, with four out of 20 patients exceeding a 2 mm separation. This indicates that in cases where high accuracy is required in dose alignment, a real-time tracking or gating process based on surrogate breathing signals should not only correlate with the tumor's motion along each axis with the breathing signal, but should have knowledge of the respiratory phase, because the phase difference is what leads to the hysteresis effect. In Fig. 3, motion trajectories during radiotherapy of lung tumors, measured using implanted gold markers, are depicted.[50]

TABLE II. Abdominal motion data. The mean range of motion and the (minimum-maximum) ranges in millimeters for each site and each cohort of subjects. The motion is in the superior-inferior (SI) direction.

		Breathing mode	
Site	Observer	Shallow	Deep
Pancreas	Suramo (Ref. 57)	20 (10–30)	43 (20–80)
	Bryan (Ref. 59)	20 (0–35)	-
Liver	Weiss (Ref. 66)	13±5	-
	Harauz (Ref. 67)	14	-
	Suramo (Ref. 57)	25 (10–40)	55 (30–80)
	Davies (Ref. 58)	10 (5–17)	37 (21–57)
Kidney	Suramo (Ref. 57)	19 (10–40)	40 (20–70)
	Davies (Ref. 58)	11 (5–16)	-
Diaphragm	Wade (Ref. 68)	17	101
	Korin (Ref. 64)	13	39
	Davies (Ref. 58)	12 (7–28)	43 (25–57)
	Weiss (Ref. 66)	13±5	-
	Giraud (Ref. 63)	-	35 (3–95)
	Ford (Ref. 76)	20 (13–31)	-

D. Summary of motion observations

A review of the respiratory motion literature leads to the following conclusion: There are no general patterns of respiratory behavior that can be assumed for a particular patient prior to observation and treatment. The many individual characteristics of breathing—quiet versus deep, chest versus abdominal, healthy versus compromised, etc.—and the many motion variations associated with tumor location and pathology lead to distinct individual patterns in displacement, direction, and phase of tumor motion.

In many cases, it is difficult or impossible to observe the tumor directly during treatment delivery prompting researchers to observe surrogate structure motion expected to have a close relationship with the tumor motion. If a surrogate structure, such as the chest wall or diaphragm, is used to signal tumor position for the purpose of beam gating or

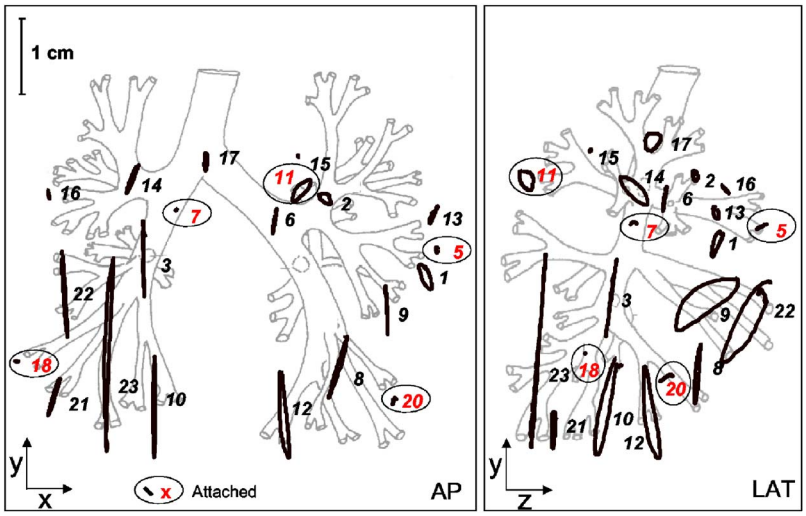

FIG. 3. Tumor trajectories (not to scale) in 23 lung tumor patients, measured using implanted markers and real-time stereoscopic fluoroscopy. From Ref. 50.

tracking, without observing the tumor directly during treatment, there will be uncertainties in the displacement and phase relationship between the surrogate and the tumor[89–91] or other anatomy.[53,92,93] A summary of such studies is given in Table III. It needs to be stressed that both surface markers and spirometers provide signals that are surrogates of tumor motion. Their applications should be validated by the users performing fluoroscopic and CT imaging studies. In a gating approach to motion compensation, the displacement correlation does not need to be known explicitly, because one is not trying to predict the absolute tumor position from the surrogate motion signal. The surrogate breathing signal only needs to indicate the phase of the breathing motion. However, it cannot be assumed *a priori* that the phase of the organ motion matches the phase of the surrogate motion, nor can it be assumed that the phase relationship is stationary. In fact, nonzero phase differences are evidence of either instability and nonstationary time behavior or multiple driving forces in complex oscillatory mechanical systems. These will be especially significant in the lung, where the mechanical coupling between the tumor and the surrogate structure is often weak, resulting in complex relationships between the two, and the breathing forces from the chest and/or the diaphragm. It should also be mentioned that implanted fiducial markers are also a surrogate for tumor motion, and their accuracy in depicting true tumor motion has yet to be studied.

TABLE III. Correlation of tumor/organ motion with the respiratory signal. 3D: Three-dimensional; AP: Anterior-posterior; CT: Computed tomography; MRI: Magnetic resonance imaging; s: Second(s); SI: Superior-inferior.

Organ/source	Respiratory signal	*N* patients (measurements)	Correlation range	Phase shift	Source
Diaphragm SI fluoroscopy	Abdominal displacement	5 (60)	0.82–0.95	Not observed	Vedam *et al.* (Ref. 53)
Tumor and diaphragm, fluoroscopy	Abdominal displacement	43	0.41–0.94	Short delays observed	Ahn *et al.* (Ref. 89)
Tumor, SI fluoroscopy	Spirometry and abdominal displacement	11 (23)	0.39–0.99	−0.65–0.5 s	Hoisak *et al.* (Ref. 90)
Tumor, 3D biplane radiography	Abdominal displacement	26	Respiratory waveform cycle agreed with SI and AP tumor motion	Principally within 0–0.3 s existence of > 1.0 s	Tsunashima *et al.* (Ref. 91)
Lung vessels, cine MRI	Abdominal displacement	4	SI 0.87±0.23, AP 0.44±0.27	-	Koch *et al.* (Ref. 92)
Lung tumor, respiration-correlated CT	Abdominal displacement	9 where tumor SI motion >5 mm	0.74–0.98	<1 s 4 pts <0.5 s 5 pts	Mageras *et al.* (Ref. 87)
Lung tumor, SI respiration-correlated CT	Diaphragm position	12	0.73–0.96	<1 s 4 pts <0.5 s 5 pts	Mageras *et al.* (Ref. 87)

V. COMMON ISSUES FOR RESPIRATORY MOTION MANAGEMENT

Issues that are common to all methods of respiratory motion management are discussed in this section, including treatment planning, QA, IMRT, and workload.

A. Treatment planning

Two useful articles that discuss important principles and provide guidelines for treatment planning for lung cancer radiotherapy have been published by Senan *et al.*[94,95] The main geometric consideration for treatment planning once the GTV and CTV have been defined is the CTV-PTV margin, which accounts for estimated geometric errors. In terms of target motion, the effect of all geometrical uncertainties is a displacement of the target during treatment relative to the dose distribution determined from the treatment plan. Considering the target as a static structure and the dose distribution as mobile allows the dose delivered to be summed over the time period of all fractions. When there are many fractions, the random errors can be accurately described as a blurring of the dose distribution.[96] The blurring is approximated as a convolution of the dose distribution with the probability distribution function of the total displacement vector of the target versus the treatment machine.[97,98] A convolution is not completely correct to describe the dose changes (see, for example, Refs. 99–101), but is quite accurate in practice.[102] Systematic errors cannot be accounted for by this approach, which makes pretreatment imaging procedures (as described above) and frequent monitoring during treatment particularly important to reduce them. The following components contribute to the overall geometric error and should be considered when designing CTV-PTV margins:

- Inter- and intraobserver variations in GTV[16–19] and CTV[20,21] delineation;
- motion artifacts in the CT scan, which cause target delineation errors;
- respiratory motion and heartbeat during delivery,[50] which are periodic functions of time;
- daily variations of respiratory motion;[50,54,55,103]
- variations caused by changing organ volumes;
- tumor growth and shrinkage;
- treatment-related anatomic changes, such as reductions in bronchiole obstructions and changes in atelectasis (collapsed lung) regions;
- patient setup error: Typical 3–5 mm (1 standard deviation).[18,22–28,104]

Note that respiration-motion management techniques not only affect the accuracy of target localization, but can also play a role in normal tissue sparing.[61,105] It is also important to note that fast tumor shrinkage occurs quite often in lung radiotherapy, which may give rise to systematic delivery errors.[104] The combined effect of random and systematic errors, including respiration, can be quantified in a dose-probability computation[106,107] or through biological modeling.[108,109]

B. Quality assurance

Quality assurance has a crucial role in all aspects of radiation oncology, as outlined in the report of AAPM Task Group 40.[110] This section describes QA techniques used in the management of respiratory motion. This section is divided into general descriptions and recommendations common to different methods of accounting for respiratory motion. QA procedures specific to each technique are described separately later.

A key issue in gated or breath-hold treatments using external respiratory monitors is the accuracy of such monitors in predicting internal target-organ position. As described earlier, internal/external correlation can be disturbed or lost completely by transient changes in breathing. For these reasons, patient training is important in allowing the patient to familiarize him- or herself with the breathing technique and for evaluating his or her ability to achieve reproducible respiratory signals. Breath-hold methods in particular require active patient participation. They also call for special staff effort, as therapists must be trained to coach and advise the patients. The limitations of equipment should also be understood (for example spirometer drifts) so that when issues occur during simulation or treatment the diagnosis and correction of the issue is timely.

Some respiratory motion management techniques involve additional devices that come into contact with the patient, thus hygiene practices for the safety of the patient and the staff need to be established. Generally, devices that come into contact with patient mucosal surfaces should be discarded after use; devices that come into contact with the patient skin can be reused provided appropriate procedures are followed.

Frequency: As with all QA procedures, the appropriate tests should be performed after any hardware or software changes or after service or changes to the respiratory motion management device itself or the equipment (CT scanner, fluoroscope or linear accelerator) interfacing with the respiratory motion management device. Furthermore, until familiarity with the system is sound, QA may be performed more frequently as determined by the physicist and the nature of the test.

Patient training: The ability to achieve reproducible breathing or breath-hold patterns is a requirement for allowing the patient to proceed to simulation and treatment. In particular, this affects the self-consistency of a CT scan that spans multiple respiratory cycles or breath holds and the reproducibility of patient anatomy between simulation and treatment. Prior to the start of simulation, the patient should be made familiar with the equipment and its purpose. A physicist or trained designee should perform the coaching and evaluation at least in the initial clinical implementation. For breath-hold techniques, the training session, consisting of a series of breath holds in the treatment position, establishes the patient's respiratory level for treatment and breath-hold duration.

Simulation: By viewing the patient with fluoroscopy or ciné CT, the magnitude of respiratory motion and the corre-

lation between the tumor motion and the respiratory signal can be evaluated. For breath-hold techniques, one should verify that the tumor position (or other anatomic surrogates if the tumor is not visible) is stable within each breath hold and reproducible between breath holds. Patients who cannot hold their breath for the entire duration of the CT scan will require segmentation of the scan region (ideally not through the target) to permit shorter breath holds. If the potential exists that the patient will be unable to comply with breathing or breath-hold techniques for treatment, a backup CT scan without such a requirement is recommended during simulation.

Treatment: At the start of the first treatment fraction, the patient should be reacquainted with the equipment, including practiced controlled breathing or breath holds. For breath-hold techniques, it is preferable to deliver a treatment field in a single breath hold. If the duration of this breath hold is too long for patient comfort, careful documentation in the chart should be made about break points for individual beams. The therapists will need to monitor the treatment machine, the patient, and the gating or breath-hold system display.

Radiographs to check internal constancy: Although external monitors may correlate well with the respiratory organs within a single session, thus reducing *intrafractional* variations, the relationship between external monitor and internal organ positions may change between sessions, which can adversely affect organ reproducibility and produce *interfractional* variations. A program of frequent radiographs of the surrogate organ (or target, if visible) throughout treatment is essential to measure interfractional variations and should be acquired during the respiratory cycle part or breath hold used for simulation and treatment. Sometimes, lung tumors are sufficiently discernible in the radiographs to allow direct confirmation of their position. Daily verification is recommended for the first few treatments, followed by (at least) weekly verification to ensure that the anatomy at the respiratory position used for treatment remains constant. If the radiographs indicate differences from simulation, the dosimetric consequences and remedies are evaluated by the physicist and the physician. For treatment machines with an exit detector, more advanced verification techniques are possible. For example, ciné-mode acquisition, by which several images are acquired during each field delivery, may be utilized.

As with all radiotherapy procedures, constant vigilance by the treatment staff is important. Training and education for all staff involved with respiratory management, as well as periodic retraining, is recommended. A physicist should be available to solve any hardware-related problems.

C. Intensity modulated radiation therapy

IMRT has seen widespread application owing to its ability to conform the spatial distribution of the dose deposited in a patient more effectively. The implications for targets in the thoracic and abdominal regions have been particularly important due to the many organs at risk in these regions. However, respiratory motion intuitively presents considerable issues for IMRT delivery, since beam-intensity gradients are no longer confined solely to the edges of the beams. Rather, such gradients can be *inside* the field defined by the primary collimators. Thus, if a target is *also* moving inside this same field with its own period unique from the MLC leaves and possibly deforming, it is easy to understand why there are concerns over the use of IMRT with targets affected by respiratory motion. Yu *et al.*[111] (see also Kissick *et al.*[112]) demonstrated this effect using theoretical models that yielded dose variations for "clinically relevant parameters" of up to 100%. In a dynamic wedge simulation, Pemler *et al.*[113] showed that the magnitude of dosimetric errors may approach 15% for a single dynamic wedge treatment. Bortfeld *et al.*[114] demonstrated dosimetric errors on the order of ±8% for a single point in the middle of the treatment field (low-dose gradient region) in the simulation of a single IMRT treatment. Kubo and Wang[115] and Keall *et al.*[116] analyzed the dosimetric error for a single MLC-based IMRT treatment using film. In each study, films of treatments delivered with and without motion were compared. To simulate motion, film was moved a distance and at a rate consistent with respiratory motion. Errors of up to 20% were reported within the field (low-dose gradient region), with even larger errors on the edges of the field (high-dose gradient regions).

Based on these findings, it would seem that the concern over potential dosimetric error introduced by respiratory motion for IMRT treatments is justified; however, Yu *et al.*[111] showed that fluence variations within a moving target tend to average out over the typical course of 30 fractions, when one assumes that the breathing phase or frequency is random from day to day. Along similar lines, Bortfeld *et al.*[114] showed that *dosimetric* errors introduced by respiratory motion also tend to average out with fractionation; this was further supported in MLC-based IMRT studies by George *et al.*[117] and Chui *et al.*[118]

In a follow-up study, Jiang *et al.*[119] experimentally verified the findings of Bortfeld *et al.*[114] for a single point in a low-dose gradient region using MLC-based IMRT; however, these studies assumed or applied simplistic, one-dimensional (1D) motion, which can be quite different from the real, complex phenomenon of breathing.[50,78] Furthermore, target deformation may be present, although this deformation has yet to be quantified. They, therefore, cautioned that fractionation alone should not be relied on, at least in cases of large (>1 cm) motion, until their findings could be verified under more realistic conditions.

To summarize, the above studies indicate that caution is warranted when considering IMRT for targets subject to respiratory motion, particularly for single or few-fraction treatments common for stereotactic body radiotherapy. For individuals who still intend on using IMRT without any direct motion-correction strategy, it needs to be emphasized that the full extent of breathing motion should be assessed and considered when assessing margins for the treatment plan. Even with correction strategies, there can still be residual target motion with respect to the beam, for example, with respiratory gated treatment, which may exhibit similar, albeit smaller, effects.

TABLE IV. Summary of intra- and inter-fractional variations for different methods of respiratory management. Abbreviations: BH—breath-hold, ABC—active breathing control, SD—standard deviation, LR—left-right, AP—anterior-posterior, SI—superior-inferior, DIBH—deep inspiration breath-hold, * includes setup error, 3D—3-dimensional error, mDIBH moderately deep inspiration breath-hold. (Ref. 200).

Reference	Technique	Organ	Intra-fraction variation (cm)	Inter-fraction variation (cm)
Cheung (Ref. 201)	BH at inspiration with ABC	Lung tumor	-	SD: 0.18 LR, 0.23 AP, 0.35 SI
Dawson (Ref. 202)	BH at exhalation with ABC	Diaphragm	SD: 0.25	SD: 0.44
Ford (Ref. 76)	Gating at exhalation with RPM	Diaphragm	Mean: 0.26 SD: 0.17	Mean: 0.0 SD: 0.39
Hanley (Ref. 61)	DIBH	Diaphragm	SD: 0.25	-
Mah (Ref. 160)	DIBH	Diaphragm	-	0.4*
Negoro (Ref. 170)	Abdominal compression with stereotactic body frame	Lung tumor	Mean 3D: 0.7 Range: 0.2–1.1	Mean 3D: 0.5* Range: 0.4–0.8*
Remouchamps (Ref. 203)	mDIBH with ABC	Diaphragm	Mean: 0.14 SD: 0.17	Mean: 0.19 SD: 0.22
Wagman (Ref. 133)	Gating at exhalation with RPM	Abdominal organs	Mean: 0.20	-

D. Workload

Respiratory motion management techniques utilize specific technology that requires increased medical supervision and longer treatment times for the delivery of this precise treatment. Additional physics, physician and therapist support is required during the simulation, planning and treatment processes, which are described in more detail below. If imaging procedures are performed, further resources are involved. When acquiring a respiratory management device for clinical use, there are capital costs, staff training costs and time, acceptance testing and commissioning procedures to be performed as well as the development and execution of ongoing QA and staff education and training programs.

Before simulation, the scheduling of patients that are identified by physicians includes relaying the information about potential patients to the physics group. Depending on the respiratory management technique, the physics group may need to schedule a training session with the patient, which can take up to one hour with the patient and an additional half-hour to full hour to assemble the equipment for this training session. A physicist (or designated staff member who is appropriately trained to manage the procedure) then needs to be present for the CT imaging session. The physicist may need to evaluate the quality of the imaging study and, if necessary, repeat the imaging study. Some respiratory management devices have patient-specific disposable accessories that need to be ordered, purchased and stored. The treatment planning may require special instructions and physics oversight which can take several hours in some cases.

At many institutions, a physicist is required to be present for the first treatment with respiratory management procedures. Coaching the patient at simulation and on the first day of treatment is fairly common and recommended. For some techniques and patients, further coaching is needed. Finally, a review and QA of the respiratory traces or images acquired at the time of treatment needs to be done. Currently, this requires approximately two hours of work per patient. There are also material and machine time considerations. Time required at the CT scanner is longer, treatment times are longer, and a room may be required for an hour-long training session. The extra time at an accelerator has the cost of decreased patient throughput. There is also the capital investment, use and depreciation costs of the equipment used for these treatments.

VI. METHODS TO ACCOUNT FOR RESPIRATORY MOTION IN RADIOTHERAPY

Methods to reduce the impact of respiratory motion in radiotherapy can be broadly separated into five major categories: Motion-encompassing methods, respiratory gating techniques, breath-hold techniques, forced shallow-breathing techniques, and respiration-synchronized techniques. These methods are discussed in detail in this section. A summary of published intra- and inter-fractional variations for the different methods is given in Table IV.

A. Motion-encompassing methods

1. Introduction

This section discusses imaging and treatment-planning guidelines for tumor sites affected by respiratory motion. Since respiratory induced tumor motion will be present during radiation delivery, it is important to estimate the mean position and range of motion during CT imaging.

The three techniques possible for CT imaging that can include the entire range of tumor motion for respiration (at the time of CT acquisition) are slow CT, inhalation and exhalation breath-hold CT, and four-dimensional (4D) or respiration-correlated CT. These are listed in order of increasing workload. It is important to understand that the

breathing patterns and, hence, tumor motion will change between simulation sessions and treatment sessions. Furthermore, the radiation dose to the patient from these imaging procedures can be greater than standard CT simulation procedures by a factor of 2–15 if no efforts are made to reduce CT dose.

2. Slow CT scanning

One solution for obtaining representative CT scans for peripheral lung tumors is slow scanning.[120–122] The CT scanner is operated very slowly, and/or multiple CT scans are averaged such that, on average, multiple respiration phases are recorded per slice. Hence, the image of the tumor (at least in the high-contrast areas) should show the full extent of respiratory motion, provided that the scanner operates at a particular couch position for longer than the respiratory cycle. This technique yields a tumor-encompassing volume, with the limitation that the respiratory motion will change between imaging and treatment, and, thus, additional margins are required to account for these variations. In addition to anatomic delineation, slow scanning is more advantageous than standard scanning, because the dose calculation is performed on a geometry that is more representative of that during the entire respiratory cycle, as occurs during treatment. The disadvantage is the loss of resolution due to motion blurring, which potentially leads to larger observer errors in tumor and normal organ delineation. Due to motion blurring, this method is only recommended for lung tumors that are not involved with either the mediastinum or the chest wall. This method is also not recommended for other tumor sites (e.g., the liver, pancreas, kidney, etc). It has been suggested that PET, with its inherently long acquisition times, is also a good solution for estimating the motion path of a tumor;[44–47] however, motion can also blur the object in the PET image such that a suspicious lesion may not even be apparent, in which case respiration-gated PET or 4D PET may be a better option.

3. Inhalation and exhalation breath-hold CT

A solution to obtaining a tumor-encompassing volume that can be implemented in most clinics is to acquire both inhalation and exhalation gated or breath-hold CT scans of the patient during the CT simulation session. Taking both inhalation and exhalation CT scans will more than double the CT scanning time and relies on the patient's ability to hold his or her breath reproducibly. The two scans require image fusion and extra contouring. For lung tumors, the maximum intensity projection[123] (MIP) tool (the MIP image in this context for a set of CT images is the maximum CT number found in a given voxel in the set) available in most visualization systems can be used to obtain the tumor-motion-encompassing volume, provided there is no mediastinal tumor involvement. The advantage of this approach over the slow scanning method mentioned above is that the blurring caused by the motion present during FB is significantly reduced. Dose calculation should be performed on the CT data set that is most appropriate for the particular patient, e.g., exhalation CT for patients generally spending more time at exhalation than inhalation. The exhalation scan will tend to underestimate the lung volumes and, hence, overestimate the percentage of lung volume receiving a specific dose. To save time, a free-breathing CT could be used for the entire scan region (typically including the entire thoracic cavity), with either breath-hold or gated CT scans at inhalation and exhalation of a scan length sufficient to cover the tumor volume to determine the range of motion of the GTV. Some form of respiratory monitoring is necessary to verify gating or breath-hold constancy and to ensure that the scans are representative of the patient's normal breathing range.

Breath-hold scans can also potentially be used for respiratory gated delivery, however, it should be noted that a respiratory gated CT scan is preferred over a breath-hold scan at the same respiratory position, because the predominant respiratory muscles can be different for breath hold and FB (e.g., intercostal vs. diaphragm), and any tumor lag (relative to the external monitor) occurring during FB will be absent during breath hold.

4. Four-dimensional CT/respiration-correlated CT

A promising solution for obtaining high quality CT data in the presence of respiratory motion is 4D CT or respiration-correlated CT (conventional and cone-beam approaches).[81–88,124,125] Four-dimensional data can be analyzed to determine the mean tumor position, tumor range of motion for treatment planning,[123,126–128] and the relation of tumor trajectory to other organs and to a respiration monitor.[87] A limitation of 4D CT is that it is affected by variations in respiratory patterns during acquisition. Breathing-training techniques have been developed,[56] however, even with these techniques artifacts can be observed.[86]

A 4D CT scan can be obtained in approximately a minute of scanning time with a 16-slice CT scanner. Generally 8–25 complete CT data sets are reconstructed, the optimal use of which has yet to be determined. Four-dimensional CT can be used to reconstruct inhalation, exhalation, and slow CT scans.[86] The MIP tool, as mentioned above, may be useful in obtaining the tumor-motion-encompassing target volume. Another motion-encompassing method is to derive a single set out of the 4D CT scan where the tumor is close to its time-averaged position. In that case, the expected dose blurring effect of respiration can be accounted for in the CTV-PTV margin.[129]

B. Respiratory gating methods

1. Introduction

Respiratory gating involves the administration of radiation (during both imaging and treatment delivery) within a particular portion of the patient's breathing cycle, commonly referred to as the "gate." The position and width of the gate within a respiratory cycle are determined by monitoring the patient's respiratory motion, using either an external respiration signal or internal fiducial markers. As the beam is not continuously delivered, gated procedures are longer than nongated procedures.

Respiratory gating is currently under study by several centers to account for respiratory motion during radiotherapy of thoracic and abdominal tumors.[53,56,76,130–134] Respiratory motion can be characterized by two variables that are recorded as part of the respiration signal or the motion of the internal anatomy. These variables are (a) displacement and (b) phase. Accordingly, the method of gating is referred to as either displacement gating or phase gating. The displacement of the respiration signal measures its relative position between two extremes of breathing motion, namely, inhalation and exhalation. In displacement-based gating, the radiation beam is activated whenever the respiration signal is within a pre-set window of relative positions. The second variable, phase, is calculated by an algorithm from the respiration signal that must satisfy periodicity criteria; the radiation beam is activated when the phase of the respiration signal is within a pre-set phase window. Further details of displacement-based and phased-based gating can be found in Vedam *et al.*[145] Typically, a gate extends over a region of the breathing cycle where the motion of the tumor is estimated to be less, (generally end exhalation), or where the lung volume is maximal (end inhalation). The ratio of the beam-on time within the gate to the overall treatment time is referred to as the duty cycle and is a measure of the efficiency of the method. Some tumor motion still occurs within the gate and is referred to as "residual motion."[135] The choice of gate width is a tradeoff between the amount of residual motion and duty cycle.

2. Gating using an external respiration signal

Currently, the commercially available respiratory gating system using an external respiration signal most widely discussed in publications is the Real-time Position Management (RPM) system (Varian Medical Systems, Palo Alto, CA); thus, the procedures described here are applicable to this device, although they can be generalized to other implementations. BrainLab (Westchester, IL) has an FDA-cleared respiratory gating device, called "ExacTrac Gating/Novalis Gating." This device uses external markers for gating the radiation beam, however, it has x-ray imaging capabilities for determining the internal anatomy position and for verifying the reproducibility of the internal anatomy during treatment. Siemens Medical Systems (Concord, CA) also has an FDA-approved linear accelerator gating interface and an Anzai belt (used for CT), also approved for use in therapy. Three-dimensional video camera surveillance has also been studied for respiratory motion management.[136]

Owing to its noninvasive nature, gating using an external respiration signal can be applied to almost all ($>90\%$) patients. Breathing training may be beneficial in many cases and can improve the likelihood of the patient completing the simulation session. With the Varian RPM system, an infrared reflective plastic box serving as the external fiducial marker is placed on the patient's anterior abdominal surface, typically midway between the xyphoid process and the umbilicus, and chosen to maximize the AP respiratory induced motion. The marker box should be placed nearly horizontally, to permit the in-room camera to accurately detect the reflective markers. If used during treatment, a durable skin mark at the box location should be made at the time of imaging to ensure reproducible positioning during treatment.

Prior to a gated CT scan, determination of gating parameters (displacement or phase, exhalation or inhalation, duty cycle) are based on observation of the external respiration signal and, if possible, tumor motion. In prospective gated CT, a respiration gating system sends a trigger to the CT scanner to acquire a CT slice. CT scan parameters (slice thickness, scanner rotation time, index, etc.) remain the same as those used for standard CT scans. Gate width and CT scan rotation time should be similar. Shorter gate width results in anatomic positions outside the intended gate to be included in the image, while longer gate width results in more anatomic motion occurring during the gate than is captured in the CT image. Either situation is a potential source of error. Note that not all CT scanners can perform prospective gating. The time required to acquire a prospective gated CT scan depends on the patient's respiratory period, since there is one slice triggered per cycle. Irregular breathing can further prolong the CT acquisition and/or lead to acquisition of slices at the wrong part of the breathing cycle.

At treatment, marker block position and patient breathing instructions are the same as during simulation. Once a stable respiration trace has been established and gating thresholds are verified, gated radiation delivery is initiated. The position of the patient's internal anatomy is verified using in-room imaging. During treatment the therapist should be alert to the graphical cues on the gating system monitor and be prepared to intervene if the patient's breathing is very irregular or different from simulation. In-room images that show the tumor, if possible, or an internal anatomic surrogate (often the diaphragm) are helpful in assessing the performance of the gating system over the course of treatment.[81,137]

For internal and external tracking systems, a possible source of error is that the surrogate for tumor motion (e.g., tracking blocks, strain gauges, etc.) tracked by the gating system does not accurately correspond with the time-dependent target position (Fig. 4). This can cause the timing of the beam-on pulse to shift relative to the actual respiratory cycle of the target. Where available, a minimum of 30 s of imaging data (fluoroscopy or CT ciné mode) should be digitally recorded in conjunction with the measured respiration trace. The motion of the GTV—or anatomic surrogate such as the diaphragm, if the GTV is not discernible—should be compared with the external respiratory signal; a time delay larger than 0.5 s between the two, if consistently observed, should be corrected or accounted for when setting the gate interval. An EPID-based approach for position verification in this manner has been proposed by Berbeco *et al.*[138]

Dynamic test phantoms that simulate respiration are needed, in order to test *in vivo* dosimetry and target localization. There are several important factors: (1) The phantom should produce cyclical motion similar to human respiration; (2) the gating feedback mechanism must detect phantom motion in a manner similar to the clinical process; (3) the device should allow attachment of dose measuring detectors, such

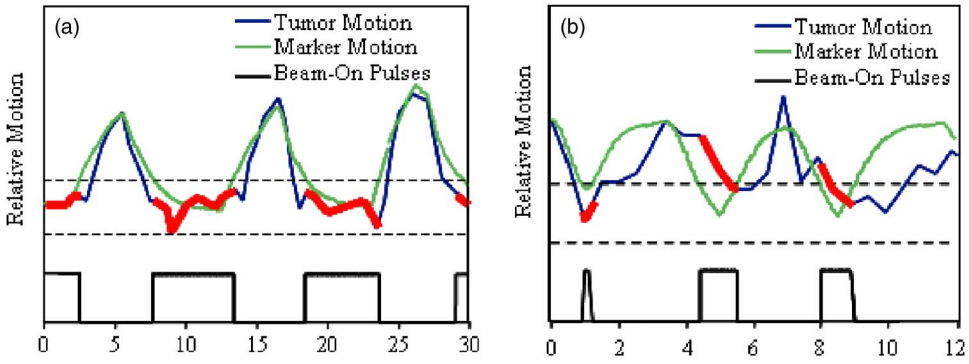

FIG. 4. Comparison of external marker block motion with internal motion of the clinical target volume (CTV) for a patient with (a) no phase shift and (b) a patient with significant phase shift. The respiratory gating thresholds are set using the external marker block motion. The beam-on pulses are highlighted in red over the internal CTV position. From Ref. 204.

as ion chambers or diodes; (4) the phantom should be reliable and have a reasonable cost. Several custom-built phantoms have been made to meet these criteria,[86,116,119,139–143] and commercial systems are available. Ramsey *et al.* describe further equipment QA tests for the Varian RPM respiratory gating system.[139]

3. Gating using internal fiducial markers

This section focuses on the real-time tumor-tracking radiotherapy system, developed jointly by Hokkaido University and Mitsubishi and based on radiographic detection of implanted fiducials to gate radiation delivery.[50,70,75,144–150] The fiducials (2 mm diameter gold spheres) are implanted in or near the tumor using a percutaneous or bronchoscopic implanting technique. Fiducial position is tracked in all three dimensions several times a second using a pair of stereotactic kilovoltage x-ray imaging systems in combination with automatic detection software. The linear accelerator delivers radiation when each fiducial is within an acceptable range of the desired (simulation) position for both stereotactic x-ray cameras.

Patient selection begins with assessment of tumor motion prior to fiducial implant, to ensure maximum benefit to the patient with this invasive procedure. The patient must be able to tolerate the implant procedure and remain motionless on the treatment couch for an extended treatment (up to 45 min). For patients with lung cancer, pulmonary function criteria are set, based on the recommendation of the pulmonologist performing the implant. Because this technique has been primarily used for stereotactic radiotherapy, most of the patients have had relatively small lesions (4 cm in diameter or less).

Treatment simulation uses a series of CT scans: a normal, free breathing scan; a breath-hold scan at inhalation, and a breath-hold scan at exhalation. Treatment plans are designed on both the inhalation and exhalation set of CT images, and the radiation oncologist selects the best plan based on the dose distribution, assessing if increased lung sparing is found on the inhalation plan. Six to ten static fields are used to deliver 48 Gy in four fractions. The implanted fiducials are identified in the planning system, and DRRs are generated to replicate the images to be acquired in the treatment room.

At the beginning of each treatment, the fiducial path is monitored for several breathing cycles and the patient repositioned, if needed, so that at the appropriate point in the breathing cycle, the fiducial marker passes near the predicted location. Two gates, one from each imaging system, must be in coincidence to enable the beam. Treatment times are typically longer than 30 min, and the duty cycle varies by patient and by the choice of respiratory cycle part to be used for treatment.

QA procedures include confirmation that the coordinate systems of the fluoroscopy unit and linear accelerator are properly aligned. The coordinate system alignment should be checked regularly, since there is a potential for drift with both systems. The magnitude of marker motion detected by the system needs to be verified, and it must also be assured that the automated tracking of the internal fiducial markers is robust.

4. Gated IMRT

Kubo and Wang[115] demonstrated the feasibility of gating the linear accelerator during a dynamic MLC delivery. They showed that the dosimetry for gated IMRT delivery that included motion (1D mechanical device) was essentially the same as that for delivery without motion. Target deformation was not considered.

Respiratory gating techniques increase the treatment time. This is more pronounced for gated IMRT in which the product of the IMRT efficiency, typically 20%–50%, and the gating duty cycle, 30%–50%,[76,133] leads to a 4- to 15-fold increase in delivery time. Increasing dose rate from 300 to 600 MU/min can reduce the clock time by approximately 40%.[134] Gated treatment session times are increased relative to standard treatments by 2–10 min depending on patient compliance.[134] Considerations with increased delivery time are patient comfort, increased likelihood of patient movement and decreased patient throughput. During substantially longer treatments, it has been suggested that tumor control may be reduced due to the increased intrafraction repair of sublethally damaged tumor cells.[151,152]

C. Breath-hold methods

1. Introduction

Breath hold methods have been predominantly applied to lung cancer radiotherapy. Breast cancer radiotherapy may also potentially benefit: although intrafraction motion is

small for normal respiration,[153] during inhalation the diaphragm pulls the heart posteriorly and inferiorly away from the breast, and thus may reduce both cardiac and lung toxicity.[154–159]

2. Deep-inspiration breath hold

A reproducible state of maximum breath hold (deep-inspiration breath hold or DIBH) is advantageous for treating thoracic tumors, because it significantly reduces respiratory tumor motion and changes internal anatomy in a way that often protects critical normal tissues. This section describes a spirometer-monitored technique that was developed and clinically implemented primarily for conformal radiation treatments of NSCLC at the Memorial Sloan-Kettering Cancer Center (MSKCC).[61,160,161] There are at least two commercial spirometry products that are compatible with the DIBH technique: The VMAX Spectra 20C (VIASYS Healthcare Inc., Yorba Linda, CA) and the SpiroDyn'RX (Dyn'R, Muret, France). Forty-five patients have been treated with DIBH at MSKCC (44 with NSCLC) between 1998 and 2004; of these, eight were treated with DIBH in combination with IMRT.

The DIBH technique involves verbally coaching the patient to a reproducible deep inhalation breath hold during simulation and treatment. The patient breathes through a mouthpiece connected via flexible tubing to a spirometer. The naris is held closed with a nose clip. A computer program displays and records the volume of air breathed in and out as a function of time. The therapist coaches the patient through a modified version of the slow vital capacity maneuver, consisting of a deep inhalation, deep exhalation, second deep inhalation and breath hold. The maneuver yields highly reproducible lung inflation at approximately 100% capacity, which can be maintained for 10–20 s (patient specific).

Applicability of DIBH is limited by patient compliance: Approximately 60% of the lung cancer patients at MSKCC cannot perform the maneuver reproducibly enough to permit its use; thus it is used only for compliant patients in whom the significant lung inflation allows treatment to a higher total dose (10% or more with acceptable normal tissue dose-volume histograms and calculated lung complication probability[161]) than is possible with free breathing treatment.

Following a brief DIBH practice session, the patient receives three helical CT scans in the treatment position: (1) With FB; (2) with spirometer-monitored deep inhalation (DI); and (3) with spirometer-monitored inhalation. The FB and inhalation scans are for QA purposes, described below. The FB scan also serves as the alternative treatment plan CT if the patient cannot be completely treated with DIBH. The simulation process—including immobilization, isocenter selection, practice, 3 CT scans and resting between scans—takes approximately 2 hr. The treatment plan and DRRs use the DI breath-hold CT scan.

During treatment, the therapists are instructed to turn on the beam only when the target breath-hold level has been achieved and to stop treatment if the level has fallen below a pre-set tolerance. For static conformal treatments at 2 Gy/fraction on linear accelerators operated at 500–600 MU/min, a single breath hold is usually sufficient for each field. More recently, IMRT in combination with DIBH has been introduced for patients able to hold their breath long enough to complete a field, approximately 20 s for a typical beam-on time of 200 MU delivered at 600 MU/min with the sliding window technique.[159] Treatment sessions usually take 5–10 min longer than a similar beam arrangement for an FB patient.

Patient-specific QA includes a check of the FB scan that the patient's state of respiration does not alter the position of the spine, thus allowing positioning of the patient for treatment while breathing normally. The inhalation scan is used to set breath-hold tolerance levels by determining the motion extent of the GTV for a known change in breath-hold volume.[160] In all imaging and treatment sessions, the therapist is instructed to wait 1 s following breath hold before turning on the beam, to allow for transient diaphragm relaxation.[160]

The spirometer is calibrated with a 3ℓ syringe for flow rates between approximately 0.5 and 3 ℓ/s. The linearity of spirometer integrated airflow versus actual (syringe) volume is checked over a range of 0–3ℓ in either flow direction; typical linearity is within 2%. The calibration is checked whenever the spirometer is gas sterilized, approximately every 2 to 3 mo. Occasionally, drift of the spirometer is observed following sterilization, which is usually correctable by reassembling the device.

3. Active-breathing control

Active-breathing control (ABC) is a method to facilitate reproducible breath hold.[157,162] The ABC method was developed at William Beaumont Hospital and is currently commercialized by Elekta Inc. (Norcross, GA) as the Active Breathing Coordinator. A device with similar capabilities, called the Vmax Spectra 20C, is available from VIASYS Healthcare Inc. (Yorba Linda, CA). The ABC apparatus can suspend breathing at any predetermined position and is often used at moderate or deep inhalation. It consists of a digital spirometer to measure the respiratory trace, which is in turn connected to a balloon valve. In an ABC procedure, the patient breathes normally through the apparatus. The operator specifies the lung volume and stage of breathing cycle stage to "activate" the system, at which the balloon valve is closed. The patient is instructed to reach the specified lung volume, typically after taking two preparatory breaths. The valve is inflated with an air compressor for a pre-defined duration of time, thereby "holding" the patient's breath. The breath-hold duration is patient dependent, typically 15–30 s, and should be well tolerated to allow for repeated (after a brief rest period) breath holds.

The Beaumont experience[157,158,163] shows that a moderate (deep) inhalation breath-hold (mDIBH) level set at 75% of deep inspiratory capacity achieves substantial and reproducible internal organ displacement while maintaining patient comfort. The intended mDIBH position is calculated from the exhalation baseline and set during an initial training ses-

sion for each patient. Verbal instructions are always given to help a patient achieve a steady breathing pattern.

Prior to the start of simulation a series of baseline measurements should be made. Depending on the system, a pulmonary function test (PFT) may be needed at this time to provide reference data on the individual patient's lung capacity. Practice breath holds should be performed, and the patient instructed of various means of indicating discomfort and signaling cessation of breath hold to the operators. The CT scan should be optimized according to the maximum reproducible length of breath hold in an immobilized position; the timing of contrast should coincide with the appropriate breath-hold scan of the region of interest. The breath-hold state, as well as duration of comfortable breath hold, should be documented for use during treatment.

Treatment plans include a margin dependent on the intended treatment verification strategy. If the patient is to be treated daily without image guidance, the margin should consider setup variation along with the long-term reproducibility of ABC. The magnitudes of these margins for the patient population in each clinic should be established for routine application of the ABC procedure.

Treatment at each beam angle should be delivered in a single breath hold, when possible. If a single breath-hold is too long, then one can "break up" the single breath-hold into two or more smaller breath-holds. These smaller breath-holds should be recorded particularly if they are coordinated with the delivery of IMRT segments on earlier accelerators which require the "breakup" segments as individual beams. Each beam needs to be delivered before releasing the patient from breath-hold.

An important concern of patient-related QA is reproducibility of breath hold. It is essential that all operating personnel understand system functions and that the patient receive and understand appropriate instruction. The process for establishing a breath hold at a given state (e.g., exhalation, inhalation, deep inhalation) should be documented and tested. A standard set of patient instructions for communication with the ABC operator and for emergency actions to reestablish breathing is recommended. It is important to establish a hygienic procedure for cleaning reusable items (e.g., rubber mouthpiece).

The key functions that should be maintained and checked frequently for safe use of an ABC system are the calibration of airflow and volume, the ability to stop and restart air flow, and the safety release mechanisms. It is important to understand how the ABC unit establishes a breathing trace. Current systems use mechanical spirometers or temperature sensors. The calibration for the temperature sensor is absolute, whereas the spirometer-based system operates by establishing a baseline at each exhalation. Both systems are typically calibrated using a 3.0ℓ syringe. Apart from the vendor's recommended calibration, the volume calibration should be checked at different flow rates similar to those seen in patients. The minimum flow rate below which the mechanical spirometer will not respond accurately should be established.

The equipment needed to provide ABC may affect the processes of simulation and treatment. The air tube exiting the mouth, the chamber for breathing monitoring and control, and ancillary hardware may occupy significant space, possibly restricting the geometry of the CT scanner or treatment unit. Prior to implementing ABC for a given body site, the processes of immobilization, simulation and delivery should be evaluated to determine an efficient means of integrating the ABC unit and support equipment.

4. Self-held breath hold without respiratory monitoring

In this technique the patient voluntarily holds his/her breath at some point in the breathing cycle, during which dose delivery occurs. A control system for its implementation has been developed[74,164] for the Varian C Series accelerators, which makes use of the "Customer Minor (CMNR)" Interlock. The patient depresses a hand-held switch to clear the CMNR interlock, allowing the therapist to activate the beam. Releasing the switch asserts the CMNR interlock, turning the beam off and disabling any further delivery until the switch is depressed again. Although only the therapist can turn the beam on, both the therapist and the patient can turn the beam off. The potential dosimetric advantages of increasing the lung volume[61,157,158,161,163] makes deep inhalation the preferred point for breath hold. Therefore, the earlier discussion of DIBH and ABC would be similar to the advantages with this method. The self-held breath-hold system is not commercially available.

This mode of treatment relies heavily on the patient's ability to understand and perform a reproducible breath hold, maintain it for at least 10 s, and simultaneously operate the hand-held switch. Another selection criterion is the stability of internal anatomy during breath hold: Some patients have been observed to have continuous diaphragm motion during breath hold, even though they believe they are holding their breath. Following evaluation under fluoroscopy on a conventional simulator, patients receive a breath-hold CT scan, in which the scan sequence is segmented into 10 s acquisitions. Patients are given a switch attached to a buzzer, which they depress to indicate to the CT therapist when they are holding their breath.

Determination of PTV margins should take into account breath-hold reproducibility, as well as patient setup reproducibility and internal motion. Setup reproducibility will depend on a department's patient-positioning procedures and immobilization devices and has been shown to have one standard deviation of about 5 mm for typical techniques.[18] Barnes *et al.*[74] showed that on average the margin for internal motion in the SI direction was reduced from 12.9 to 2.8 mm using the held-breath self-gating technique. Until sufficient statistical data are available, it is recommended that the margin be tailored to the individual patient by measuring the reproducibility during the simulator session, remembering that interfractional variations do occur and should be considered. The choice of breath-hold position will affect the volume of lung and hence the dose distributions that are potentially achievable.

Treatment with self-held breath-hold gating is relatively straightforward and efficient. When the therapist is ready to switch the beam on, he/she instructs the patient over the intercom to perform the breath-hold maneuver and depress the switch. If the patient needs to breathe prior to the field being completed, he/she simply releases the button to turn off the beam, then repeats the breath-hold maneuver and presses the button, allowing the therapist to resume treatment.

The "held-breath self-gating" technique[74] has been studied in 28 patients (up to 2004) with eight of them treated with the technique. As of this writing, the technique has been used almost exclusively with an IMRT step-and-shoot delivery technique, typically five fields with approximately 10 segments per field, for a prescribed dose of 2.4 Gy/fraction. Each field requires about 150–200 MU, corresponding with 15–20 s at a dose rate of 600 MU/min, and usually delivered in 2 or 3 breath holds. The increased time may become burdensome if the patient can maintain the breath hold for only the minimum 10 s; however, the majority of patients are capable of significantly longer intervals, making it easier to tolerate the procedure.

Important patient-related QA issues are ensuring accurate setup, breath-hold stability and reproducibility. The amount of anatomic motion seen during a breath hold and reproducibility in position between breath holds should be within 5 mm. If the tumor cannot be visualized with fluoroscopy, an anatomic surrogate is used. This information is used to determine the patient suitability and margin requirements. There is minimal QA required for the equipment itself. Every time it is used, there is visual confirmation on the treatment console that the CMNR interlock is operational.

5. Self-held breath hold with respiratory monitoring

This technique uses a commercially available device (Varian RPM system), to monitor patient respiration and control dose delivery, but requires patients to voluntarily hold their breath during a specific part of the respiratory cycle. One advantage of this technique is that the simulation and treatments can be delivered more efficiently than with FB respiratory gated techniques, because the radiation is delivered continuously during the breath hold. An additional advantage is that patient respiration is constantly monitored, and a beam-hold condition automatically occurs if the breath-hold level deviates from the intended one.

At the time of consultation, patients are tested for their ability to hold their breath for periods of 10 s. Patients must also be able and willing to follow verbal breathing instructions and actively participate in their treatments. Programmed audio instructions such as "breathe in, breathe out, hold your breath" are used to synchronize the helical CT scan with breath hold. The patient holds his/her breath at exhalation for periods of 7–15 s depending on ability. At the end of a scan segment, the CT scanner is programmed to issue a "breathe" command followed by a 20 s break. Typically multiple breath holds are required to scan the thorax. The CT therapist monitors the respiration trace on the RPM system during the breath hold to verify that the trace is within the threshold window.

When choosing PTV margins, the treatment planner should take into account the patient setup uncertainty, breath-hold reproducibility, treatment goals, frequency of portal imaging, and the presence or absence of implanted fiducial markers. A means of reducing the number of MUs required to deliver treatment, and thereby the number of breath holds needed, is to eliminate the use of wedges and replace them with forward planning techniques that utilize the MLC.[165] For QA purposes, the dome of the diaphragm is delineated and displayed on both the AP and lateral DRR reference images for later comparison with portal images.

Prior to treatment, portal image verification of patient position and gating interval is performed. Dose is delivered only when the marker position is within the gated interval. The patient should be instructed to take a break at any time by simply inhaling, which will trigger a beam-hold condition. In this event, the therapist depresses the "Beam-off" button, allows the patient to take a 20 s break, and then instructs the patient to "exhale and hold your breath when ready," for resumption of treatment.

Berson *et al.*[166] have reported on 108 patients treated with either an FB respiratory gating technique or the breath-hold technique described in this section. They found several advantages to the breath-hold technique, including the elimination of a possible time lag between the tumor and the external fiducial, efficiency gains in CT simulation and treatment, and improved diaphragm positional reproducibility. Time to deliver a treatment with the FB respiratory gating technique was approximately twice that with the breath-hold technique. Similarly, for a single-slice CT, scan time was approximately one-half with breath-hold, relative to FB gating. The breath-hold technique has the additional advantage of not requiring specialized hardware or software to synchronize the CT scanner with the respiratory gating system.

6. Breath hold in combination with IMRT

As indicated in the above sections, breath-hold methods are applicable to IMRT. The technological requirements are similar to those for respiratory gating: an accurate signal is needed to enable and disable dose delivery. For dynamic MLC, this signal controls the interruption and resumption of leaf motion, whereas for helical tomotherapy, the signal in addition would enable and disable couch motion. Another possible approach is to incorporate breath holds into the IMRT delivery sequence, that is, to segment the leaf-motion sequence into active (dose delivery) and inactive (no dose) periods, corresponding with the breath-hold and rest periods, respectively. The duration of these periods would be set by the planner. For helical tomotherapy, the gantry would continue to move during the rest period between breath holds; when the treatment delivery was about to resume, the patient could be made aware with audio and/or visual cues. Another option specific to helical tomotherapy is delivery of a low, but relatively uniform dose, to the entire longitudinal extent

of the tumor with each breath hold, essentially giving the patient a partial fraction. This partial fraction would be repeated until the prescribed dose was delivered. The technique avoids problems with inner-field abutment between breath holds to which other techniques are susceptible.

D. Forced shallow breathing with abdominal compression

Forced shallow breathing (FSB) was originally developed for stereotactic irradiation of small lung and liver lesions by Lax and Blomgren at Karolinska Hospital in Stockholm.[167–169] and has been used elsewhere.[8,170–176] The technique employs a stereotactic body frame with an attached plate that is pressed against the abdomen. The applied pressure to the abdomen reduces diaphragmatic excursions, while still permitting limited normal respiration. The accuracy and reproducibility of both the body frame and the pressure plate have been evaluated by several groups, with the most comprehensive assessment reported by Negoro *et al.*[170] FSB has predominantly been applied to early stage lung and liver tumors without mediastinal involvement or nodal disease. Typically, FSB has been used for stereotactic treatments, although the technology is also applicable to conventional lung treatments.

At treatment simulation, the patient is immobilized and positioned using the stereotactic body frame (SBF), consisting of a rigid frame with an attached "vacuum pillow" that is custom fitted to each patient. Tumor motion in the cranial—caudal direction is assessed using a fluoroscopic simulator. If the motion exceeds 5 mm, a small pressure plate is applied to the abdomen such that the two superior, angled sides of the plate are positioned 2 to 3 cm below the triangular rib cage. The position of the bar that is attached to the SBF and supports the plate is read from a scale on the side of the frame and is reproduced at each treatment setup. The position of the plate is controlled by a screw mechanism and is measured on a scale marked on the screw, in order to reproduce the amount of compression at each treatment. Measurements of diaphragm motion (under fluoroscopy) on different days can be made to verify reproducibility.

Negoro *et al.* reported on 18 patients treated in 4 fractions to a total dose of either 40 or 48 Gy. Daily orthogonal-view portal imaging was used for patient alignment. Setup tolerance was a 3 mm total deviation from the planned position using the SBF, requiring repositioning in 25% of the daily setups. Ten of eighteen patients required abdominal compression: the range of motion before compression was 8–20 mm (12.3 mm mean), reduced to 2–11 mm (7.0 mm mean) with compression.

Patient-related QA at simulation involves evaluation of tumor excursion under fluoroscopy from orthogonal directions, and application of abdominal compression when tumor excursion exceeds clinical goals. Usually, the maximum pressure that the patient can comfortably tolerate for the treatment session duration is used. Because of difficulty in reproducibly positioning the abdominal compression device, imaging is essential at each treatment fraction to verify tumor position, either via CT or by means of implanted fiducials visible in radiographs.

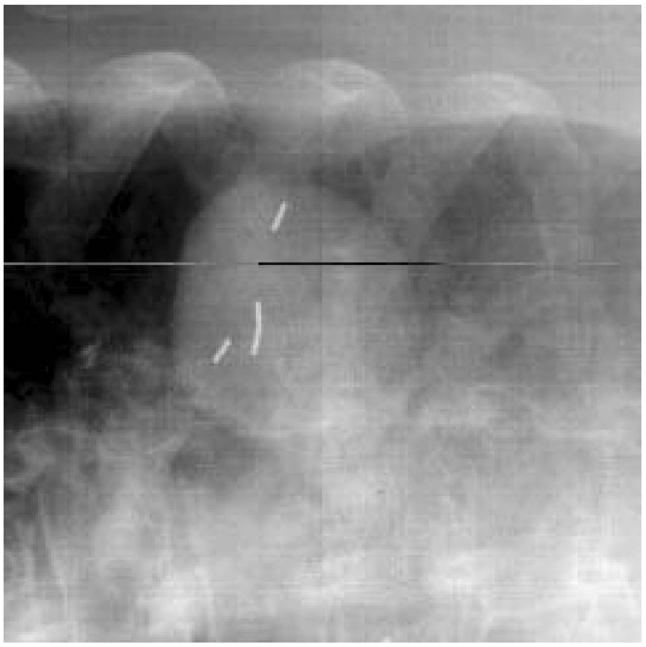

FIG. 5. A lung tumor observed with a flat-panel amorphous silicon detector forming part of the CyberKnife image-guided radiosurgery system. The tumor has four gold fiducial seeds implanted in it to enhance its position measurement. From Ref. 177.

E. Real-time tumor-tracking methods

Another means of accommodating respiratory motion is to reposition the radiation beam dynamically so as to follow the tumor's changing position, referred to as real-time tumor tracking. Under ideal conditions, tracking can eliminate the need for a tumor-motion margin in the dose distribution, while maintaining a 100% duty cycle for dose delivery. To succeed, this method should be able to do four things: (1) Identify the tumor position in real time; (2) anticipate the tumor motion to allow for time delays in the response of the beam-positioning system; (3) reposition the beam; and (4) adapt the dosimetry to allow for changing lung volume and critical structure locations during the breathing cycle.

1. Determining the tumor position

Detecting the tumor position is the most important and challenging task in real-time tracking. Currently, there are four possible means of locating the tumor during treatment: (1) Imaging of the tumor itself via, e.g., fluoroscopy; (2) imaging of fiducial markers implanted in the tumor; (3) inference of the tumor position from surrogate breathing motion signals; and (4) nonradiographic tracking of an active or passive signaling device implanted in the tumor. All of these methods are currently under development or used clinically.

Direct tumor imaging: In certain situations, it can be possible to detect a lung tumor directly in radiographic/fluoroscopic images acquired during treatment. Figure 5

shows a lung tumor image from an amorphous silicon x-ray detector at an exposure level of approximately 0.50 mGy.[177] Most lung tumors will not present a well-defined, high-contrast object suitable for automatic segmentation and image registration, nor will tumors in the pancreas and liver. Therefore, it is usually necessary to use an artificial marker as a surrogate for tumor position.

Tumor location using implanted fiducial markers: One or more high-Z metal markers implanted in lung, pancreas, or liver tumors can be readily observed in x-ray images (Fig. 5). If only one fiducial marker is used it is not possible to determine from the images whether the fiducial has moved with respect to the tumor. Three or more fiducial markers allow measurement of tumor translation and rotation, and marker migration can be inferred by monitoring the distance between markers. Murphy *et al.*[72] have used 2 mm diameter spherical gold balls sewn into the pancreas during exploratory laparotomy. Chen,[73] Murphy,[178] and Shirato[70] have used 0.8 by 4 mm cylindrical gold seeds implanted into or near lung tumors percutaneously or bronchoscopically. Gold fiducial markers are detectable in fluoroscopic images of the abdomen and pelvis at exposures as low as 0.18 mGy per image,[70] allowing continuous monitoring in the treatment room. Additional radiation dose from imaging should be considered; the report of AAPM Task Group 75 provides a detailed review and guidelines for implementation of these techniques. To reduce radiographic imaging exposure, hybrid tumor-tracking techniques combine episodic radiographic imaging and continuous monitoring of external breathing signals, based on the premise that external motion surrogates can accurately predict the internal tumor position in the time interval between image acquisitions.[73,78,177–181]

Tumor position prediction based on surrogate breathing signals: In situations when continuous fluoroscopic imaging of the tumor is not feasible, it is necessary to infer the tumor position from external respiration signals. If the correlation is simple and stationary, it can be sufficient to measure it before treatment with a fluoroscope, and used to predict tumor motion during treatment. However, the physiology of breathing motion suggests that stationary correlation is not necessarily a safe assumption.[78,89–91,182,183] Nonstationary correlation should be monitored and updated continually during treatment by acquiring images of the tumor position synchronously with the respiratory signal.[179] This can be accomplished with adaptive filter algorithms, which are designed to predict nonstationary signals by periodically updating the empirical relationship between the input (e.g., breathing) and the output (e.g., tumor position) signals.[178]

Nonradiographic tumor tracking: Seiler *et al.*[184] have described a miniature, implantable powered radiofrequency (rf) coil that can be tracked electromagnetically in three dimensions from outside the patient. Balter *et al.*[185] have reported on the performance of a wireless rf seed-tracking system for tumor localization. The electromagnetic approach could provide an alternative to the use of radiological imaging to track the tumor position.

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

The response of a beam-positioning system to a tumor signal cannot occur instantaneously. Seppenwoolde *et al.*[50] report a delay of 90 ms between the recognition of a fiducial marker in a fluoroscopic image and the onset of irradiation in their gated beam-delivery system. This includes computational time to locate the marker in the image as well as delays in triggering the beam onset. Mechanical systems to realign the beam have longer delays. The CyberKnife (Accuray, Sunnyvale, CA) system (described below) has a 200 ms delay between acquisition of tumor coordinates and repositioning of the linear accelerator. This delay is in addition to image acquisition, read-out, and processing times. Repositioning an MLC aperture will likewise involve a time delay of 100–200 ms or more.

The presence of a time delay requires that the tumor position be predicted in advance, so that the beam can be synchronized to arrive at the actual position of the tumor once the adjustment has been made. The problem is further complicated in that a typical human breathing cycle, while nominally periodic, has significant cycle-to-cycle fluctuations in displacement, as well as longer-term fluctuations in both displacement and frequency.[78,182] However, these fluctuations are not purely random,[186] suggesting the possibility to predict a particular breath cycle from the observed characteristics of its predecessors. This is the basis for time series prediction by an adaptive filter. Murphy *et al.*[178] have analyzed breathing prediction using a variety of adaptive filters and have found that the tumor position can be predicted with up to 80% accuracy (i.e., 20% residual uncertainty) in the presence of a 200 ms system delay, but accuracy degrades rapidly with longer delay intervals, which is consistent with findings by Sharp *et al.*[180] and Vedam *et al.*[187]

3. Repositioning the beam

There are presently two real-time beam-positioning methods. The first one is MLC repositioning.[116,188–195] The second method uses a robotic manipulator to move the entire linear accelerator with six degrees of freedom. In this approach, the robot (CyberKnife image-guided radiosurgery system) is coupled through a real-time control loop to an imaging system that monitors the tumor position and directs the repositioning of the linear accelerator.[72,73,78,179] It has the advantage of adapting to the full 3D motion of the tumor. Both methods can use the same algorithms to satisfy the requirements for tumor position identification, time delay compensation, and dosimetric corrections for breathing. It should be noted that cardiac motion can also cause tumor motion on the order of 2 mm.[50,72] In principle, couch,[196] block,[197] or jaw motion can also be used for beam repositioning.

4. Correcting the dosimetry for breathing effects

The effect of breathing on dosimetry was recently discussed by Bortfeld *et al.*[198] The treatment-planning imaging study used to calculate the dosimetry necessarily captures the anatomy in one static configuration, whereas during breath-

ing, the anatomy and the air volume in the lung are continually changing. This perturbs the attenuation of the treatment beam and changes the relative positions of tumor, normal tissue, and critical structures. Compared with the alternative of treating with a motion margin, or missing the target completely, these issues are second-order effects, but their impact needs to be studied.

5. Recommendations for the implementation of a real-time tracking response to respiratory motion

Observations of lung tumor motion show that it can follow a complex 3D trajectory.[50] Therefore, a tracking method should preferably provide 3D coordinates of the tumor, although 2D motion in the plane perpendicular to the beam direction is also acceptable. Three-dimensional information requires simultaneous acquisition from dual fluoroscopes. Breathing irregularity makes it difficult to predict more than 0.5 s with sufficient accuracy to give real-time tracking a clear advantage over other respiratory compensation methods. Therefore, the total time delay of a real-time tracking system should be kept as short as possible and, in any case, not more than 0.5 s.

6. Quality assurance

These procedures must address two fundamental sources of potential error in dose delivery: (1) Determination of the tumor position as a function of time and (2) calibration of the spatial relationship between the tracking coordinate system and the beam-delivery coordinate system.

Sources of tumor-position uncertainties during tracking are essentially the same as for gating, and QA for both methods will follow a similar methodology. The accurate translation of tumor coordinates from the tracking device to the beam-alignment system is of extreme importance. If the tumor is tracked directly via radiographic or fluoroscopic imaging, the imaging system should either have a mechanically rigid relationship with the beam delivery system or be localizable with an in-room tracking system, which itself will introduce imprecision to the tumor/beam alignment. In hybrid tracking that involves imaging coordinated with external respiratory signals, the imaging and the external monitoring systems should maintain a calibrated relationship with each other and with the beam-delivery system. The CyberKnife system uses a specially designed composite imaging/dosimetry phantom to check the geometrical relationship between tracking system and beam-delivery systems. The phantom is localized with the imaging/tracking system and irradiated with the planned dose. The position of the delivered dose, relative to the plan, reveals any systematic coalignment errors. This test takes approximately 1.5 h and should be performed monthly.

7. Synchronization of IMRT with motion

The most sophisticated and yet challenging methods involve those that attempt to synchronize IMRT delivery with respiratory motion. Keall *et al.*[116] demonstrated the feasibility of such an approach. In this study, the respiratory motion (as simulated by a 1D mechanical device) was superimposed on the original planned intensity pattern. They showed that the dosimetric results obtained with the motion-synchronized approach were very similar (within a few percent) to those for the static IMRT delivery that did not include motion. Target deformation was not considered.

One of the key dependencies of respiratory synchronized approaches is the derivation of a stable input trace that accurately reflects the target's motion during respiration. In a study of this topic, Neicu *et al.*[188] termed this reference breathing trace the "average tumor trajectory (ATT)." Using 11 lung data sets obtained from a real-time tracking system, they found that an ATT could be derived from patient data and applied successfully. However, coaching was recommended as a means to make the ATT more reliable. Delivery efficiency is driven by the accuracy of the ATT, since the system turns off radiation whenever the input trace deviates from the ATT and waits until agreement is reestablished. Other dynamic MLC-based approaches to respiration-synchronized radiotherapy have also been proposed.[189–195] Zhang *et al.* describe an approach in which an ATT is derived and used *during* planning in conjunction with a 4D CT data set and applied this method to helical tomotherapy planning.[199] The transition of one breathing stage to the next is anticipated in the planning stages using the CT data as opposed to being superimposed *after* planning.

VII. SUMMARY AND RECOMMENDATIONS

This section summarizes the Task Group report and gives recommendations for both the clinical and, particularly, the technical management of patients for whom respiratory motion may be a concern and areas requiring further study. It is important to restate here that respiratory motion is just one of the many geometric errors in thoracic and abdominal radiotherapy and that respiratory patterns change from cycle to cycle and day to day.

Unless imaging the entire treatment volume continuously, respiratory surrogates are used to infer tumor motion. Internal markers implanted in the tumor offer the most accurate information regarding target position during treatment; however, the benefits of accuracy need to be weighed against the cost and invasive procedure of implanting markers in tumors as well as against possible marker migration. If external markers are used as the respiratory surrogate, the relationship with the internal target should be established, for example, by sampling the target position fluoroscopically for brief periods of time at a number of intervals.

A. Clinical process recommendations

The Task Group recommends that for patients in whom respiratory motion may be a concern that the flowchart in Fig. 6 be followed. Box 1 of Fig. 6 asks if a method of measuring motion is available. EORTC guidelines[95] recommend that "An assessment of 3D tumor mobility is essential for treatment planning and delivery in lung cancer." When measuring tumor motion, the motion should be observed

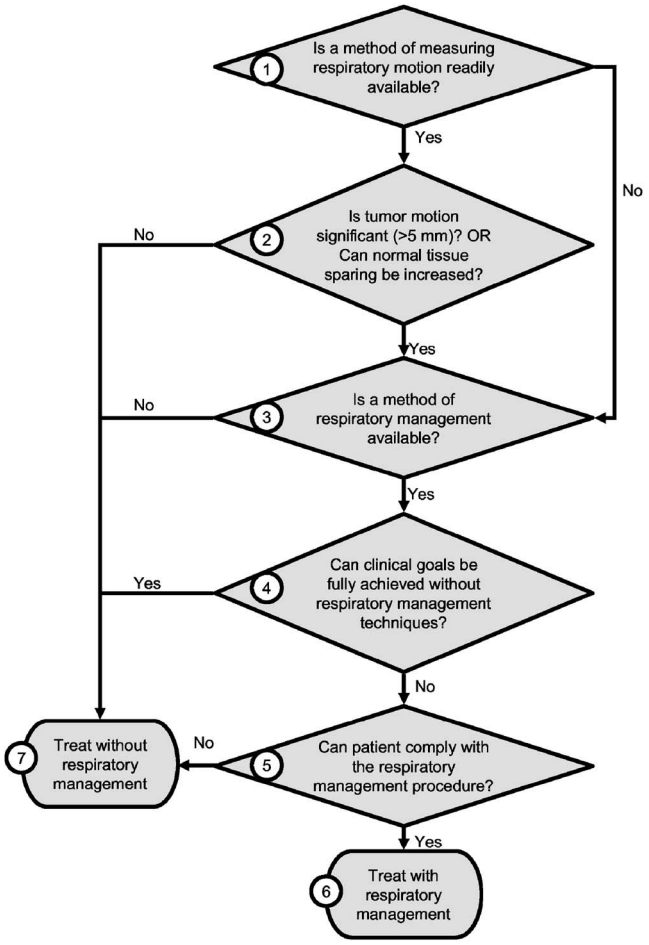

FIG. 6. Recommended clinical process for patients with whom respiratory motion during the radiotherapy process is a concern.

over several breathing cycles if possible. It is important to note that respiratory patterns change over time. If no method exists for measuring motion, for example, with a standard respiratory gated CT procedure, the prudent approach is to assume that motion is significant and treat with respiratory management (box 6). If a method of measuring motion, such as fluoroscopy, is readily available (box 1), it can be worthwhile to measure the motion for three reasons:

(1) If the magnitude of the motion is significantly small (<5 mm of range of motion in any direction), relative to other errors in radiotherapy, the extra effort of using respiratory management techniques is unwarranted (box 2), unless significant normal tissue sparing (as determined by your clinic) can be gained with the respiration-management technique. The 5 mm motion-limit criterion value was chosen, because this level of motion can cause significant artifacts and systematic errors during imaging procedures. Note that due to respiratory variations the motion magnitude may increase or decrease during the treatment course, and that if practical the motion can be re-evaluated during treatment.
(2) If a patient-specific tumor-motion measurement is made, this information can and should be used in the CTV-to-PTV margin used for treatment planning. If a respiratory management device is not used, the dosimetric effect of the motion should be considered and an appropriate margin should be derived. The most simple way is to consider the entire range of motion when establishing the internal margin.[42] If respiratory management devices are used, only the motion expected during the radiation treatment delivery should be considered when establishing the respiratory motion component of the internal margin.
(3) If the motion measurement and respiratory signal to be used for treatment are acquired simultaneously, phase shifts or time lags between the internal and external motion can be calculated and corrected.

The Task Group recommends that respiratory management techniques be considered if either of the following conditions occur:

- A greater than 5 mm range of motion is observed in any direction; or
- significant normal tissue sparing (as determined by your clinic) can be gained through the use of a respiration management technique (box 2 of Fig. 6).

The recommended 5 mm motion-limit criterion value may be reduced for special procedures, such as stereotactic body radiotherapy. This value may be reduced in the future as other errors in radiotherapy, such as target delineation and setup error, are reduced, with respiratory motion thereby becoming the accuracy limiting factor. Furthermore, depending on practicality, the motion may be re-evaluated during the treatment course.

If a method of respiratory management is not available (box 3 of Fig. 6), as is the case with most facilities, the guidelines in Section VI A should be followed. If a method of respiratory management is available, the next question to be answered (box 4 of Fig. 6) is whether the clinical goals can be achieved without explicit respiratory management. This question is very complex and difficult to assess *a priori*. An example could include palliative cases in which the treatment-related toxicity is expected to be low. Another example is the irradiation of very small metastases where even with a substantial margin the irradiated volumes may still be small enough that no significant risk of treatment-related toxicity exists. A confounding factor is that the patient's future need for radiation therapy is unknown, and patients with metastases are often treated multiple times, which may cause the extra dose to become a concern.

The next important question to be answered is whether an individual patient can tolerate the respiratory management technique (box 5). As outlined previously in the report, there are many factors that may cause patients to be unsuitable for a particular respiratory management technique, and, in most cases, there are few predictive factors to determine who will or will not be able to tolerate the procedure. The prudent approach is to try respiratory management and, if unsuccessful, to treat without explicit respiratory management.

At the time of printing, some systems do not have software interlocks in the record-and-verify systems that prevent treatment of the wrong patient with respiration management devices (or vice versa) or the use of the wrong patient parameters. Thus, the Task Group recommends that manufacturers of the respiratory management devices collaborate with record-and-verify system companies to ensure that the relevant parameters for a patient's treatment are included in the patient's electronic file.

B. Treatment-planning recommendations

When deriving CTV–PTV margins for treatment planning, the following factors specific to respiratory motion should be taken into account:

- The distortion of the planning CT due to respiratory motion-induced artifacts is an important source of systematic error these artifacts are found to varying degrees in free-breathing, slow, gated, and 4D CT scans.
- If a structure, such as the chest wall or diaphragm, is used as a surrogate for tumor motion for the purpose of breath hold, beam gating or tracking, without observing the tumor directly during treatment, there will be uncertainties in the displacement and phase relationship between the surrogate and the tumor.[78,89–91]
- There are variations within and between respiratory cycles and also residual motion during both respiratory gating and breath-hold procedures.
- If a patient-specific tumor-motion measurement is made, the information should be used in the CTV-to-PTV margin used for treatment planning. If a respiratory management device is not used, the entire range of motion should be considered when establishing the internal margin.[42]

Other factors such as setup error and tumor changes during the course of radiotherapy are common to all sites.[42] An obvious problem is that the errors listed above have yet to be adequately quantified, and, thus, informed guesses as to the magnitude of these errors need to be made. In areas where knowledge is lacking, the next section details a list of recommendations for further investigations to fill in the knowledge gaps.

Due to the complex nature of radiation transport in low-density regions such as the lung, the Task Group recommends that the most accurate dose calculation available be used.

C. Personnel recommendations

The Task Group recommends that, due to the complexity of the management of the respiratory motion problem and the technology used, a qualified medical physicist be present at all treatment-simulation (virtual or otherwise) imaging sessions in which respiratory management devices are used and also for at least the first treatment for each patient. A physicist should also be available for consultation during the treatment-planning process and for all treatment sessions. The physicists involved with the procedures should have an appropriate understanding of the equipment and have attended, when possible, training on the specific device(s) used. In certain cases, a well-trained radiation oncology professional may perform the tasks of a qualified medical physicist, provided that a qualified medical physicist is available for consultation. Additional dosimetry or therapy staff may also be needed during imaging and treatment to operate or assist on the operation of the respiratory management devices.

D. Quality assurance recommendations

Strict QA procedures for the imaging, planning, and delivery of radiotherapy using respiratory management devices are required to ensure the safe and effective use of these devices. QA procedures are given in Sec. V B and discussed under each described motion management technique. The Task Group recommends that these procedures be documented and followed and that the results of the procedures be appropriately documented and stored. Where possible, QA of each fraction delivered using respiratory management devices should be pursued as well.

E. Recommendations for further investigations

The management of respiratory motion in radiation oncology is an evolving field with many current and, no doubt, future issues still to be adequately addressed. The Task Group recommends research in the following areas for which the current scientific knowledge is absent or sparse:

- Changes in respiratory patterns between treatment simulation and treatment;
- relationship between respiration signals and tumor motion and changes in this relationship throughout a course of radiotherapy;
- tumor deformation from cycle to cycle and day to day;
- new imaging methods at treatment to directly detect tumor positions or to verify the relationship between respiration signals and tumor motion;
- methods, such as audiovisual feedback, that can improve respiration reproducibility throughout the course of radiotherapy;
- effects of cardiac and gastrointestinal motion on thoracic radiotherapy.
- relationships between normal tissue and tumor motion, particularly for normal tissue that is dose limiting and/or from which a useful motion signal (for imaging and treatment) can be obtained;
- more accurate determination of the magnitude of respiratory motion that should be explicitly managed using the respiratory management techniques—given other errors in radiotherapy;
- optimal respiratory motion management strategies stratified by disease site, patient characteristics, and treatment regimen;

- respiratory motion patterns and treatment implications in children and young adults treated with radiotherapy for lymphoma and other pediatric diseases involving thoracic radiotherapy;
- robust deformable image-registration algorithms to facilitate dose accumulation due to anatomy deformation;
- treatment-planning solutions that can be integrated into commercial treatment-planning systems;
- appropriate margin formalisms including respiratory motion for the various respiratory motion management strategies;
- deformable phantoms to which anatomically accurate respiratory motion can be applied;
- analysis of clinical outcome data in the presence of respiratory motion and other errors.

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[a)]This manuscript is a moderately condensed version of the full report of the Task Group. The full report contains further background material and is available through the AAPM.

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