



Optimizing immobilization, margins, and imaging for lung stereotactic body radiation therapy

Jason K. Molitoris¹, Tejan Diwanji², James W. Snider III¹, Sina Mossahebi¹, Santanu Samanta², Nasarachi Onyeuku², Pranshu Mohindra¹, J. Isabelle Choi¹, Charles B. Simone II¹

¹Department of Radiation Oncology, University of Maryland School of Medicine, Baltimore, MD, USA; ²Department of Radiation Oncology, University of Maryland Medical Center, Baltimore, MD, USA

Contributions: (I) Conception and design: JK Molitoris, JI Choi, CB Simone II; (II) Administrative support: CB Simone II; (III) Provision of study materials or patients: JK Molitoris, T Diwanji, N Onyeuku, JW Snider III, S Mossahebi, S Samanta, P Mohindra, JI Choi; (IV) Collection and assembly of data: JK Molitoris, T Diwanji, N Onyeuku, JW Snider III, S Mossahebi, S Samanta; (V) Data analysis and interpretation: JK Molitoris, T Diwanji, N Onyeuku, JW Snider III, S Mossahebi, S Samanta, P Mohindra, JI Choi, CB Simone II; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

Correspondence to: Charles B. Simone II, MD. Department of Radiation Oncology, University of Maryland School of Medicine, Maryland Proton Treatment Center, 850 W. Baltimore St., Baltimore, MD 21201, USA. Email: charlessimone@umm.edu; Jason K. Molitoris, MD, PhD. Department of Radiation Oncology, University of Maryland School of Medicine, 22 S. Greene Street, GGJ 35, Baltimore, MD 21201, USA. Email: jmolitoris@umm.edu.

Abstract: The simultaneous advancement of technologies for the delivery of precisely targeted radiation therapy and the paradigm shift to substantial hypofractionation have led to significant improvements in the treatment of early stage non-small cell lung cancer (ES-NSCLC). Stereotactic body radiation therapy (SBRT) has become a well-established option for the treatment of ES-NSCLC and is now becoming widely available within the radiation oncology community. Implementation of this technique, however, requires highly accurate target delineation, thorough evaluation of tumor motion, and improved on-board imaging at the time of treatment for patient alignment, each of which is critical for successful tumor control and mitigation of risks to normal tissues. In this article, we review updates and issues related to immobilization and image guidance for SBRT in the treatment of ES-NSCLC.

Keywords: Radiation; non-small cell lung cancer (NSCLC); motion management; image guidance; margins

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Introduction

Stereotactic body radiation therapy (SBRT) is defined by the delivery of high doses of radiation over 1–5 treatments to a tumor volume known in 3D coordinates using image-guided conformal treatment plans. This technique was initially adapted from cranial stereotactic radiosurgery (SRS) to the treatment of cT1-2N0 early stage non-small cell lung cancer (ES-NSCLC) in medically inoperable patients (1). The use of SBRT has rapidly gained acceptance in the treatment of medically inoperable patients due to excellent disease control rates (2). More recently, it has also been employed as an alternative to surgical resection

in operable patients due to its relative clinical equipoise from randomized trial data (3). It has also been proven an excellently effective treatment for small lesions in patients with oligometastatic disease (4,5).

Advances in the delivery of radiation therapy (RT) has led to the ability to deliver SBRT accurately and safely, and utilization will likely only continue to increase. NSCLC is the leading cause of cancer-related death in the United States (6). While the majority of patients traditionally present with advanced stage disease, the proportion diagnosed with ES-NSCLC is rising due to increases in medical imaging and the early adoption of CT-based screening of high-risk populations that is associated with

survival benefits (7). While, historically, these patients have been managed primarily with surgery, a significant proportion are unable to undergo resection due to medical comorbidities. In limited prospective evaluations, SBRT has demonstrated relative equivalency to lobar resection (8), and additional clinical trials are ongoing in surgical candidates with early stage disease. Finally, SBRT is currently being used in the treatment of limited metastatic disease to many areas of the body, including lung metastases (9,10).

The goal of SBRT is to accurately target the tumor and deliver sufficient dose to achieve local control while minimizing the dose to highly sensitive surrounding organs at risk (OARs) including the lungs and airways, heart and great vessels, esophagus, brachial plexus, and spinal cord. As fraction numbers decrease and dose per fraction rises, treatments have necessarily become more conformal to decrease adverse events. More emphasis is necessarily placed for this technique on accurately targeting the tumor and verifying position at the time of delivery. While SBRT for ES-NSCLC was pioneered based on the principles of SRS in the brain, the lack of a truly stereotactic frame and the unique challenge of intrafractional breathing motion of the tumor require particular attention to immobilization and tumor motion management or mitigation.

Increases in the positional uncertainty of the tumor and normal tissues in ES-NSCLC from breathing motion requires incorporation of motion management into the treatment simulation procedure, radiation planning, and treatment delivery to achieve adequate tumor control. This challenge has led to the development of multiple methods to monitor and mitigate motion during simulation. Additionally, accurate verification of tumor location at the time of treatment using onboard image guidance is necessary to ensure accurate target coverage despite the necessary reductions in the planning target volume (PTV) margins to decrease dose to OARs. Broadly defined, image-guided RT (IGRT) is the utilization of various imaging modalities prior to or during radiation treatments to align and verify anatomical agreement between the simulation anatomy, RT treatment plan, and the patient at the time of treatment. Additionally, changes in anatomy between simulation and treatments are common in thoracic malignancies, and alterations can lead to overtreatment of OARs and/or inadequate dose to the target (11-13). As complications from SBRT can potentially be life-threatening (14), adequate verification is essential to the delivery of high-quality treatments.

Motion management strategies

Introduction

The treatment of ES-NSCLC with SBRT requires understanding, modeling, and controlling two different types of motion: (I) inter-fractional motion resulting from setup uncertainties inherent to fractionated radiation treatments based on a prior CT simulation and (II) intra-fractional motion mostly stemming from the respiratory cycle that has proved to have a significant impact on RT planning and delivery (15). Methodologies have been developed to aid in accurately defining, targeting, computing, aligning, and finally delivering a prescribed radiotherapy treatment.

Inter-fraction motion is largely addressed at the time of simulation. While fixed immobilization was initially used in cranial SRS, this strategy is not directly translatable within the thorax. Early efforts led to a number of solutions to enhance fixation of the thoracic cavity and improve reproducibility of patient set up. While a number of solutions including external coordinate systems and whole-body wrapping were developed, some concerns remained about the reproducibility of deep thoracic tumors despite external fixation (12). Additionally, technological advances in image guidance and motion management, as described below, have led to decreased emphasis on extensive external immobilization techniques.

With respect to management of respiratory cycle-induced intra-fraction motion, there are multiple solutions to evaluate motion in a patient-specific manner and then to manage this motion during treatment delivery. Some such measures include 4-dimensional imaging, respiratory-gating, breath-hold, motion mitigation, and tumor tracking. Compared to locally advanced tumors, ES-NSCLC tumors are often highly mobile, especially in the lower lung lobes. When selecting a motion management strategy for an individual patient, several factors are important to consider, including clinical tolerability, target reproducibility, and OAR positioning. These techniques can often be combined for effective and efficient delivery.

Techniques

The most straightforward solution to manage the uncertainty of respiratory motion is to encompass the entire potential range of tumor motion through the breathing cycle in the treatment field. In practice, this method consists of capturing and targeting the full extent of tumor motion

as part of the treatment target. Broadly, the three ways to encompass motion are breath-hold CT, slow CT, and four-dimensional CT scanning (4DCT). Breath-hold CT scans are obtained by performing CT scans at a minimum of two discrete points in the respiratory cycle, including end inspiration and end expiration (16-18). Slow CT scanning refers to performing multiple CT scans over several cycles of respiration. These scans are registered to one another, and subsequently the tumor is drawn on each CT scan to generate the internal target volume (ITV), encompassing all areas where the tumor lies throughout the respiratory cycle. While these methods provide some additional snapshots of tumor location during the breathing cycle, they do not always do so systematically or in positions the patient is likely to be during treatment.

4DCT scanning has largely supplanted both slow CT and breath-hold CTs (19,20). 4DCTs provide clinicians with multiple CT scans spanning the breathing cycle, including the tumor path during the interval portions of the breathing cycle. This method is less vulnerable to the distortion of tissue planes that can appear using the slow CT method. Additional reconstructions, including average CT, maximum intensity projection (MIP) images or cine-mode, should be used with caution as they can decrease the benefit of 4DCT for ITV generation (21-23).

As an example, researchers at Thomas Jefferson University evaluated ITV generation based on utilization of only selective phases of previously acquired 4DCTs. They reported that contouring on all phases of the inhalation portion of the breathing cycle led to a good estimate of the ITV from all contoured phases. In contrast, contouring only on the extreme phases generated an ITV that did not account for centripetal motion of the tumor during the breathing cycle (24).

Drawbacks of 4DCT include requirement for additional software and hardware to gather and reconstruct the acquired images, higher patient radiation exposure, and increases in workload for physician target delineation. Additionally, changes in respiration pattern can occur between 4DCT acquisition and treatment and are not accounted for with this method (25). However, a drawback of all techniques is the lack of method to accurately account for changes in breathing patterns between the time of image acquisition and treatment. Only intra-fractional, fluoroscopic or MR-based imaging can monitor motion in real-time to ensure tumoral position within the target throughout the breathing cycle. Finally, and perhaps most importantly, the 4DCT method leads to increasing target

volumes and, therefore, greater exposure of normal tissues to potentially unnecessary radiation.

In an effort to address these concerns, respiratory gating has been evaluated, which utilizes a trigger to activate and deactivate treatment. As an example, when the tumor or tumor surrogate is outside the treatment field, the “gate” is closed and treatment is placed on hold until the tumor or surrogate moves back into position, at which point the “gate” is reopened and treatment is reinitiated or continued.

Respiratory gating has been studied at multiple centers and across multiple disease sites (26-29). As the primary motion of concern for SBRT is respiratory in nature, numerous technology systems have been employed using chest wall motion or breath air volume as surrogates for tumor location (30-32). An alternative or complementary strategy includes placement of intra- or peritumoral fiducials or real-time imaging to monitor tumor location (33,34).

While respiratory gating provides an opportunity to decrease irradiation of normal tissues compared to motion inclusion, treatment during only a portion of the respiratory cycle necessarily prolongs treatment delivery time, which can lead to patient comfort/movement concerns (35), as well as operational inefficiencies. Treatment duration is dependent on the gating parameters, and as the parameters become more relaxed, the treatment time difference decreases; however, the benefit of gating will also be somewhat sacrificed. Gating also often relies on a surrogate in SBRT, and decoupling of the surrogate from the tumor can lead to systematic uncertainty (35).

Breath-hold is a similar approach to respiratory gating except that it includes active participation from the patient during simulation and treatment in an effort to decrease target volume. Deep-inspiration breath hold (DIBH) and mid-inspiration breath hold (MIBH) are two techniques preferably performed with some form of verification such as spirometry (36). Visual coaching during simulation and treatment are used to generate a reproducible point at which the patient will hold his/her breath, and the treatment is interrupted when the patient begins to breathe again.

The Active Breathing Control (ABC) system is one such method to achieve breath-hold that can be used for SBRT. A spirometer measures respiratory levels, and glasses worn by the patient provide feedback to the patient, providing a target inspiration level for the patient that is determined at simulation and subsequently utilized for treatment (37).

Another method to decrease tumor motion that does

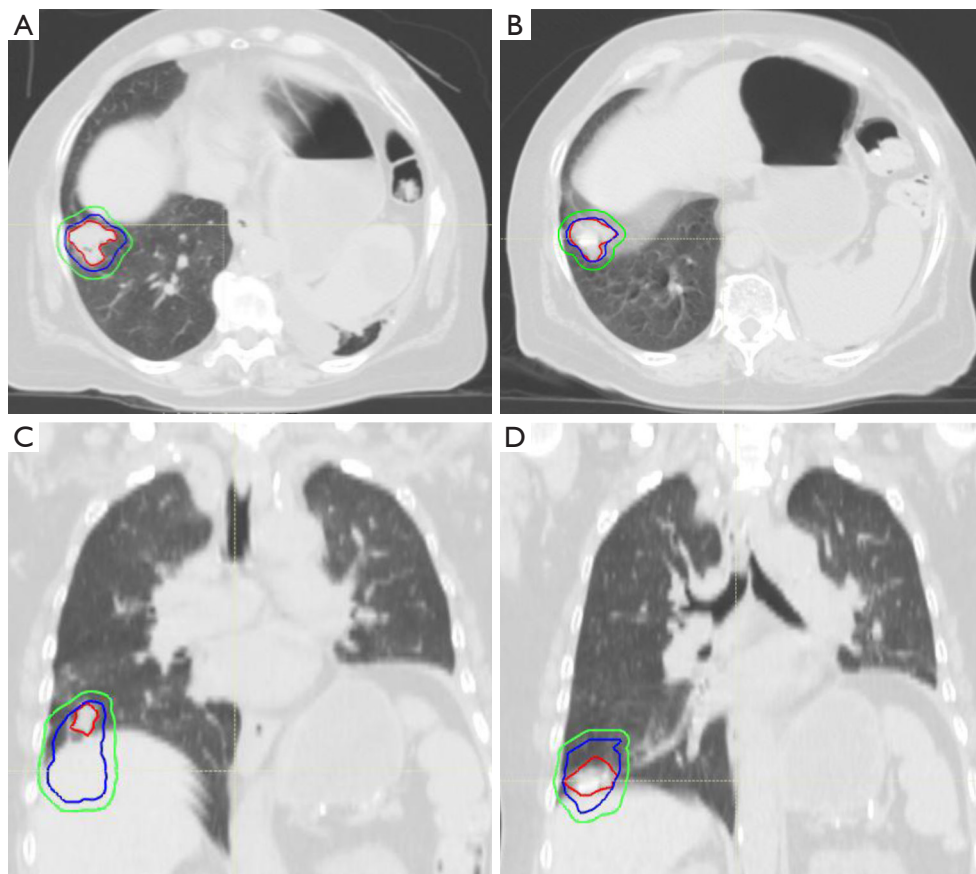


Figure 1 Lung motion with and without abdominal compression. Axial (A,B) and coronal (C,D) CT images of a patient with a right lower lobe stage I non-small cell lung cancer planned for SBRT with contours after CT simulation of GTV (red), iGTV (blue) and PTV (green). (A,C) CT simulation without motion mitigation; (B,D) CT simulation with abdominal compression. SBRT, stereotactic body radiation therapy; GTV, gross tumor volume; iGTV, internal GTV; PTV, planning target volume; CT, computed tomography.

not include active participation from the patient is the use of a motion mitigation apparatus to limit tumor excursion during the breathing cycle. These methods allow the patient to continue breathing during simulation and treatment and may make tumor motion more regular and limit artifacts from irregular breathing cycles. This technique is typically combined with generation of a 4DCT scan.

For example, abdominal compression forces more shallow breathing by the patient and thus less tumoral excursion, and it is a commonly used technique during SBRT treatment courses for both lung and upper abdominal tumors (38-40) (*Figure 1*). Abdominal compression can be achieved using a belt-like device or a stereotactic body frame which applies a constant pressure to the upper abdomen and reduces potential diaphragmatic excursion. Similar to breath-hold, appropriate patient selection is key given that

erratic breathing from distress in some patients can obviate any benefits achieved from compression. Motion mitigation is predominantly useful in patients with pre-mitigation tumor excursions of >8–10 mm. It is our clinic's practice to recommend attempts to mitigate motion when above this threshold (41).

Tumor tracking is the final broadly defined method for motion management with a goal of dynamically tracking the tumor while delivering treatment. This theoretically provides an opportunity to treat the patient more quickly than breath-hold while also minimizing treatment volume and irradiation of normal tissues. Tumor tracking can be accomplished through direct monitoring of the tumor using radiography/fluoroscopy, often coupled with implanted fiducial markers (42) or surrogate chest wall evaluations (43). One particularly compelling approach

for tumor tracking of lung cancer involves implantation of electromagnetic radiofrequency (RF) transponders into the tumor. The transponders provide localization to an external electromagnetic array allowing for real-time positional feedback during treatment delivery (44).

Overall, the clinical benefits of SBRT for ES-NSCLC and unique features including significant intra-fraction motion and high-density changes between lung and tumor have led to significant advances in motion management technologies that have been subsequently adapted to multiple disease sites and clinical presentations. Continued research and clinical evaluation are ongoing and have the potential to lead to decreases in toxicities to normal tissues while ensuring accurate, reproducible, and effective tumor treatment.

Image guidance

Introduction

Image guidance at the time of treatment delivery is an important aspect of stereotactic treatment delivery and essential when using the high doses per fraction for treatment of ES-NSCLC. The primary goal of IGRT is to improve treatment accuracy by accurately aligning the patient and his/her tumor prior to delivery. Improved image guidance can lead to smaller PTV margins and, therefore, decreased doses to OARs, while maintaining optimal target coverage. One study demonstrated a systemic uncertainty of 3.4 mm and random uncertainty of 2.7 mm in SBRT with body fixation alone. These values were decreased to 0.6 and 0.9 mm, respectively, with the use of advanced image guidance, highlighting the importance of the complementary nature of these techniques (45).

Accurate alignment is the first goal of IGRT and can be accomplished using orthogonal kilovolt (kV)/megavolt (MV) X-rays or cone-beam (CB) kV/MV CT scans. CBCT provides volumetric imaging and thus the opportunity to assess for changes in tumor size, position relative to critical structures, and tumor position in the PTV. Here, we discuss methods for implementation of IGRT with a specific focus on use in SBRT for ES-NSCLC.

Imaging modalities

Image guidance initially utilized planar film and subsequently electronic portal imaging devices (EPIDs). MV imaging using the treatment beam is still routinely

used for treatment field verification. While very useful for soft tissue delineation, MV imaging has lower quality compared to kV imaging for bone. The addition of kV imaging arms to linear accelerators along with EPID data acquisition have been widely adopted due to their lower dose to the patient and superior image quality. Orthogonal kV/EPID arrays can be utilized as a tracking device during treatment (34,46,47) along with their routine use for pre-treatment static imaging. Room-mounted EPIDs are also commercially available for certain stereotactic systems. Limitations include imaging dose, fiducial requirement, lack of volumetric spatial resolution, and directional beam entrance limitations.

Volumetric-based imaging allows for the generation of 3D image sets that can be overlaid onto the simulation CT scan for matching. Initially, this was performed with CT with the patient on a treatment couch; however, this has been largely supplanted by volumetric imaging on-board the linear accelerator that can perform CBCT. CBCT permits patient setup and correction of positional errors based on an assessment of 3D soft tissue anatomy compared to the planning scan (48). Corradetti *et al.* evaluated kV X-ray matching of bony anatomy to tumor matching using volumetric CBCT datasets. Using data from 87 patients, they demonstrated a difference of 2.2 mm in the anterior-posterior, 1.8 mm in the superior-inferior and 1.6 mm in the right-left directions, suggesting kV matching to bone was inferior to CBCT matching to tumor. They also studied the intra-fractional tumor motion by immediate post-treatment CBCT. Finally, they document significant intra-fraction shifts were required using CBCTs for 27% of treatment fractions (49).

CBCTs significantly increase target accuracy and reduce errors and are routinely utilized, and they are thus recommended for treatment using SBRT in ES-NSCLC (50-52). CBCTs do have some limitations, which include their decreased quality compared to diagnostic scanners due to helical scattering and longer acquisition time. Respiratory correlated 4D CBCT is a novel solution to overcome the acquisition time limitation and uses relative positioning of the diaphragm to prepare a 4D CBCT for evaluation (53).

IGRT in SBRT

Due to the high dose per fraction, interplay between the breathing cycle and tumor location (54), and small PTV margins, evaluation of pretreatment IGRT is critical to the success of SBRT for ES-NSCLC. The close proximity of

thoracic SBRT targets to critical, radiosensitive structures necessitates precision and accuracy.

A significant amount of effort has been devoted to determining the optimal alignment paradigm for SBRT. Evidence suggests that the use of stereotactic body frames are not, alone, as accurate as image guidance, and, consequently, motion management and image guidance are essential for the safe delivery of SBRT (11,12). While matching bony landmarks by using X-ray-based kV imaging is widely prevalent even for SBRT treatments in the thorax/abdomen, studies have shown that matching soft tissue/tumor by CBCT/volumetric imaging can be very advantageous (55). Therefore, the use of volumetric imaging is recommended for all thoracic SBRT patients to reduce treatment errors.

Conclusions

Motion management and image guidance are essential to the optimal delivery of SBRT for ES-NSCLC. Continued investigation and technological advances promise to increase accuracy and decrease toxicity with SBRT in the future. As more patients are being recommended to undergo SBRT for ES-NSCLC and for lung metastases—including oligometastatic and oligoprogressive disease—it will be imperative to carefully implement strategies to ensure optimal dose delivery and quality assurance.

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Footnote

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