AAPM REPORT NO. 91

The Management of Respiratory Motion in Radiation Oncology

Report of AAPM Task Group 76

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The Management of Respiratory Motion in Radiation Oncology

Report of AAPM Task Group 76

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DEDICATION

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.

CONTENTS

ABSTRACT

This document is the report of a task group of the American Association of Physicists in Medicine (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. Knowledge in the field of respiratory motion in radiation oncology is continually growing. This report is intended to reflect the current state of the scientific understanding and technical methodology in imaging, treatment planning, and radiation delivery for radiation oncology patients with tumors affected by respiratory motion.

I. INTRODUCTION AND SCOPE

A. How to read this document

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

Respiratory motion affects all tumor sites in the thorax and abdomen (even the pelvis[1-3]), though the disease of most prevalence and relevance for radiotherapy is lung cancer. Lung cancer accounts for 28% of all cancer deaths in the United States.[1] An estimated 173,770 new cases were diagnosed in 2004, with an estimated 160,440 deaths.[1] The five-year survival rate for all stages combined is 15%.[1] However, there is clinical evidence of a local control and survival advantage for higher dose levels.[4-12] Recently, Machtay et al.[10] in a review of 1290 Radiation Therapy Oncology Group (RTOG) lung cancer patients found an estimated 18% decrease in the risk of death with every 10-Gy increase in biologically equivalent dose. Martel et al.[6] estimate from their data that to achieve a 50% local progression-free survival at 30 months, 85 Gy is required; this dose level is considerably higher than that used routinely in clinics due to the risk of lung complications. These lung complications have been shown to correlate with mean lung dose (or similar surrogate, such as V_{20}).[13-18] 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. Methods that explicitly account for respiratory motion in radiation oncology comprise one such technology class. Ling et al.[19]

[1] American Cancer Society *Cancer Facts and Figures 2004.*

hypothesize that high-tech radiotherapy, of which respiratory motion management is an essential component, can significantly improve the treatment results of non–small-cell lung cancer (NSCLC) patients.

It is important to note that respiratory motion is just one potential source of error in radiotherapy. Other important errors, particularly for lung tumors, are gross tumor volume (GTV) and clinical target volume (CTV) definition variations and setup errors. Large inter-physician GTV variations for lung cancer[20-23] and CTV variations for breast cancer[24,25] have been published. The dosimetric consequences of these variations are almost an order of magnitude larger than those caused by respiration-induced motion (see section IV). Also, setup errors for lung[22,26-32] and breast[33-40] 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 other concomitant therapies.

C. Scope

Specific issues addressed by this report are:

- The magnitude of respiratory motion
- The problems that respiratory motion causes during the imaging, planning, and delivery of three-dimensional conformal radiotherapy (3DCRT) and intensity-modulated radiation therapy (IMRT)
- A description of the methods that have been used to explicitly account for this motion
- Recommendations for clinical implementation of methods that explicitly account for respiratory motion
- Recommendations for radiotherapy to sites affected by respiratory motion, both in the presence and absence of methods that account for this motion
- Recommendations for the types and frequency of QA procedures for methods that account for respiratory motion
- Recommendations for research studies that address currently unresolved or disputed issues.

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 (VI.A). 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[41-44] and other emerging technology to reduce the magnitude of respiratory motion, 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:

Term	**Meaning**
4-D	Four-dimensional
ABC	Active-breathing control
CTV	Clinical target volume[45-46]
Deep exhale	Maximum expiratory level[47]
Deep inhale	Maximum inspiratory level[47]

Term	Meaning
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
Exhale	Resting expiratory level[47]
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[45,46]
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 inhale and exhale
Inhale	Resting inspiratory level[47]
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[45,46]
Range of motion	Displacement between inhale and exhale
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

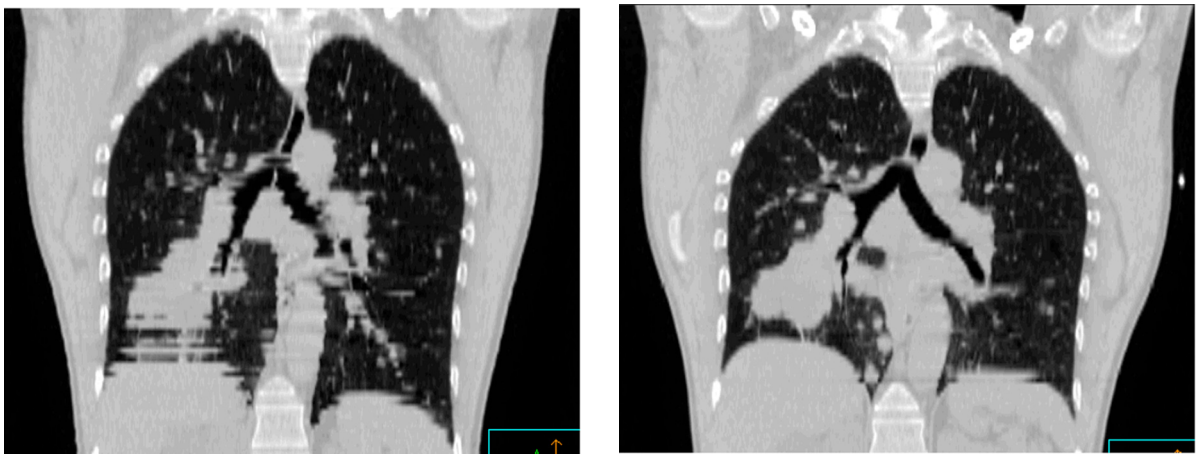
III. PROBLEMS OF RESPIRATORY MOTION DURING RADIOTHERAPY

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. These artifacts cause distortion of the target volume and incorrect positional and volumetric information.[48-60] These motion artifacts occur because different parts of the object move in and out of the computed

tomography (CT) slice window during image acquisition. Artifacts can be generated within a slice, since CT reconstruction algorithms assume that the imaged anatomy is invariant during data acquisition. Motion artifacts are commonly seen with thoracic CT images. An example of the difference between a respiratory-gated and a non-gated CT scan for a patient and a sinusoidally moving sphere is shown in Figures 1 and 2, respectively. 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,[61-64] which is becoming a standard-of-care imaging technique for NSCLC. If not accounted for, tumor motion will further blur the PET image, leading to difficulties in clearly delineating boundaries as well as failure to detect small mobile volumes that are potentially cancerous.



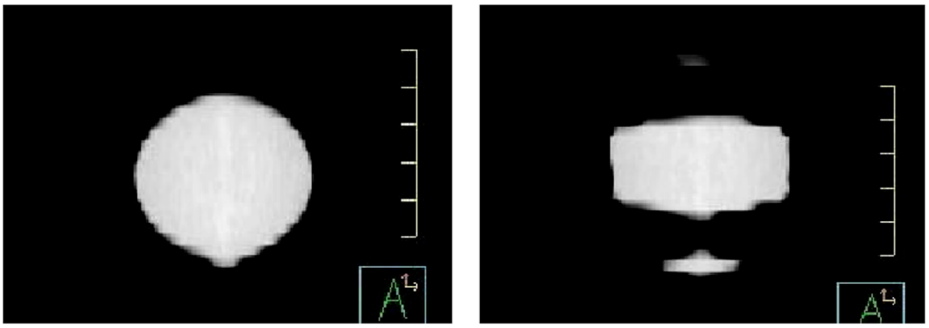
(**a**) (**b**)

Figure 1. Coronal views of CT scans of the same patient taken during free breathing (FB) (a) and with respiratory-gated scanning at exhale (b). [Reproduced from reference 53: P. J. Keall, V. R. Kini, S. S. Vedam, and R. Mohan, "Potential radiotherapy improvements with respiratory gating," *Australas Phys Eng Sci Med* 25(1):1–6, Figure 1. © 2002, with permission from APESM.]

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 GTV[45,46] is outlined, and a margin is added to include the suspected microscopic spread[65] (which when added to the GTV creates the CTV). Thus, using International Commission on Radiation Units and Measurements (ICRU) report 62[46] nomenclature, to obtain the planning target volume (PTV) from the CTV involves the addition of the margins to account for intrafraction motion (due to respiration), 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. This increased treatment volume increases the likelihood of treatment-related complications. 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.[66,67]



(a) **(b)**

Figure 2. Coronal views of CT scans of a static sphere (a) and a sinusoidally moving sphere (b) (2-cm range of motion and a 4-second period). [Reproduced from reference 56: S. S. Vedam, P. J. Keall, V. R. Kini, H. Mostafavi, H. P. Shukla, and R. Mohan, "Acquiring a four-dimensional computed tomography dataset using an external respiratory signal," *Phys Med Biol* 48(1):45–62, Figure 1. © 2003, with permission from IOP Publishing Limited.]

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. 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-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)[2] and the component of target motion perpendicular to the beam. Further discussion of IMRT effects is given in section V.C.

[2] Motion artifacts in dose distributions may be encountered with both DMLC and SMLC IMRT delivery.

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. Of these, the most important is P_{CO_2}. Reducing P_{CO_2}, as occurs with hyperventilation, is a very effective means for reducing the urge to breathe, or sustaining a breath-hold. Under normal conditions, the O_2 and blood pH stimuli play a small role in ventilation control.

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, as shown in Figure 3. Exhalation is passive for quiet breathing. The lung and chest walls are elastic and return passively to their pre-inhalation positions at exhale. Other ventilation muscles are involved only during active exhalation.

The tendency of the lung to recoil to its deflated volume is opposed by the tendency of the chest cage to bow out. The lung volume at the end of exhale, termed "functional residual capacity," is at equilibrium or in the most relaxed state. Typically, the time taken to breathe in is longer than the time taken to breathe out. 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.

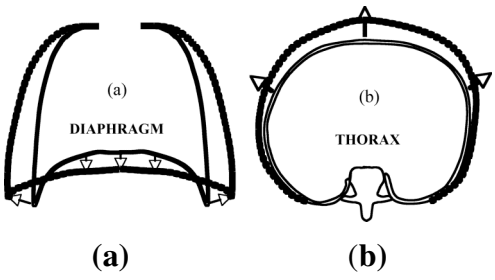


Figure 3. (a) During inhalation, the diaphragm contracts, the abdomen is forced down and forward, and the rib cage is lifted. (b) The intercostal muscles also contract to pull and rotate the ribs, resulting in increasing both the lateral and anterior–posterior (AP) diameters of the thorax. [Reproduced from reference 226: J. B. West, *Respiratory Physiology: The Essentials*, Figures 3a,3b. © 1974, with permission from Lippincott Williams, and Wilkins.]

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). For example, when the change in abdominal circumference was more than 10 mm greater than the change in chest circumference, Davies et al.[68] classified the breath as abdominal. During normal quiet respiration, the lung volume typically changes by 10%[3] to 25%; at deep inhale, the increase in lung volume is approximately three to four times that of normal breathing.[69] For radiotherapeutic purposes, data measured in the upright posture are relevant only in limited situations (e.g., total body irradiation with the patient standing); therefore, we include only data taken from prone, supine, and lateral positions.

B. Measuring respiratory motion

The lungs, esophagus, liver, pancreas, breast, prostate, and kidneys, among other organs, are known to move with breathing. The degradation of image quality due to this motion and subsequent effects on radiotherapy dose planning and delivery have prompted medical physicists and clinicians to study the motion using a variety of imaging modalities. 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. In some cases, the object is a surrogate organ such as the diaphragm.

Patients' breathing patterns can vary in magnitude, period, and regularity during imaging and treatment sessions,[67,70-72] as demonstrated in Figure 4. Systematic changes in the respiratory baseline also occur. Motion also varies markedly between patients, indicating that an individual approach to

[3] D. Low, personal communication.

respiratory management is advised. Audiovisual biofeedback[71-73] has been demonstrated to improve respiratory reproducibility.

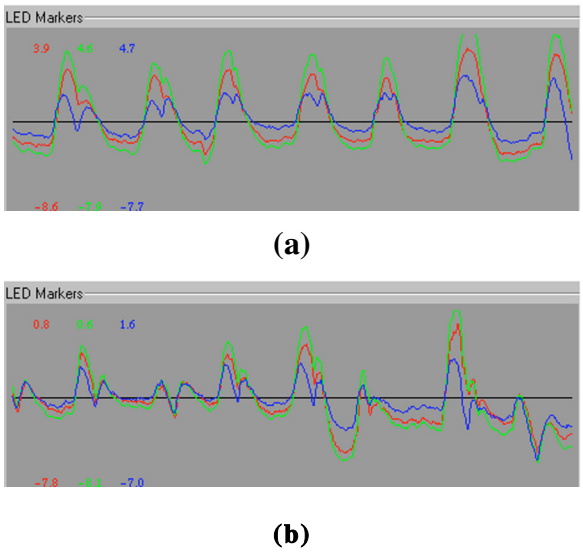


Figure 4. Variations in respiratory patterns from the same patient taken a few minutes apart. The three curves in each plot correspond to infrared reflector measured patient surface motion in the SI, AP, and ML directions, with each component arbitrarily normalized. In (a), the motion pattern is relatively 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. Observables

Organ motion has been detected via ultrasound,[68,74,75] CT,[55,76-78] magnetic resonance (MR),[79] and fluoroscopy.[2,26,28,36,52,67,80-88] Stevens et al.[66] made double-exposure radiographs at deep inhale and deep exhale to establish the full range of lung tumor motion. Weiss et al.[89] and Harauz and Bronskill[90] measured liver and diaphragm motion with a gamma camera following administration of ^{99}Tc-sulphur colloid. Table 1 identifies the published observations by organ site and imaging modality.

Respiratory motion studies have tracked the movement of the tumor,[28,66,76,77,85,91,92] the host organ,[68,74,75] radiographic fiducial markers imbedded at the tumor site,[2,36,67,83,84,88] radioactive tracers targeting the tumor,[89,90] and surrogate organs, such as the diaphragm, which are assumed to correlate with the tumor.[70,78,82,86]

A single fluoroscopic study can provide detailed two-dimensional (2-D) information on organ motion trajectories and timing/phase shift relationships among different moving structures, but two simultaneous projections (e.g., angiography) are necessary for a complete three-dimensional (3-D) reconstruction of real-time tumor motion. These statements assume that either the anatomy or a suitable surrogate, such as an implanted fiducial marker, can be visualized. A single 2-D projection may lack the information or achieve the sufficient contrast required to recognize out-of-plane motion, rotation, or deformation of the tumor during breathing. Two CT studies acquired at inhale and exhale breath-hold may retrospectively define the full range of tumor motion in three dimensions, but do not provide

trajectory or time-profile details for the motion. This method relies on the geometric relationship between organs during breath-hold being similar to that during free breathing (FB).

Four-dimensional (4-D) or respiratory correlated CT[56,57,93-100] using single-slice, multislice, or cone-beam acquisition can provide 3-D data on tumor position at several points along the breathing cycle with a somewhat reduced spatial resolution, as compared with conventional CT, thus providing a compromise between the good time resolution of a fluoroscopic study and the detailed 3-D information of a CT scan.

Multiple fiducial markers can provide a valuable indicator of tumor rotations and deformation during respiration, which is an issue that has not yet received sufficient attention in discussions of respiratory motion compensation.

Table 1. Measurement techniques.

Site	Technique					
	CT	**MRI**	**Fluoroscopy**	**Ultrasound**	**Nuclear imaging**	**EPID**
Pancreas				Suramo et al.[74] Bryan et al.[75]		
Liver		Korin et al.[79]		Suramo et al.[74] Davies et al.[68]	Weiss et al.[89] Harauz et al.[90]	
Kidney				Suramo et al.[74] Davies et al.[68]		
Diaphragm	Giraud et al.[78]	Korin et al.[79]	Wade et al.[80] Ford et al.[86] Minohara et al.[82]	Davies et al.[68]		
Prostate			Malone et al.[2]			
Lung	Ross et al.[76] Hanley et al.[77] Shimizu et al.[55] Essapen et al.[219] Stevens et al.[66] Sixel et al.[92] Grills et al.[91]	Plathow et al.[220]	Kubo et al.[36] Ekberg et al.[26] Shirato et al.[221] Murphy et al.[83] Chen et al.[84] Engelsman et al.[28] Barnes et al.[85] Shimizu et al.[52] Murphy et al.[87] Seppenwoolde et al.[67] Ozhasoglu et al.[88]			Erridge et al.[101]
Breast						van Tienhoven et al.[35]

CT: computed tomography; EPID: electronic portal imaging device; MRI: magnetic resonance imaging.

D. Motion observations

The investigators referenced in this section have published data based on anywhere from four[52,87] to fifty-one[90] subjects. Most of the published reports are based on cohorts of 10 to 30 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. These data are summarized in Table 2 (lung) and Table 3 (abdomen).

There are significant differences in organ motion during quiet (shallow) and deep breathing. Therefore, some of the observers have distinguished their measurements by breathing mode.

Table 2. 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).

Observer	Direction		
	SI	AP	LR
Barnes[85]: Lower lobe	18.5 (9–32)	--	--
Middle, upper lobe	7.5 (2–11)	--	--
Chen et al.[84]	(0–50)	--	--
Ekberg et al.[26]	3.9 (0–12)	2.4 (0–5)	2.4 (0–5)
Engelsman et al.[28]:			
Middle/upper lobe	(2–6)	--	--
Lower lobe	(2–9)	--	--
Erridge et al.[101]	12.5 (6–34)	9.4 (5–22)	7.3 (3–12)
Ross[76]: Upper lobe	--	1 (0–5)	1 (0–3)
Middle lobe	--	0	9 (0–16)
Lower lobe	--	1 (0–4)	10.5 (0–13)
Grills et al.[91]	(2–30)	(0–10)	(0–6)
Hanley et al.[77]	12 (1–20)	5 (0–13)	1 (0–1)
Murphy et al.[87]	7 (2–15)	--	--
Plathow[220]: 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 et al.[67]	5.8 (0–25)	2.5 (0–8)	1.5 (0–3)
Shimizu et al.[52]	--	6.4 (2–24)	--
Sixel et al.[92]	(0–13)	(0–5)	(0–4)
Stevens et al.[66]	4.5 (0–22)	--	--

AP: anterior–posterior; LR: left–right; SI: superior–inferior.

Table 3. 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.

Site	Observer	Breathing mode	
		Shallow	Deep
Pancreas	Suramo et al.[74]	20 (10–30)	43 (20–80)
	Bryan et al.[75]	20 (0–35)	--
Liver	Weiss et al.[89]	13 +/– 5	--
	Harauz et al.[90]	14	--
	Suramo et al.[74]	25 (10–40)	55 (30–80)
	Davies et al.[68]	10 (5–17)	37 (21–57)
Kidney	Suramo et al.[74]	19 (10–40)	40 (20–70)
	Davies et al.[68]	11 (5–16)	--
Diaphragm	Wade[80]	17	101
	Korin et al.[79]	13	39
	Davies et al.[68]	12 (7–28)	43 (25–57)
	Weiss et al.[89]	13 +/– 5	--
	Giraud et al.[78]	--	35 (3–95)
	Ford et al.[86]	20 (13–31)	--

Generally, abdominal organ motion is in the SI direction, with no more than a 2-mm displacement in the AP and lateral directions.[68,79] However, in some individuals, the kidneys show more complex patterns.[68] 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.[66] found that out of 22 lung tumor patients, 10 subjects showed no tumor motion in the SI direction. 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.

Barnes et al.[85] found the average motion of tumors in the lower lung lobe to be significantly greater than that in the middle lobe, upper lobe, or mediastinal tumors (18.5-mm vs. 7.5-mm average SI displacement). This observation has generally been corroborated by other observations,[36] although the individual ranges of motion are such that some individuals will show less motion in the SI direction than others will show in the AP and left–right directions.

At the time of writing, the most detailed lung tumor-motion data reported in the literature comes from the measurements of Seppenwoolde et al.,[67] who measured 3-D 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 4 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 Figure 5, motion trajectories during radiotherapy of lung tumors, measured using implanted gold markers, are depicted.[67] The amount of motion ranges from a 1-mm displacement to more than a 2-cm displacement. Furthermore, it can be seen that the motion is nonlinear for about half of the fiducial markers. The majority of the fiducial markers (78% in this study) move with less than a 1-cm range of motion. Similar results, based on portal imaging studies, have been reported.[101]

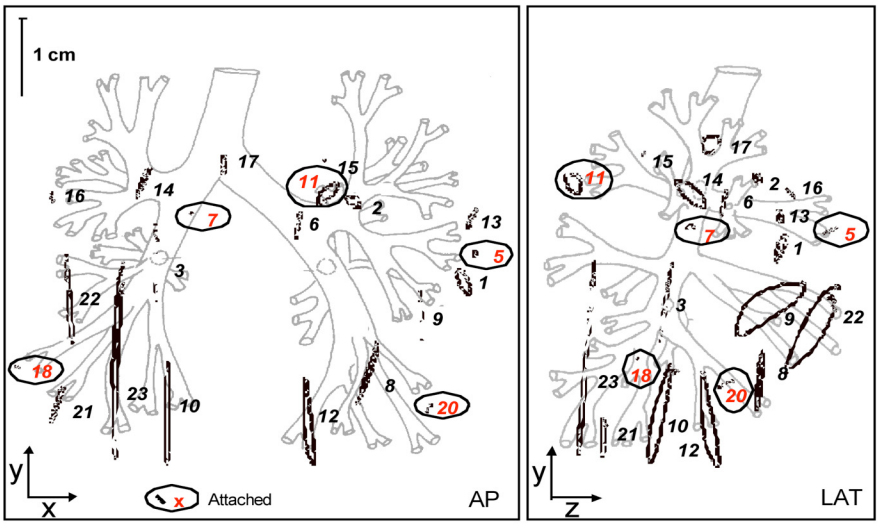


Figure 5. Tumor trajectories (not to scale) in 23 lung tumor patients, measured using implanted markers and real-time stereoscopic fluoroscopy. [Reproduced from reference 67: *Int J Radiat Oncol Biol Phys*, vol 53, "Precise and real-time measurement of 3D tumor motion in lung due to breathing and heartbeat, measured during radiotherapy," Y. Seppenwoolde, H. Shirato, K. Kitamura, S. Shimizu, M. van Herk, J. V. Lebesque, and K. Miyasaka, pp. 822–834. © 2002, with permission from Elsevier.].

E. 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. Therefore, the respiratory motion pattern for each individual patient should ideally be assessed prior to treatment. Furthermore, the respiratory compensation procedures and algorithms should be adaptable to each patient's particular breathing behavior.

In many cases, it is difficult or impossible to observe the tumor directly during treatment delivery with fluoroscopic or portal images, prompting researchers to observe surrogate internal structures, such as the diaphragm, which would be expected to have a close relationship with the tumor motion for abdominal organs and lower-lobe lung tumors, in which the mechanical coupling between tumor and diaphragm will be the strongest. However, this practice has not yet been adequately validated with data that directly correlates tumor motion with diaphragm motion, and there are known instances where it will lead to errors. For example, Iwasawa et al.[102] reported observations of diaphragm motion in patients with emphysema. They noticed instances in which the diaphragm moved paradoxically, both as a single structure and with respect to the ventral rib cage. Because the population of lung cancer patients presenting for radiotherapy contains many patients with compromised pulmonary function, concerns are raised about the use of the diaphragm as a surrogate indicator of lung tumor motion even in the lower lobes, where the tumor, diaphragm, and external surface motions are assumed to be the most closely coupled. Other observers notice that diaphragm motion is not necessarily related to the motion of other organs and structures in either displacement[66,78] or phase.[82,88]

If a surrogate structure, such as the chest wall or diaphragm, is used to signal tumor position for the purpose of 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[103-105] or other anatomy.[70,106,107] A summary of such studies is given in Table 4. 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 4. Correlation of tumor/organ motion with the respiratory signal.

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.[70]
Tumor and diaphragm, fluoroscopy	Abdominal displacement	43	0.41–0.94	Short delays observed	Ahn et al.[103]
Tumor, SI fluoroscopy	Spirometry & abdominal displacement	11 (23)	0.39–0.99	–0.65–0.5 s	Hoisak et al.[104]
Tumor, 3-D 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.[105]
Lung vessels, cine MRI	Abdominal displacement	4	SI 0.87 ± 0.23, AP 0.44 ± 0.27	--	Koch et al.[106]
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.[100]
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.[100]

3-D: three-dimensional; AP: anterior–posterior; CT: computed tomography; MRI: magnetic resonance imaging; pts: patients; s: second(s); SI: superior–inferior.

Ultrasound and MR real-time imaging procedures are being developed and their application to volumetrically monitor respiratory motion is appealing.

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.[108,109] 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.[110] 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.[111,112] A convolution is not completely correct to describe the dose changes (see for example references 113, 114, 115), but is quite accurate in practice.[116] Systematic errors cannot be accounted for by this approach, which makes pretreatment imaging procedures (as described above) and frequent monitoring during treatment particularly important. The following components contribute to the overall geometric error and should be considered when designing CTV–PTV margins:

- Inter- and intraobserver variations in GTV delineation for lung cancer[20-23] and CTV delineation for breast cancer[24,25]
- Motion artifacts (respiration and cardiac) in the CT scan, which are random in nature but cause systematic errors during delivery
- Respiratory motion and heartbeat during delivery,[67] which are periodic functions of time
- Daily variations of respiratory motion[67,71,72,117]
- 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).[22,26-32,101]

Note that respiration-motion management techniques not only affect the accuracy of target localization, but can also play a role in normal tissue sparing.[77,118] It is also important to note that fast tumor shrinkage occurs quite often in lung radiotherapy, which may give rise to systematic delivery errors.[101]

The distortion of the planning CT is an important source of systematic error that should be combined with other sources of systematic error to estimate the required margin.

A recent publication by van Herk et al.[119] found that for sufficiently small range of motion, and for idealized respiratory motion, respiratory motion can be assumed to be normally distributed and included with other errors. George et al.[115] also concluded, based on measured data, that for most

treatment-planning purposes respiratory motion can be considered to be normally distributed. The combined effect of random and systematic errors, including respiration, can be quantified in a dose-probability computation[58,120] or through biological modeling.[119,121]

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.[122] This section describes QA techniques used in the management of respiratory motion, and 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's skin can be reused provided appropriate procedures are followed.

1. 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.

2. 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.

3. Simulation

By viewing the patient with fluoroscopy or ciné CT, the magnitude of respiratory motion and the correlation 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.

4. 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.

5. 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. An AP radiograph showing the diaphragm provides a confirmation that the lung inflation, as indicated by the distance of the dome of the diaphragm to a stationary anatomical landmark, remains constant. Sometimes, lung tumors are sufficiently discernable 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 that diaphragm position is repeatedly different 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. Each image in the sequence can then be reviewed to identify inter– and intra–breath-hold motion. Although the analysis of such image sequences is very time-consuming and may not be performed for every patient, it does give useful insights into the accuracy of the treatment.

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.[123] (see also Kissick et al.[124]) 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.[125] showed that the magnitude of dosimetric errors may approach 15% for a single dynamic wedge treatment. Bortfeld et al.[126] 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[127] and Keall et al.[128] 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). The distance to agreement on the edges of the field was much larger than 2 mm, which is a typical clinical benchmark value used for steep-dose gradient regions.[129] It should be mentioned that none of these studies included the potential impact due to target deformation, thus the effects of such conditions remain unknown.

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.[123] 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.[126] 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.[130] and Chui et al.[131] The distribution of dose values of four sample points was Gaussian about the expected dose value with a standard deviation of about 1% for a typical 30-fraction treatment. Three of the four points were at field edges (high-dose gradient regions), with the last point in the middle of the field (low-dose gradient).

In a follow-up study, Jiang et al.[132] experimentally verified the findings of Bortfeld et al.[126] for a single point in a low-dose gradient region using MLC-based IMRT; however, these studies assumed or applied simplistic, one-dimensional (1-D) motion, which can be quite different from the real, complex phenomenon of breathing. 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.

D. Workload

Respiratory 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 1 hour with the patient and an additional half 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 2 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

The methods that have been developed 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 interfractional variations for the different methods is given in Table 5.

Table 5. Summary of intra- and interfractional variations for different methods of respiratory management.
[Reproduced from reference 222: S. Mageras, E. Yorke, and S. Jiang, "4D IMRT delivery" in *Image-guided IMRT*, T. Bortfeld, R.K. Schmidt-Ullrich, W. DeNeve et al. (eds.), Table 1, pp. 269–285.
]

Reference	Technique	Organ	Intrafraction variation (cm)	Interfraction variation (cm)
Cheung et al.[223]	BH at inspiration with ABC	Lung tumor	--	SD: 0.18 LR, 0.23 AP, 0.35 SI
Dawson et al.[224]	BH at exhale with ABC	Diaphragm	SD: 0.25	SD: 0.44
Ford et al.[86]	Gating at exhale with RPM	Diaphragm	Mean: 0.26 SD: 0.17	Mean: 0.0 SD: 0.39
Hanley et al.[77]	DIBH	Diaphragm	SD: 0.25	--
Mah et al.[180]	DIBH	Diaphragm	--	0.4*
Negoro et al.[191]	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 et al.[225]	mDIBH with ABC	Diaphragm	Mean: 0.14 SD: 0.17	Mean: 0.19 SD: 0.22
Wagman et al.[156]	Gating at exhale with RPM	Abdominal organs	Mean: 0.20	--

* includes setup error; ABC: active breathing control; AP: anterior–posterior; BH: breath-hold; DIBH: deep inspiration breath-hold; LR: left–right; mDIBH: moderately deep inspiration breath-hold SD: standard deviation; SI: superior–inferior; 3-D: 3-dimensional error.

A. Motion-encompassing methods

1. Introduction

Most radiotherapy facilities do not currently have methods that explicitly account for respiratory motion, the problems of which were outlined in section III. In the current section, we give the 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, inhale and exhale breath-hold CT, and four-dimensional (4-D) or respiration-correlated CT. These are listed in order of increasing workload. For these techniques, 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 to 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.[133-135] In the slow-scanning method, the CT scanner is operated very slowly, and/or multiple CT scans are averaged such that multiple respiration phases are recorded per slice. Slow CT scanning is available on most CT scanners; therefore, is generally the method most available. Hence, the image of the tumor (at least in the high-contrast areas) should show the full extent of respiratory motion that occurred during the time the anatomy was scanned, 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; 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. For slow CT scanning, one CT scan is obtained, so the overall treatment process does not increase in complexity over that of a free-breathing CT scan.

The disadvantage of slow CT scan methods 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;[61-64] 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 4-D PET may be a better option. Another disadvantage is the increased dose from slow CT scanning compared with conventional CT scanning.

3. Inhale and exhale breath-hold CT

A solution to obtaining a tumor-encompassing volume that can be implemented in most clinics is to acquire both inhale and exhale gated or breath-hold CT scans[49,136-138] of the patient during the CT simulation session. Taking both inhale and exhale CT scans will more than double the CT scanning time and relies on the patient's ability to hold his or her breath reproducibly. Two scans will be obtained; thus, image fusion and extra contouring are required. For lung tumors, the maximum intensity projection[140] (MIP) tool[4] 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 during breath-hold. Dose calculation should be performed on the CT data set that is most appropriate for the particular patient, e.g., exhale CT for patients generally spending more time at exhale than inhale. The exhale 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 inhale and exhale of a scan length sufficient to cover the tumor volume to determine range of motion of the GTV. Some form of respiratory monitoring is necessary to verify gated 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 (4-D) CT/respiration-correlated CT

A promising solution for obtaining high-quality CT data in the presence of respiratory motion is 4-D CT or respiration-correlated CT (conventional and cone-beam approaches).[56,57,93-100,141-144] Four-dimensional data can be analyzed to determine the mean tumor position, tumor range of motion for treatment planning,[140,145-147] and the relation of tumor trajectory to other organs and to a respiration monitor.[100] A limitation of 4-D CT is that it is affected by variations in respiratory patterns during

[4] 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.

acquisition. Breathing-training techniques have been developed,[73] however, even with these techniques artifacts can be observed.[99] A schematic of 4D CT using a ciné acquisition process is shown in Figure 6.

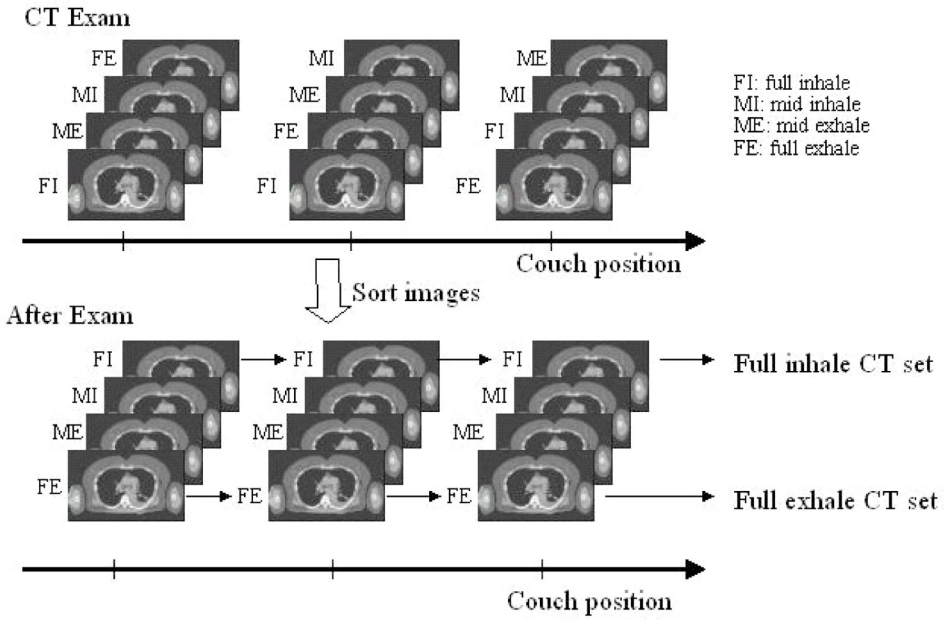


Figure 6. A schematic of the 4-D CT process using ciné acquisition. Images are acquired at each couch position for many respiratory phases. The image acquisition is time synchronized with the respiratory signal acquisition, allowing all images of a particular stage of the respiratory cycle to be concatenated into a complete 3-D CT image. All of the phases put together make up a 4-D CT data set. [Figure courtesy Dr. Sonja Dieterich.]

A 4-D CT scan can be obtained in approximately 1 minute of scanning time with a 16-slice CT scanner. Generally 8 to 25 complete CT datasets are reconstructed, the optimal use of which has yet to be determined. Four-dimensional CT can be used to reconstruct inhale, exhale, and slow CT scans.[99] If 4-D CT is used for these purposes, the procedures described above can be followed. The MIP tool, as mentioned above, may be useful in obtaining the tumor-motion–encompassing target volume.

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. Since the beam is not continuously delivered, gated procedures are longer than nongated procedures.

The applicability of respiratory gating in radiotherapy was first studied in Japan in the late 1980s and early 1990s.[148] Initial studies monitored respiratory motion using some form of an external marker that generated the required respiratory signal. Gating was successfully applied by adopting such an approach on a phantom and on patients with tumors close to the diaphragm.[148] Early clinical studies[149] using respiratory gating as a treatment delivery approach on patients reported successful implementation with treatment times up to a maximum of twice the time required for conventional radiation delivery. More recently, Minohara et al. have reported on gated heavy ion-beam treatments.[82] Hara et al. have reported on stereotactic single high-dose irradiation of lung tumors under respiratory gating.[150]

In the United States, early research into this approach began around the mid 1990s. Kubo et al.[36] evaluated different external respiratory signals (by employing thermistors, thermocouples, strain gauge methods, and a pneumotachograph) to monitor respiratory motion and concluded that temperature and strain gauge methods produce the most desirable signals in terms of reproducibility, accuracy, and dynamic response. Subsequent studies further investigated the requirements for applying respiratory gating as a routine clinical tool, among them, the clinical efficacy of respiratory gating,[151] desired beam characteristics,[152] potential for gating in combination with IMRT (gated IMRT),[153] determination of optimal parameters,[128] and potential radiotherapy improvements.[53]

Respiratory gating is currently under study by several centers to account for respiratory motion during radiotherapy of thoracic and abdominal tumors.[70,73,86,153-157] The treatment procedure is essentially the same as the 3-D conformal therapy approach. More importantly, imaging and treatment are synchronized with the patient's respiration cycle, thereby increasing the potential for CTV–PTV margin reduction. In spite of these potential advantages, some important issues require attention, as discussed in the paragraphs below, to achieve the best results with this technique.

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, inhale and exhale. 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. A complete breathing cycle corresponds with a phase interval from 0 to 2π (for fully periodic

motion, 0 is at the inhale level of the respiration trace). In phase-based gating, 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.[154] Typically, a gate extends over a region of the breathing cycle where the motion of the tumor is estimated to be less, compared with the rest of the respiratory cycle (such as at exhale), or where the lung volume is maximal (such as at inhale). The ratio of the time spent by the signal 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. The thresholds for the gate are manually determined based on the motion learned by the system.

2. Residual tumor motion within the gating window

Some tumor motion still occurs within the gate and is referred to as "residual motion."[158] The choice of gate width is a trade-off between the amount of residual motion and duty cycle.

3. Gating using an external respiration signal

a. Introduction. Currently, the commercially available respiratory gating system using an external respiration signal most widely discussed in publications is the Varian Real-time Position Management™ (RPM) system (Varian Medical Systems, Palo Alto, CA); thus, the procedures described are applicable to this device, although they can be generalized to other implementations. BrainLab (Heimstetten, Germany) has a U.S. food and Drug Administration (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.[159]

b. Patient selection. 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.

c. CT simulation. 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. The exact position is 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. A thin patient with a concave-shaped abdomen or sloping chest may require placing the marker box either superior or inferior to the standard location. Alternatively, one can make a patient-specific shim out of convenient and durable material such as Styrofoam™. Some patients with throbbing descending aortas may need the box located off midline. 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. Also, the relative anatomic location (e.g., 6 cm superior to the xyphoid process) should be included in the patient's chart in case the skin mark is erased.

Following initial physician consult, selected patients receive a gated CT scan. Gating parameters (displacement/phase, exhale/inhale, duty cycle) are determined prior to the scan based on observation of the external respiration signal and, if possible, respiration-synchronized fluoroscopy. In what is termed "prospective gated CT," a respiration gating system sends a trigger to the CT scanner once per breathing cycle, typically through the injector port, 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. Note that the CT image is not gated in a strict sense, but is initiated by the trigger. Gate width and CT scan rotation time should be similar. If the gate width is short compared with the scanner rotation time, anatomic positions outside the intended gate will be included in the image. If the gate width is large compared to the scanner rotation time, more anatomic motion will be occurring during the gate than was captured in the CT image. Gate width/scanner rotation mismatches can lead to differing amounts of motion included in the CT images and in the actual treatment, which 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, not the duty cycle, 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. Thus, for a single-slice CT scanner the CT acquisition process takes the time required for 100 breaths or more (at least 6 to 7 minutes); however, for multislice scanners, this time is reduced proportionately by the number of detector rows. For CT simulation, the camera is fastened on the couch to maintain a fixed distance from the marker box as the couch moves. It is important that the mount be secure, because unintended camera motion is interpreted by the system as irregular breathing.

Note that a subset of a 4-D CT scan (section IX.A.4) can be used to acquire the equivalent of a gated CT scan.

d. Treatment. Following patient setup, the marker box is positioned as in simulation, and the patient is instructed to relax and breathe normally, or to follow audio and/or visual prompting if it was used 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 gated radiographs or portal images and comparing them with digitally reconstructed radiographs (DRRs) from the gated planning CT. Although the commercial system enables the radiation beam automatically, the therapist should be alert to the graphic cues on the system monitor and be prepared to intervene if the patient's breathing is very irregular or different from simulation. Portal 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.[57,160]

e. Patient-related quality assurance. For internal and external tracking systems, there is a possibility that the time-dependent internal target position will not match the respiration monitoring. 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 (Figure 7).

Note that these differences can occur not just with gating, but for any system using a surrogate for respiratory motion. This effect can cause the position of the beam-on pulse to shift relative to the actual respiratory cycle of the target. The positioning of the gating thresholds, with respect to the anatomic respiratory motion, should be validated for each patient. Where available, a minimum of 30 seconds 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 discernable—should be compared with the external respiratory signal; a time delay larger than 0.5 seconds between the two, if consistently observed, should be corrected or accounted for when setting the gate interval. An electronic portal imaging device (EPID)-based approach for position verification in this manner has been proposed by Berbeco et al.[161]

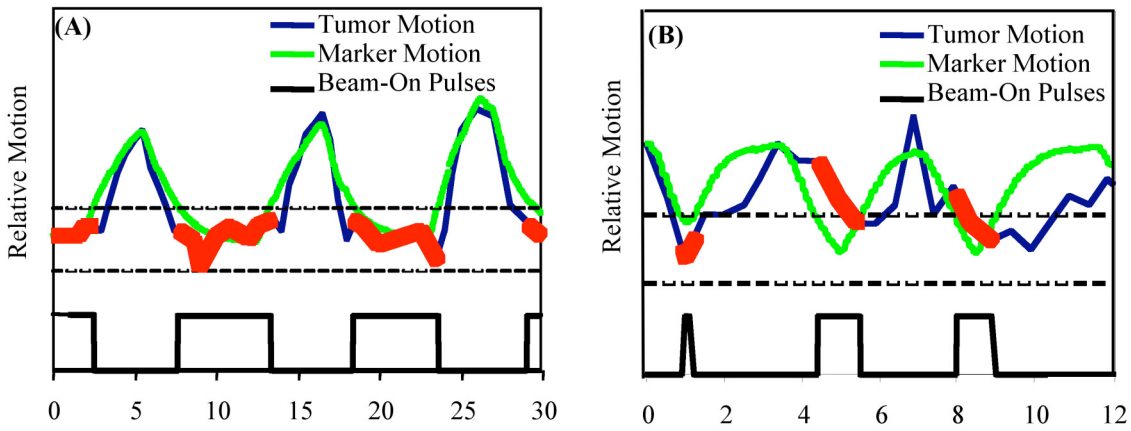


Figure 7. Comparison of external marker block motion with internal motion of the clinical target volume (CTV) for a patient with (a) no phase shift and (b) a patient with significant phase shift. The respiratory gating thresholds are set using the external marker block motion. The beam-on pulses are highlighted in red over the internal CTV position. [Reproduced from reference 227: *Int J Radiat Oncol Biol Phys*, vol 48, "Clinical experience with a commercial respiratory gating system." C. R. Ramsey, D. D. Scaperoth, and D. C. Arwood, pp. P164-165. © 2000, with permission from Elsevier.]

f. Equipment quality assurance. Because respiratory gating is a dynamic feedback process, in order to test in vivo dosimetry and target localization, dynamic test phantoms that simulate respiration are needed. Several important factors are to be taken into consideration: (1) The test phantom should be capable of producing cyclical and/or motion similar to human respiration. (2) The gating feedback mechanism must be able to detect test phantom motion in a manner similar to the surrogate used in the clinical process. (3) The device should allow detectors, such as ion chambers or diodes, to be attached during motion, such that absolute dosimetric measurements can be made. (4) The phantom should also be reliable and have a reasonable cost. Several custom-built phantoms have been made to meet these criteria,[53,99,128,132,151,162,163] and commercial systems are available from several vendors. Further equipment QA tests developed for use with the Varian RPM respiratory gating system are described in reference 151, which should be consulted when developing a QA program for this device.

4. Gating using internal fiducial markers

a. Introduction. Although in principle there are several options for using internal fiducial markers for respiratory-gated treatments, this section will focus on the real-time tumor-tracking radiotherapy system, developed jointly by Hokkaido University and Mitsubishi and based on radiographic detection of implanted fiducial markers to gate the radiation delivery.[1,52,67,81,164-170] 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. When each fiducial is within an acceptable range of the desired (simulation) position for both stereotactic x-ray cameras, the linear accelerator delivers radiation.

b. Patient selection. Tumor motion is assessed prior to 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 minutes). 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).

c. Simulation. The clinical studies using the internal motion-gated system have used a series of CT scans: a normal, FB CT simulation scan, a second image set at inhale, and a third set at exhale. The patients perform voluntary breath-hold during the second and third CT scans. Patients are immobilized with an Alpha Cradle® and their arms positioned overhead.

d. Planning. Treatment plans are designed on both the inhale and exhale 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 inhale 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. Most patients are treated at exhale, resulting in a larger duty cycle than at inhale.

e. Treatment. At the beginning of each treatment, the fiducial marker 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 minutes, and the duty cycle varies by patient and by the choice of respiratory cycle part to be used for treatment.

f. Quality assurance. The coordinate systems of the fluoroscopy unit and linear accelerator must be properly aligned. The coordinate system alignment should be checked regularly, particularly if substantial drifts are seen, 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.

5. Gated IMRT

Kubo and Wang[127] 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 (1-D mechanical device) was essentially the same as that for delivery without motion. Target deformation was not considered.

Gated arc therapy and tomotherapy are also feasible. In this scenario, an arc (conventional gantry system) or continuous rotation (ring gantry system) is repeated while gating the accelerator until the correct number of pulses is delivered from each beam angle. The couch is stationary until all beam pulses are delivered, then indexed to the next position. The same technique can also be used with helical delivery: the treatment helix would need to be repeated until all of the pulses for each angle had been delivered. The ability to quickly start and stop gantry rotation or patient breathing irregularity need to be resolved before clinical implementation of gated arc therapy or tomotherapy.

Respiratory gating techniques increase the treatment time. This is more pronounced for gated IMRT in which the product of the IMRT efficiency, typically 20% to 50%, and the gating duty cycle, 30% to 50%,[86,156] leads to a 4- to 15-fold increase in delivery time over a conventional treatment. By treating at the highest dose rate, the increase in treatment time can be reduced. The increase in dose rate from 300 to 600 monitor units per minute (MU/min) can reduce the clock time by approximately 40%.[157] Gated treatment session times are increased relative to standard treatments by 2 to 10 minutes depending on patient compliance.[157] Increases in delivery time should be considered in the context of patient comfort, increased likelihood of patient movement and decreased patient throughput. Furthermore, there is a suggestion that during substantially longer treatments, tumor control may be reduced due to the increased intrafraction repair of sublethally damaged tumor cells.[171,172]

c. Breath-hold methods

1. Introduction

Breath-hold methods of respiratory motion immobilization are discussed in the following paragraphs. Though predominantly applied to lung cancer radiotherapy, breast cancer radiotherapy is also an attractive option with breath-hold methods. Though the intrafraction motion is small for normal respiration,[173] during inhalation the diaphragm pulls the heart posteriorly and inferiorly away from the breast, and thus the is potential reduction of both cardiac and lung toxicity.[174-179]

2. Deep-inspiration breath-hold

a. Introduction. A reproducible state of maximum breath-hold (deep-inspiration breath-hold [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).[77,180,181] 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).

The DIBH technique involves verbally coaching the patient to a reproducible deep inhale 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. To facilitate the patient's ability to hold the mouthpiece, the connective tubing is supported by a flexible, metal gooseneck and base fixed to the couch above the patient's head. The pneumotach spirometer is a differential pressure transducer that measures air flow; a computer program integrates the signal to obtain the volume of air breathed in and out, which is displayed and recorded as a function of time. While watching the display, the therapist coaches the patient through a modified version of the slow vital capacity maneuver, consisting of a deep inhale, deep exhale, second deep inhale, and breath-hold. At each stage of the maneuver, the therapist waits for the breathing trace to plateau before coaching the patient to the next stage. The program compares air volumes at deep exhale and second deep inhale with user-set thresholds and changes the color of the bar graph at the right of the display to help the therapist verify the reproducibility of the maneuver. The maneuver yields highly reproducible lung inflation at approximately 100% capacity, which can be maintained for 10 to 20

seconds (patient specific). After completion of each breath-hold, the mouthpiece is removed to prevent CO_2 buildup in the tubing, and the spirometer is reinitialized prior to mouthpiece reinsertion.

b. Patient selection. The 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. Because DIBH is relatively demanding for patients, 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[181]) than is possible with FB. To familiarize the patient with the DIBH maneuver and to determine the patient's ability to perform it reproducibly, a training session with the spirometer is given a few days before simulation, which also provides initial threshold values.

c. Simulation. 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 inhale (DI); and (3) with spirometer-monitored inhale. The FB and inhale scans are for QA purposes; see section g. 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, three CT scans, and resting between scans—takes approximately 2 hours.

d. Planning. The treatment plan and DRRs use the DI breath-hold CT scan. Despite the reduced respiratory motion, at MSKCC the PTV margin has not been reduced for three reasons: first, DI lung expansion allows sufficient target dose escalation with acceptable estimated lung toxicity, as described above; second, the margins protect against possible expansion of microscopic disease due to DI; and third, the treatment-planning dose-calculation algorithm (pencil-beam based) at present does not handle lateral disequilibrium in low-density tissue.

e. Treatment. 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 to600 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 seconds 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 to 10 minutes longer than a similar beam arrangement for an FB patient.

f. Treatment studies. Forty-five patients were treated with DIBH at MSKCC (44 with NSCLC) between 1998 and 2004; of these, eight patients were treated with DIBH in combination with IMRT. For the first seven NSCLC patients treated with DIBH, Rosenzweig et al. found that the average lung volume increased by a factor of 1.9 relative to normal breathing.[181] Since dosimetric predictors of radiation pneumonitis depend strongly on the fraction of irradiated lung, DIBH may permit higher total treatment doses for the same predicted lung toxicity. By comparing the 3D conformal radiation treatment plans for standard normal breathing and DIBH CT scans, restricting the Lyman model[182] lung normal tissue complication probability to not more than 25% and maintaining the same PTV margin, the average prescription dose could have been increased from 69.4 Gy with FB to 87.9 Gy with DIBH.[181] In some cases, DIBH increases the separation between the GTV and the spinal cord, giving more freedom in the choice of beam directions.[183]

g. Patient-related quality assurance

Simulation: As described in the earlier section, in addition to the DIBH CT scan there is an FB scan and an inhale breath-hold scan. In addition to providing an alternative treatment-planning image set, the FB scan provides a check 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 inhale 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.[180]

Treatment: In all imaging and treatment sessions, the therapist is instructed to wait 1 second following breath-hold before turning on the beam, to allow for transient diaphragm relaxation.[180]

h. Equipment-related quality assurance. The spirometer is calibrated with a 3.0-liter syringe for flow rates between approximately 0.5 and 3.0 liters per second (L/s). The linearity of spirometer integrated airflow versus actual (syringe) volume is checked over a range of 0 to 3 L in either flow direction; typical linearity is within 2%. The calibration is checked whenever the spirometer gas sterilized, approximately every 2 to 3 months. Occasionally, drift of the spirometer is observed following sterilization, which is usually correctable by reassembling the device.

3. Active-breathing control

a. Introduction. Active-breathing control (ABC) is a method to facilitate reproducible breath-hold.[139,177] 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. The ABC apparatus can suspend breathing at any predetermined position and is often used at moderate or deep inhale. The device 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. When an operator "activates" the system, the lung volume and the breathing cycle stage at which the balloon valve will be closed are specified. The patient is then instructed to reach the specified lung volume, typically after taking two preparatory breaths. At this point, 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 to 30 seconds, and should be well tolerated to allow for repeated (after a brief rest period) breath-holds without causing undue patient distress. A timer display counts down the remaining breath-hold duration in seconds.

The Beaumont experience[177,178,184] shows that a moderate (deep) inhale breath-hold (mDIBH) level set at 75% of deep inhale achieves substantial and reproducible internal organ displacement while maintaining patient comfort. With the ABC system, the intended mDIBH position is calculated from the exhale baseline and set during an initial training session for each patient. Variation of the baseline between breaths is possible. In operation, verbal instructions are always given to help a patient achieve a steady breathing pattern. For each breathing cycle, the lung volume is intentionally renormalized to a zero baseline each time zero flow is detected at exhale. Renormalization occurs mostly at the beginning of a study. Once the patient achieves normal respiration in a relaxed manner, both the frequency and magnitude of the renormalization becomes minimal. It is from this stable baseline that three measurements of the inspiratory capacity are made. The mDIBH threshold is then set to approximately 75% of the average inspiration capacity. The value is recorded and used for all subsequent sessions. Given the relatively large lung volume at mDIBH, the renormalized baseline provides a sufficiently stable reference for achieving reproducible breath-holds.

b. Simulation. Prior to the start of simulation (potentially at the beginning of the session), 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 should be made aware 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. Specifically, 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.

c. Treatment planning. Treatment plans will 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 to manage respiratory motion.

d. Treatment. Potential collisions between the ABC equipment and the linear accelerator should be evaluated when choosing gantry and couch angles for treatment. The documented breath-hold state and duration should be used as guidelines for assisted breath-hold. If possible, each beam angle should be delivered in a single breath-hold. 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 linear accelerators that require the breakup segments as individual beams. Each beam needs to be delivered before the patient is released from breath-hold.

e. Patient-related quality assurance. As with DIBH, an important concern with ABC is reproducibility of breath-hold. It is essential that the function of this system be well understood prior to use by all personnel operating the system and that the patient has received and understands appropriate instruction. The process for establishing a breath-hold at a given state (e.g., exhale, inhale, deep inhale) should be documented and tested. If different patients are to exercise a breath-hold at different relative states, appropriate procedures and documentation are necessary. A standard set of patient instructions for communication with the ABC operator and for emergency actions to reestablish breathing is recommended. All of the ancillary components will require both inventory and maintenance procedures. It is important at the outset to understand the use of consumable items (nose clips, filters, gas canisters, etc.), to establish a hygienic procedure for cleaning reusable items

(e.g., rubber mouthpiece), and to establish possible failures of the system from the use of this equipment so that a proper set of use and maintenance procedures can be implemented.

f. Equipment-related quality assurance. A typical ABC system has three major components: a system to provide proper hygienic use of ABC over multiple patients, a system to monitor the breathing cycle, and a means to stop the flow of air to the patient. Ancillary equipment includes systems to monitor air pressure and to sense relative oxygen and carbon dioxide concentrations. The ABC system has safety devices to permit rapid restoration of airflow by the patient, a remote operator, or both.

The key functions that should be maintained 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. These functions form the core of a QA program for ABC and should be checked frequently. It is reasonable to establish the calibration of airflow for each session and to test safety features at regularly scheduled intervals.

Maintenance of calibration: 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 exhale. Both systems are typically calibrated using a 3.0-L syringe. It is recommended that, apart from the vendor's recommended calibration, the volume calibration should be checked at different flow rates similar to those seen in patients (it is very easy to establish physiologically unrealistic flow rates when operating the syringe, and the calibration software may not require a varying flow rate to establish a calibration). It is theoretically possible to achieve a flow rate that is so slow that a mechanical spirometer will not respond accurately (hence, the need to reestablish calibration at exhale), and this flow limit should be established.

Activation/cessation of breath-hold: The flow sensor is located within a chamber through which the patient breathes, and the balloon valve is typically found at the end of the chamber. When deflated, air can pass from the room or an ancillary gas supply through the chamber to the patient. When inflated, the airflow is blocked, essentially sealing the patient/chamber system. Inflation may be accomplished by air from a compressor or high-pressure canister, such as those used to provide supplemental oxygen to patients. Unless the fixation to the patient involves a mask that covers the nose and mouth, it is expected that airflow through the nose would be restricted via a nose clip. The breath-hold duration may be established via a timer on the control computer, manual interaction of

the operator via control keys, or both. Some ABC systems use a second computer monitor in the simulation/treatment rooms for visual feedback to the patient.

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.

Commissioning and routine QA: QA procedures for the ABC system include establishing written procedures for use of the system, testing the system performance establishing a breath-hold and reestablishing FB, testing all emergency procedures, performing mock setups and treatments in the geometries that patients will follow, establishing the necessary periodicity of system calibration, testing calibration at realistic flow rates, ensuring adequate supplies of consumables are available, and establishing and testing an online adjustment process, if needed.

4. Self-held breath-hold without respiratory monitoring

a. Introduction. As the name "self-held breath-hold techniques" implies, the patient voluntarily holds his/her breath at some point in the breathing cycle. During a breath-hold, the beam is turned on, and the dose is delivered to the tumor. As part of the implementation of the self-held breath-hold technique, a control system has been developed[85,185] for the Varian C Series accelerators, which make use of the "Customer Minor (CMNR)" interlock. The patient is given a hand-held switch that is connected to the CMNR interlock circuit. When the switch is depressed, the CMNR interlock is cleared at the console, allowing the therapist to activate the beam. When the switch is released, the CMNR interlock is active, turning the beam off and disabling any further delivery until the switch is depressed again. It should be noted that although the therapist is the only person who can turn the beam on, both the therapist and the patient can turn the beam off. Since this makes use of the existing interlock circuitry, there are no modifications to the beam-delivery system or any of the safety features of the accelerator. Studies have shown that the most reproducible position tends to be at deep inhale or deep exhale. This, along with the potential dosimetric advantages of increasing the lung volume,[77,177,178,181,184] makes deep inhale the preferred point for breath-hold. Therefore, the discussion in earlier sections regarding the advantages of DIBH and ABC would be similar to the advantages with this method. The self-held breath-hold system is not commercially available. A description of materials and methods for assembling such a system are given in references 85 and 185.

b. Patient selection. This mode of treatment relies heavily on the ability of the patient to perform a breath-hold independently and to control the CMNR interlock circuit. The patient must be able to understand and perform these functions, be capable of performing a reproducible breath-hold, and be able to maintain it for at least 10 seconds. 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.

c. Simulation. Following evaluation under fluoroscopy on a conventional simulator, patients receive a breath-hold CT scan, in which the scan sequence is segmented into 10-second 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.

d. Planning. 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.[85] showed that on average the margin for internal motion in the SI direction was reduced from 12.9 mm 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.

e. Treatment delivery. Treatment with self-held breath-hold gating is relatively straightforward and efficient. The patient is set up in the usual way and holds the switch connected to the CMNR interlock system. 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. As soon as the CMNR interlock clears, the therapist presses "Beam On" to initiate treatment. 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.

f. Treatment studies. At the Cross Cancer Institute, the "held-breath self-gating" technique[85] has been studied in 28 patients (up to 2004) with 8 of them treated with the technique. As of this

writing, the technique has been used almost exclusively with IMRT using a step-and-shoot delivery technique, although more routine use for 3-D conformal treatments is planned. The IMRT technique typically uses five segmental MLC fields with approximately 10 segments per field, for a prescribed dose of 2.4 Gy/fraction. Each field requires about 150 to 200 MU, corresponding with 15 to 20 seconds at a dose rate of 600 MU/min, and is usually delivered in two or three breath-holds. The increased time may become burdensome if the patient can maintain the breath-hold for only the minimum 10 seconds; however, the majority of patients are capable of significantly longer intervals, making it easier to tolerate the procedure.

g. Patient-related quality assurance. Important QA issues are ensuring accurate setup, breath-hold stability, and reproducibility. Only those patients that are able to benefit from this technique and can reproducibly hold their breath should be enrolled. 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 suitability of each patient for the technique and the margins that should be used.

h. Equipment-related quality assurance. 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. Since a standard accelerator interlock is used, it should be sufficient to test annually that interrupting the beam does not cause a change in output.

5. Self-held breath-hold with respiratory monitoring

a. Introduction. This technique uses a commercially available device (Varian RPM), to monitor patient respiration and to control dose delivery, but requires patients to voluntarily hold their breaths 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 (which is discussed further in the section on treatment and clinical imaging studies [section V.f]). 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.

b. Patient selection. At the time of consultation, patients are tested for their ability to hold their breath for periods of 10 seconds. Patients must also be able and willing to follow verbal breathing instructions and actively participate in their treatments. Patients are evaluated further at simulation.

c. CT simulation. Programmed audio instructions such as "breathe in, breathe out, hold your breath" are used to synchronize the CT scan with breath-hold. The patient holds his/her breath at exhale for periods of 7 to 15 seconds, depending on ability. CT images are acquired using a helical scan mode. At the end of a scan segment, the CT scanner is programmed to issue a "breathe" command followed by a 20-second break. The sequence may be automatically repeated until the entire region of interest has been scanned; 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. If the patient is unable to comply with the breath-hold instructions, another attempt may be made after additional patient instruction. Subsequent attempts may involve reducing the time of the breath-hold as necessary.

d. Planning. 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.[186] 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.

e. Treatment delivery. Prior to treatment, portal image verification of patient position and gating interval is performed. Following breath-hold instruction, and once the marker trace is within the gated interval, the therapist turns on the beam. 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-second break, and then instructs the patient to "exhale and hold your breath when ready," for resumption of treatment.

f. Treatment and clinical imaging studies. Berson et al.[187] 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. Reproducibility, as determined by the diaphragm position, was improved using the breath-hold technique: the mean and standard deviations were 0 mm and 4 mm, respectively, compared with 2 mm and 7 mm for FB gated ($p = 0.06$).

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 would also control 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 inner-field abutment issues between breath-holds to which other techniques are susceptible.

D. Forced shallow breathing with abdominal compression

1. Introduction

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[188-190] and has been used

elsewhere.[11,191-197] 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.[191]

2. Patient selection

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.

3. 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. At simulation, laser markers are attached to the rigid frame; they later aid in the initial positioning for treatment. Marks are also placed on the anterior surface of the patient, to help realign the patient in the SBF as well as to reposition the SBF in the treatment room. 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.

4. Treatment planning

Negoro et al. reported on 18 patients treated in four fractions to a total dose of either 40 Gy or 48 Gy.[191] Six to eight non-coplanar beams were used with a desired dose uniformity of 10% within the PTV. Based on daily isocenter verification measurements, the recommended PTV margins were 5 mm in both the AP and the right–left directions and 8 to 10 mm in the SI direction.

5. Treatment

In Negoro's study, 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. The pressure plate was required in 11 of 18 patients with tumor motion greater than 5 mm. For 10 patients, the range of motion before abdominal compression was 8 to 20 mm (12.3-mm mean), reduced to 2 to 11 mm (7.0-mm mean) with compression. For one patient, the pressure plate was not used, because respiratory motion had increased.

6. Quality assurance

Simulation: Tumor excursion is evaluated under fluoroscopy from orthogonal directions, and abdominal compression is used when tumor excursion exceeds clinical goals. Usually, the maximum pressure that the patient can comfortably tolerate for the treatment session duration is used.
Treatment: 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 fiducial markers visible in radiographs.

E. Real-time tumor-tracking methods

1. Introduction

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. Real-time tumor tracking can in principle be achieved by using an MLC or a linear accelerator attached to a robotic arm or, alternatively, by aligning the tumor to the beam via couch motion. The Synchrony™ Respiratory Tracking System integrated with the CyberKnife® robotic linear accelerator (Accuray Incorporated, Sunnyvale, CA) is a realization of real-time tumor tracking. Under ideal conditions, continuous real-time tracking can eliminate the need for a tumor-motion margin in the dose distribution, while maintaining a 100% duty cycle for efficient 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. This section will address current techniques to accomplish each of these tasks, discuss known and potential difficulties, and recommend development efforts to address them.

2. 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) real-time imaging of the tumor itself via, e.g., fluoroscopy; (2) real-time imaging of artificial 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.

The most direct form of real-time tumor tracking currently involves imaging the target site during treatment at a sufficiently high frequency. Given the period and irregularity of breathing-induced motion, this requires several images per second, which is equivalent to near-continuous fluoroscopy. The more frequent this imaging procedure, the lower the delivery error; however the x-ray dose will also increase. In each image, it is necessary to automatically locate the tumor (or its surrogate) and calculate its 3-D coordinates, which are then automatically transmitted to the beam-delivery system.

a. Direct tumor imaging. In certain situations, it can be possible to detect a lung tumor directly in radiographic/ fluoroscopic images acquired during treatment. Figure 8 is one such example, showing a lung tumor imaged with an amorphous silicon x-ray detector at an exposure level of approximately 50 mrad.[198] 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.

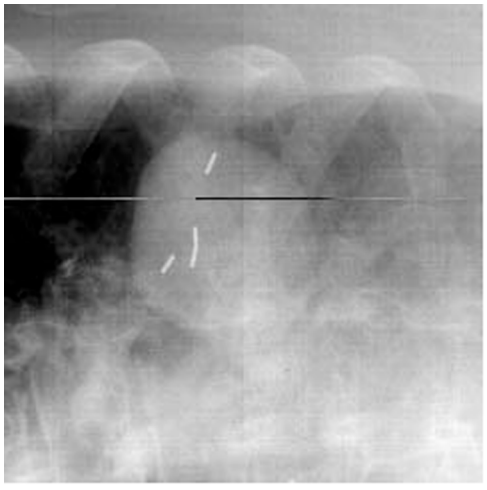


Figure 8. A lung tumor observed with a flat-panel amorphous silicon detector forming part of the CyberKnife image-guided radiosurgery system. The tumor has four gold fiducial seeds implanted in it to enhance its position measurement. [Reproduced from reference 198: *Semin Radiat Oncol,* vol 14, "Tracking moving organs in real time," M. J. Murphy, Figure 1, pp. 91–100. © 2004, with permission from Elsevier.]

b. 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 (Figure 8). 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. Fiducial marker designs that minimize migration through tissue are preferable. Murphy et al.[83] have used 2-mm-diameter spherical gold balls sewn into the pancreas during exploratory laparotomy. Chen,[84] Murphy,[199] and Shirato[81] have used 0.8-mm by 4-mm cylindrical gold seeds implanted into or near lung tumors percutaneously or bronchoscopically.

The high radiopacity of gold fiducial markers makes them detectable in fluoroscopic images of the abdomen and pelvis at exposures as low as 18 mrad per image,[81] allowing continuous monitoring of fiducial position using dual fluoroscopes mounted in the treatment room. Additional radiation dose from imaging should be considered, and readers are directed to the report of AAPM Task Group 75[5] for a detailed review and guidelines for implementation of these techniques. To reduce radiographic imaging exposure, hybrid tumor-tracking techniques are being developed that 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 for the time interval between image acquisitions.[84,88,198-202]

c. Tumor position prediction based on surrogate breathing signals. In situations when continuous fluoroscopic imaging of the tumor position is not feasible, it is necessary to infer the tumor position from external respiration signals. To succeed, this technique requires that there be a robust correlation between the measured respiratory signal and the position of the tumor in three dimensions. If the correlation is simple and stationary, it can be sufficient to measure it before treatment using a fluoroscope to document tumor position simultaneously with the external respiratory signal. The observed correlation can then be used to predict tumor motion during treatment. However, the physiology of breathing motion suggests that stationary correlation is not necessarily a safe assumption.[88,103-105,203,204] If the correlation is not stationary, it should be monitored and updated continually during treatment by acquiring images of the tumor position synchronously with the respiratory signal.[200] 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.[199]

[5] Radiographic Imaging Doses in Radiation Therapy (currently being compiled).

d. Nonradiographic tumor tracking. Seiler et al.[205] have described a miniature, implantable powered radiofrequency (RF) coil that can be tracked electromagnetically in three dimensions from outside the patient. Balter et al.[206,207] 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.

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

The adaptive response of a radiotherapy system to a tumor position signal cannot occur instantaneously. Seppenwoolde et al.[67] 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 delay, measured with a film and phantom, is the total delay and includes computational time in post-processing the image to locate the marker as well as delays in triggering the beam onset. Developers of mechanical systems to realign the beam should anticipate longer delays. The CyberKnife, for example, 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 on the order of 100 to 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. This is necessary regardless of the method by which the tumor position is determined and applies to both beam gating and real-time tracking systems. The problem is complicated by the fact 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.[88,203] However, these fluctuations are not purely random,[208] which means that it should be possible (at least in principle) to predict the character of a particular breath from the observed characteristics of its predecessors. This is the basis for time series prediction by an adaptive filter. Murphy et al.[199] 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.[201] and Vedam et al.[209]

4. Repositioning the beam

There are presently two methods by which the treatment beam can be repositioned in real time in response to tumor motion. The first one is MLC repositioning.[128,210-212] The second method for adaptation uses a robotic manipulator to move the entire linear accelerator with 6 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.[83,84,88,200] It has the advantage of adapting to the full 3-D motion of the tumor. Both methods present the same requirements for identification of the tumor position, prediction compensation for lag time in beam repositioning, and dosimetric corrections for breathing. Both methods can use the same algorithms to meet these requirements. It should be noted that cardiac motion can also cause tumor motion on the order of 2 mm.[67,83] In principle, couch,[213] block,[214] or jaw motion can also be used for beam repositioning.

A concern with realigning the beam to the tumor position is that the beam may pass through a sensitive critical structure that was apparently avoided during the CT planning process. Note that this concern also exists for patient set-ups in which the beam is initially aligned with the tumor.

5. Correcting the dosimetry for breathing effects

Correcting the dosimetry for breathing effects was recently discussed and surveyed by Bortfeld et al.[215] The treatment-planning imaging study used to calculate the dosimetry necessarily captures the anatomy in one static configuration, whereas during breathing, 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.

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

Observations of lung tumor motion show that the tumor can follow a complex 3-D trajectory.[67] Therefore, any tracking method, whether using direct imaging of the tumor during treatment or indirect tumor tracking inferred from external respiration, should preferably provide 3-D coordinates of the tumor, although 2-D motion in the plane perpendicular to the beam direction is also acceptable. Three-dimensional coordinate acquisition requires simultaneous acquisition of two 2-D images from different

directions. Therefore, fluoroscopic studies of tumor motion before treatment should make use of dual fluoroscopes, as would be found, for example, in an angiographic imaging facility. The system described by Shirato et al.[81] uses four fluoroscopes arranged so that, at any time, two of the fluoroscopes have an unimpeded view of the patient. The CyberKnife uses two x-ray imaging cameras arranged to have unimpeded views during treatment.

The beam-delivery system will require a certain amount of time to respond to information about the tumor position. This requires predicting the tumor position to compensate for the time delay. The irregularity of the breathing cycle makes it difficult to predict more than 0.5 seconds ahead 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/compensation system should be kept as short as possible and, in any case, not more than 0.5 seconds.

7. 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 real-time tracking are essentially the same as for beam gating methods, 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, because this represents a source of systematic error that will offset the beam from the tumor by a fixed amount throughout the treatment. 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. If the tumor tracking is accomplished via hybrid tracking methods that involve imaging coordinated with external respiratory signals, the imaging system and the external monitoring system should maintain a calibrated relationship with each other and with the beam-delivery system.

For the CyberKnife system, the geometrical relationship between the tracking system and the beam-delivery system is monitored and verified via an end-to-end dose-delivery test utilizing a specifically designed composite imaging/dosimetry phantom. The phantom is localized within the CyberKnife dose-delivery system using the imaging/tracking system and irradiated with the planned dose. The position of the delivered dose, relative to the plan, reveals any systematic co-alignment error of the tracking and delivery systems. If this alignment is compromised, the delivered dose will be

shifted from its intended location in the phantom. This test takes approximately 1.5 hours and should be performed monthly.

8. Synchronization of IMRT with motion

The most sophisticated and yet challenging methods involve those that attempt to synchronize IMRT delivery with respiratory motion. The primary advantage of these methods is that the patient is allowed to breathe freely, *and* linear accelerator operation may not be interrupted (as in gated and breath-hold methods). Keall et al.[128] demonstrated the feasibility of such an approach. In this study, the respiratory motion (as simulated by a 1-D 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.[210] termed this reference breathing trace the "average tumor trajectory (ATT)." Using 11 lung data sets obtained from a real-time tracking system, Neicu et al. 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. Dynamic MLC-based approaches to respiration-synchronized radiotherapy have also been proposed by Papiez.[211,212]

A similar approach is feasible with tomotherapy. The principal difference is that the respiratory motion would be superimposed on some combination of the MLC leaves, primary collimators, and couch. Treatment planning and delivery would proceed in a similar fashion: a plan is generated based on static CT data, an ATT is derived from patient studies, and the implied motion is superimposed on the plan.

In a different but related approach applicable to IMRT generally, an ATT is derived that would be used *during* planning in conjunction with a 4D CT data set.[216] 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. The problem with this approach is the reliance on deformation techniques, as information from each breathing cycle part would need to be deformed to a common frame of reference to allow for plan evaluation. Such deformation techniques have yet to be rigorously proven. The technique also

assumes that the 4-D CT remains representative of the patient's anatomy throughout individual treatments as well as the entire course of radiotherapy.

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 also for 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 Figure 9 be followed. Box 1 of Figure 9 asks if a method of measuring motion is available. European Organization for the Research and Treatment of Cancer (EORTC) guidelines[109] 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 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 entire range of motion should be considered when establishing the internal margin.[46] 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 Figure 9).

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.

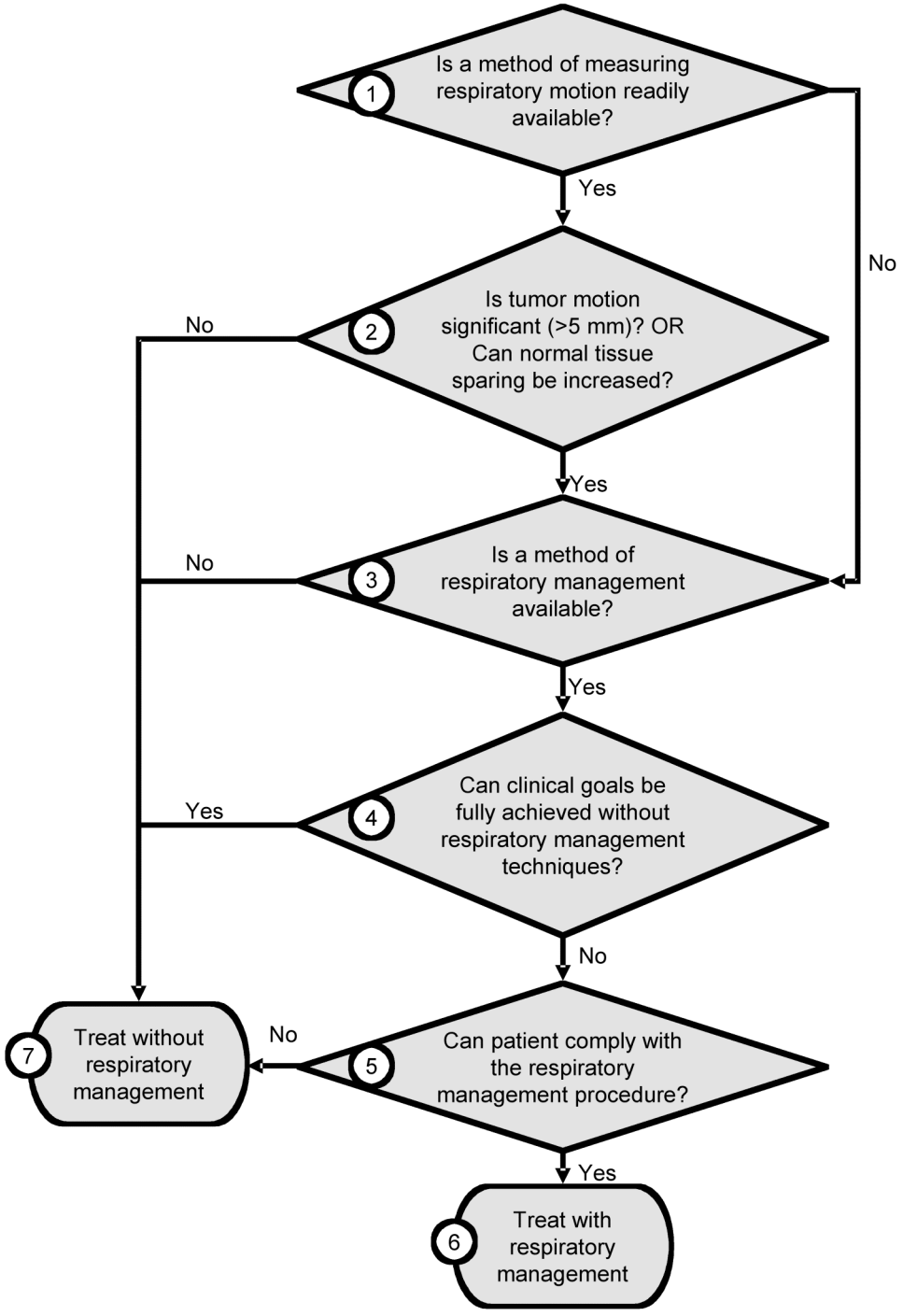


Figure 9. Recommended clinical process for patients with whom respiratory motion during the radiotherapy process is a concern.

If a method of respiratory management is not available (box 3 of Figure 9), 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 Figure 9) 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 4-D 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[88,103-105]

- 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.[46]

Other factors such as setup error and tumor changes during the course of radiotherapy are common to all sites.[46] 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 section VII.E 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. The procedures should be written, and the results from each test recorded and stored. QA procedures are given in

section V.B and discussed under each described motion management technique. The Task Group recommends that these procedures be 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.

VIII. POTENTIAL CONFLICTS OF INTEREST

This task group report details and gives recommendations for the use of vendor-specific devices. Though the authors of this report have strived to maintain objectivity per established principles,[217] particularly relevant for clinical practice guideline documents,[218] we wish to disclose the agreements between the authors of this report and companies that offer products for respiratory motion management in radiation oncology. Paul Keall is the principal investigator (PI) of a sponsored research agreement between Varian Medical Systems and Virginia Commonwealth University (VCU) and is the director of a respiratory gating training course. Standard Imaging has licensed the design of a motion platform developed at VCU. Gig Mageras is an investigator on a sponsored research agreement between Varian Medical Systems and MSKCC and between GE Medical Systems and MSKCC. James Balter is a member of the scientific advisory board for Calypso Medical Technologies. Steve Jiang is the PI for two sponsored research agreements between Varian Medical Systems and Massachusetts General Hospital (MGH). Jeffrey Kapatoes is an employee of TomoTherapy, Inc. Marcel van Herk is a co-developer on patent applications with Varian, Radionics, and Elekta and is an investigator in a sponsored research agreement between Elekta and The Netherlands Cancer Institute (NKI). Elekta has licensed the design of the ABC device developed by John Wong and colleagues. All other authors report no conflicts.

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