Published in final edited form as:

Phys Med Biol. 2010 May 21; 55(10): 2983–2995. doi:10.1088/0031-9155/55/10/012.

A Phantom Model Demonstration of Tomotherapy Dose Painting Delivery, Including Managed Respiratory Motion without Motion Management

Michael W. Kissick¹, Xiaohu Mo¹, Keisha C. McCall¹, Leah K. Schubert², David C. Westerly³, and Thomas R. Mackie^{1,4}

¹ Department of Medical Physics, Wisconsin Institutes for Medical Research, 111 Highland Avenue, University of Wisconsin – Madison, Madison, WI 53705 USA

² Radiation Oncology Department, University of Nebraska Medical Center, Omaha, NE 68198 USA

³ Department of Radiation Oncology, University of Colorado – Denver, Aurora, CO 80045

⁴ TomoTherapy, Inc., 1240 Deming Way, Madison, WI 53717 USA

Abstract

Purpose—To demonstrate a potential alternative scenario for accurate dose painting (non-homogeneous planned dose) delivery at the 1 cm beam width with helical tomotherapy (HT) in the presence of 1 cm, three dimensional, intra-fraction respiratory motion, but without any active motion management.

Method and Materials—A model dose painting experiment was planned and delivered to the average position (proper phase of a 4DCT scan) with three spherical PTV levels to approximate dose painting to compensate for hypothetical hypoxia in a model lung tumor. Realistic but regular motion was produced with the Washington University 4D Motion Phantom. A small spherical Virtual Water™ phantom was used to simulate a moving lung tumor inside of the LUNGMAN™ anthropomorphic chest phantom to simulate realistic heterogeneity uncertainties. A piece of 4 cm Gafchromatic EBT™ film was inserted into the 6 cm diameter sphere. The TomoTherapy, Inc. DQA™ software was used to verify the delivery performed on a TomoTherapy Hi-Art II™ device.

Results—The dose uncertainty in the purposeful absence of motion management and in the absence of large, low frequency drifts (periods greater than the beam width divided by the couch velocity) or randomness in the breathing displacement yields very favorable results. Instead of interference effects, only small blurring is observed because of the averaging of many breathing cycles and beamlets and the avoidance of interference.

Conclusion—Dose painting during respiration with helical tomotherapy is feasible in certain situations *without* motion management. A simple recommendation is to make respiration as regular as possible without low frequency drifting. The blurring is just small enough to suggest that it may be acceptable to deliver without motion management if the motion is equal to the beam width or smaller (at respiration frequencies) when registered to the average position.

Keywords

Dose Painting; Respiratory Motion; Tomotherapy

I. Introduction

‘Dose painting’ refers to the prescription and delivery of inhomogeneous dose distributions within planning treatment volumes (PTV) for patients undergoing radiotherapy (Ling *et al* 2000, Bentzen 2005, Tanderup *et al* 2006). The inhomogeneous dose prescriptions are based on functional imaging from, for example, positron emission tomography (PET) using biologically relevant surrogates for conditions such as hypoxia (Chao *et al* 2001, Lin *et al* 2008), or dynamic contrast enhanced magnetic resonance imaging of hypoxia (Malinen *et al* 2006, Søvik *et al* 2007). ‘Theragnostics’ is the process of analyzing functional imaging to determine which sub-volumes of the gross tumor volume (GTV) should receive dose painting (Bentzen 2005).

Numerous studies have been conducted demonstrating the feasibility of optimizing dose painting plans with fixed-beam intensity modulated x-ray therapy (IMXT) (Chao *et al* 2001, Yang and Xing, 2005, Alber *et al* 2003, Thorwarth *et al* 2007), helical tomotherapy (HT) (Bowen *et al* 2009), and intensity modulated proton therapy (IMPT) (Thorwarth *et al* 2008, Flynn *et al* 2008), but none of these studies have focused on the actual delivery of such plans, in particular in the presence of intra-fraction patient motion. Since dose distributions delivered with dose painting are inhomogeneous, intra-fraction patient motion can cause a blurring effect or possible interference (Yu *et al* 1998) on the delivered dose distribution that could either reduce its predicted effectiveness, or result in over-dosage of nearby organs at risk.

A previous study demonstrated the benefits of maintaining *regular* respiratory motion with HT during the delivery of uniform dose prescriptions with HT (Kissick *et al* 2008). That study indicated negligible longitudinal motion blurring of 1 cm motion in a 2.5 cm beam width in a homogeneous phantom planned with a uniform dose prescription. No interference effects between the beam modulation and the applied phantom motion were observed when the parameters of respiratory motion were constant (when respiratory motion did not display drifts or long/short-term variation amplitude and period). These results suggest a potential alternative technique to active motion management. This alternative technique involves planning and registering the therapeutic dose to a position corresponding to the average of the motion trajectory; however, no active motion management such as gating or tracking (Keall *et al* 2006) is required. Of course, making the patient breath regularly is an ideal (George *et al* 2006), and future work will further explore how regular it needs to be for HT for a variety of parameters. However, the consequences of a certain amount of randomness were explored in a previous study (Kissick *et al* 2008).

The purpose of this paper is to report on the potential of this technique to deliver dose-painting plans to a lung tumor in the presence of managed or regularized respiratory motion. The following effects were incorporated to demonstrate their impact, or lack thereof, on the planning and delivery: 1. Heterogeneity deformation from the motion, 2. Small structures and a small beam width typical of dose painting plans, and 3. Non-uniform dose distributions. This paper presents a model demonstration of the ability to deliver a dose-painting plan in the presence of respiratory motion and without the use of active motion management.

II. Methods and Materials

A. Helical Tomotherapy

The Hi-Art II™ TomoTherapy, Inc. (Madison, WI USA) device is a HT device (Mackie *et al* 1993) that uses a 6 MV fan beam, mounted on a computed tomography (CT) style gantry, to deliver radiation treatments. The longitudinal width of the HT fan beam, with settings at 1.0 cm, 2.5 cm, and 5.0 cm at isocenter, is controlled with a pair of adjustable collimator jaws. In this case, the smaller 1 cm setting is used, as it is likely to be more appropriate for painting

small structures due to the steeper dose falloff of the 1 cm beam in the craniocaudal direction compared with larger widths. The beam intensity is modulated with a 64-leaf binary multileaf collimator (MLC) (Olivera *et al* 1999), with leaves that project to a transverse width of 6.25 mm at the isocenter plane. During a treatment, the couch translates at a constant speed (usually much less than 1 mm/s) in the longitudinal direction, while the gantry rotates at a constant speed with a period ranging between 15 s and 60 s. The opening and closing times of the MLC leaves are on the order of milliseconds, and the time scale of the leaf motion staying open or staying closed is less than 1 s which is much faster than the couch translation through the beam. The map of leaf opening times for each of the 51 projections per gantry rotation, called the delivery sinogram, is optimized by the TomoTherapy Treatment Planning System software (Olivera *et al* 1999). The average value in this sinogram is about 1/3 to 1/2 for most plans: determined by the modulation factor. The modulation factor is the ratio of the maximum to the average sinogram value at each projection for all non-zero values. It is therefore about 2 or 3 for most plans and could be higher for complex dose painting plans.

The simultaneous rotation of the gantry and translation of the couch during delivery of the HT device forms a helix with a constant pitch for the whole treatment. The pitch is defined as the longitudinal motion relative to the beam width set by the jaws at isocenter for a full gantry rotation. Because the pitch is set to $0.86/n$ for correct helical field matching, where n is an integer larger than 2 generally (Kissick *et al* 2005), the helix is really a *tight* helix with longitudinally overlapping fan-beam elements (beamlets). In addition, the beam collimation in the longitudinal direction is $10.0\text{mm}/6.25\text{mm} \approx 1.6$ times larger than the collimation in the transverse directions for the 1 cm beam. Therefore, the intensity modulation in HT is mostly in the transverse plane during the time it requires for several to tens of the 51 planning projections that small arcs are centered about for modulation. The higher order modulation in time is in the longitudinal direction because the pitch is small, and it takes hundreds of projections to modulate structures in this direction. The intensity modulation scheme for HT beams is therefore in tight helices that can be dynamically separated into longitudinal and transverse components that are approximately independent. These separable dynamics are an important simplifying concept. The average human breathing frequency, ~ 0.2 Hz, occurs between two fundamental frequency scales of HT delivery: ~ 0.02 Hz for the jaws/couch and ~ 2 Hz for the leaves. These distinct time scales and dynamics are responsible for some remarkably good results because interference effects can be avoided and the minimal blurring can potentially be predicted.

B. The Model Dose Painting Treatment Plan

A HT treatment dose painting plan was designed with three nested spherical (but not concentric) planning treatment volumes (PTVs). The PTV was set equal to the GTV, as is typical for most phantom studies. The base PTV was prescribed 62.5 Gy (48.74 cc) to 98% of the base PTV and two nested boost PTVs were assigned as follows: 72.5 Gy (21.75 cc), 82.5 Gy (5.74 cc), with the highest dose receiving the highest overlap priority. This treatment plan was designed to simulate a dose painting plan that would be used to counter the effects of hypoxia in a lung tumor (Dehdashti *et al* 2003, Postema *et al* 2009, Rasey *et al* 1996).

The plan was divided into 30 equal fractions. The pitch for the helical delivery was set at 0.287, and the beam width was set at 1.0 cm. The actual modulation factor (MF) was 1.9, and the slow, but typical couch speed was 0.16 mm/s. The gantry period was 17.9 s. With these settings, the total time any voxel experiences the primary beam is about $1.0\text{ cm} / 0.016\text{ cm/s} = 62.5\text{ s}$, and the time each beamlet is 'on' is less than $17.9\text{ s} / 51 = 0.35\text{ s}$. On average, it will be about 1/2 of this value or about 0.18 s which is typical. One fraction was delivered to the film.

The dose was calculated on a 4DCT (GE DiscoveryTM VCT) image that corresponded to the average position of the motion. This image was one of 10 phases from a 4DCT, which were

acquired of a lung-tumor anthropomorphic phantom and simulated lung tumor undergoing 4D-respiratory motion. This phantom and simulated tumor are described in Section II.E, and the motion model is described in the next section. The technique of planning and registering to the average motion position has been used by other groups (Wolthaus *et al* 2006), and 4DCT motion artifacts arise from the fact that the average of the motion is the phase of fastest speed of motion. However, these image artifacts did not cause problems for planning or notable dose errors for this study.

C. The Model Respiratory Motion

The Washington University 4D Motion Phantom was used for the model respiratory motion; this motion positioning device is accurate to within 0.2 mm (Malinowski *et al* 2007). In this study, the motion platform was used to move a lung-tumor phantom during 4DCT acquisition and HT delivery along reasonably realistic (although regular) 3D motion trajectories. The motion was meant to approximate the respiratory motion for a lower lobe tumor (Seppenwoolde *et al* 2002): the motion magnitude and path is not atypical for an average unattached lower lobe lung tumor (see Fig. 1.a).

The motion was approximated by interpolating a 1D motion trace onto an ellipse, as shown in Fig. 1.a. The longitudinal motion was approximated with the formulation similar to Lujan *et al* (1999): $y_{breathing}(t) = A \cdot \sin^{2n}(\pi \cdot t/T)$. The period $T = 5s$, and the amplitude, $A = 1cm$. The craniocaudal direction is the longitudinal direction into the bore, and the lateral and/or anteroposterior directions lie in the transverse plane. The lateral and longitudinal (craniocaudal) motion is equal in magnitude at 1.0 cm peak to peak for transverse to longitudinal comparisons, but the anteroposterior motion is much less at 2.5 mm peak to peak.

The value $n=2$ in the exponent of the breathing trace was chosen in the current work in order to model the situation for which more time is spent at exhale than inhale which requires that $n > 1$. This choice of n was also somewhat arbitrary, however, as evidence exists suggesting that the use of $n = 1, 2$, or 3 will all result in similar correlations between measured breathing data and the model above (George *et al* 2005).

D. The Film Dosimetry Equipment and Procedure

The film dosimetry for these experiments used ISP (International Specialty Products, Wayne NJ USA) Gafchromatic EBT™ film scanned in the red component with an Epson 10000XL™ scanner. Scanning, developing time, and film handling was consistent for all films. The inner 10 cm in the direction of the CCD array of the scanner was used in order to avoid the complexity of needing to properly account for separate, dose dependent scanner light scatter correction files (Menegotti *et al* 2008, Saur *et al* 2008). The film was cut into small, 4 cm wide pieces that slide into a thin slot in the Virtual Water™ sphere described below, but it then extended out the back side and was about 5 cm long.

E. The Anthropomorphic Chest and Spherical Lung Tumor Phantom

A 6 cm diameter Virtual Water™ sphere is attached to a Lucite™ arm that is then attached to the 4D motion phantom motion stage. This tumor phantom is then placed inside the anthropomorphic 'Multipurpose Chest Phantom N1 LUNGMAN™ (Kyoto Kagaku co. LTD Japan), with the mediastinum removed to allow the tumor to move freely within the lung cavity (see Fig. 1.b). The sphere was not as large as many lung tumors, but our other experiments with larger, but less realistic phantoms, yielded very consistent results demonstrating that size was not a limiting factor for the overall results of this study. The overall effect is a simulation of a lung tumor moving with respect to realistic ribs, a *moving* heterogeneity not accounted for in the plan. This lung-tumor phantom (spherical tumor plus anthropomorphic chest) was designed and used to investigate the presence or absence of the anticipated averaging effects

from heterogeneity changes during the delivery of non-uniform dose prescriptions to moving targets. A piece of Gafchromatic EBTTM film was inserted into a sub-millimeter slot at the midplane of the sphere through the boost regions.

Because the green lasers of the HT gantry which mark the virtual isocenter to the machine could not be used to *directly* verify the position of the internal tumor phantom (sphere), the initial set-up uncertainty was larger than most phantom studies. However, this uncertainty is much like a real situation where alignment is done on the outside of the patient, and the internal localization of the tumor was achieved by registering with the on-board megavoltage CT (MVCT), taken prior to delivery, to the planned (motion average) 4DCT.

One fraction of the dose-painting plan, described in section B, was delivered to the lung-tumor phantom. The film was placed in the midplane of the spherical tumor, ensuring that the film extended into both boost regions.

III. Results

The results of this demonstration are consistent with previous work that indicated no interference patterns from regular respiratory motion (Fig. 12 of Kissick *et al* 2008). In this case, however, the film is calibrated and the structures are smaller. The beam width equals the motion peak to peak amplitude longitudinally in this study such that the motion blurring will be apparent. In Kissick *et al* (2008), the blurring from the 1 cm motion was negligible relative to the beam width blurring from the 2.5 cm beam width. The transverse (lateral) motion was also much smaller in Kissick *et al* (2008) such that its ratio to the beam width was equal to the longitudinal ratio. Here, the transverse motion is equal in absolute magnitude to the longitudinal motion, but the relative beam width between the longitudinal and transverse directions are still different.

In Fig. 2.f, one can observe the blurring from the motion: compare to Fig. 2.c without motion. The transverse or lateral direction shows less difference between the stationary (Fig. 2.b) and the motion (Fig. 2.e) cases, but one can still notice the dose blurring in the motion case. The profiles are sliced through both boost regions, indicated by the transparent gray lines in the contour plots for the stationary (Fig. 2.a) and the moving (Fig. 2.d) cases. The plan contours are shown in heavy dashed lines and the film results are the thin solid lines. The three isodose contours correspond to the three PTV prescriptions used for planning. The 4DCT artifacts can be seen to have small but not important effects on the lower, base PTV, dose levels near the edges of the phantom.

The TomoTherapy DQATM software also calculates the ‘gamma distribution,’ a metric for assessing both dose and dose gradient accuracy as described in Low *et al* (1998) to which the reader is referred. The settings for the Fig. 3 gamma maps use a 5% dose tolerance (0.104 Gy), 5 mm distance to agreement and a 5 mm search radius. In Fig. 3.a, the gamma for the stationary case is shown, and typically, this gamma map would indicate a ‘pass’ for the treatment check at values less than or equal to unity for all voxels. The gamma map for the motion case (Fig. 3.b) is noticeably worse, but still passes. In fact, if one requires that at least 85% of these voxels to be within 5% of the dose and 5 mm distance to agreement, and both films exceed this requirement easily. It may be that the locally higher gammas are fine because they are only in the boost region boundaries. These boundaries, in a real situation, would be obtained from some discretization from a PET image (Bowen *et al* 2009) and should perhaps be blurred. At the very least, these results indicate that it is not impossible to dose paint with motion and without active motion management. The blurring from the motion is noticeable when the beam width is less than or equal to the motion amplitude *at frequencies typical of respiration*.

IV. Discussion

Even though many lung treatments with HT are currently performed without the motion management developed by TomoTherapy, Inc. (Adkison *et al* 2008), they generally yield good results, and this study helps provide an explanation for the quality of those results. The situation could be improved though both from the vendor side and from the clinic side.

The TomoTherapy treatment planning software uses an optimizer to provide the intensities for each leaf as it arcs around each projection with the approximation of 51 static projections per gantry rotation, and therefore discrete couch positions as well. Even though it is a very good approximation for most situations (Kissick *et al* 2007), there is a possibility that if one were to estimate the alteration in beamlet averaging with patient motion, then one could improve the detection of interference phenomena at particular frequencies (such as a gantry period coherence with the modulation, see Kim *et al* 2009), and help predict the expected dose blurring as well that is presented in Fig. 2.

The patient and the HT machine motions are coupled under a time integral described below in a 1D simplification of the relevant equations – their motions can therefore interfere.

The dose, $D(x)$, is an integral in time of a dose rate:

$$D(x) = \int_{-\infty}^{\infty} T(x') B(x - x') dx' \quad \& \quad T(x') = \int_0^{\infty} \psi(t) \delta(x' - x_{\text{motion}}(t)) dt, \quad (1)$$

where $x_{\text{motion}}(t) = v_{\text{couch}}t + x_{\text{breath}}^{\text{reg}}(t) = v_{\text{couch}}t + A \sin(\omega t)$ for example, with amplitude A and frequency ω . In the static case (no breathing), $x_{\text{motion}}(t) = v_{\text{couch}}t$. The units of the dwell 'time,' $T(x)$ are fluence; the units of $\delta(x)$ are $1/[x]$. The units of $\psi(t)$ are $1/[t]$: the fluence rate. The optimizer produces an optimized fluence rate as a function of time: a deconvolution of Eqs. 1 above with the prescription in place of D to deconvolve for $\psi(t)$. The modulation factor alters how much this varies: maximum relative to average within each projection. Setting the modulation factor lower acts to smooth or reduce the variations in the sinogram and makes the motion mixing of beamlets less impactful. The couch velocity is v_{couch} , and $\delta(x)$ is a Dirac delta function that scores the crossing of the center of the beam. The beam profile is represented by $B(x)$.

In the limit of *many* breathing cycles per time in the beam (not a bad approximation for HT), then the sum total of the many little fluence bits as breathing will cause many crossing of the beam center will add up to the same as the treatment plan – one crossing of the beam center:

$$\lim_{\omega \rightarrow \infty} \int_0^{\infty} \delta(x' - x_{\text{motion}}(t)) dt = \text{constant} \Rightarrow 1/v_{\text{couch}}. \quad (2)$$

Next, one should define a motion averaged fluence rate: still has $1/[t]$ units, but it is only a function of space:

$$\langle \psi \rangle(x') \equiv \frac{\int_0^{\infty} \psi(t) \delta(x' - x_{\text{motion}}(t)) dt}{\int_0^{\infty} \delta(x' - x_{\text{motion}}(t)) dt}. \quad (3)$$

By substitution in to Eqs. 1, one obtains an estimate of the dose with respiratory motion:

$$D(x) \approx (1/v_{couch}) \int_{-\infty}^{\infty} \langle \psi \rangle(x') B(x - x') dx'. \quad (4)$$

The observation for most cases with regular motion (Kissick *et al* 2008, Chaudhari *et al* 2009 among others) is that $\langle \psi \rangle_{motion}^{regular}(x') \approx \langle \psi \rangle_{static}(x')$. Because there are so many beamlets (hundreds per voxel) and breathing cycles (tens per voxel), the chances of a modulation (including the projection cosine as the gantry rotates) coherent with the breathing frequency are very small in real life, and we have not observed it in these fairly realistic experiments. However, Kim *et al* 2009 does produce one case of leaf motion interference; their fig. 3. So, in that particular case: $\langle \psi \rangle_{motion}^{regular}(x') \neq \langle \psi \rangle_{static}(x')$. If the motion has significant randomness, as explored in Kissick *et al* 2008, $\langle \psi \rangle_{motion}^{random}(x') \neq \langle \psi \rangle_{static}(x')$ will also be observed because effectively the motion probability density function is changing as the beam is scanning over the PTV. Therefore, one idea is for the treatment planning software to estimate Eq. 4 above and determine if there is a potential for a significant dose error from the motion averaging or interfering. Of course, TomoTherapy, Inc. does have a motion management scheme that involves an electromagnetic implant to actively track any type of tumor motion and adjust the beamlet instructions to account for the motion if the patient can tolerate and the physician can recommend the implant procedure.

For any typical HT plan, each beamlet would dwell for a maximum of the gantry period divided by 51 projection angles or for this case, $17.9 \text{ s} / 51 = 0.35 \text{ s}$ at each of the 51 angles. The delivery sinogram specifies an intensity which further reduces this time by a factor of 2 to 3 typically. For the beam to fully scan over a voxel, the time required is the longitudinal beam width divided by the couch velocity or for this case, $1 \text{ cm} / 0.016 \text{ cm/s} = 62.5 \text{ s}$. That means on average, about 178 beamlets, almost equally spaced in time on average are available to sample the respiratory motion for each voxel. The respiration modeled here has a 5 s period. Each cycle therefore has about $5 \text{ s} / 0.35 \text{ s} = 14$ to 15 beamlets sampling its movement. It has therefore reached the well-sampled limit to which the moving compensator approximation used in Bortfeld *et al* (2002) becomes more valid.

In that approximation (Bortfeld *et al* 2002), a simple expression for the dose error is obtained in their Eq. 11 by assuming harmonic motion of a wedge-shaped compensator similar to the motion used here in this study. They state that it is impossible to solve for a general solution for all types of modulations and tumor motions, but one aspect of the solution should remain robustly similar across all situations in which the explicit time-dependence of the modulation is negligible relative to the tumor motion. When the period of the tumor motion is on the same order as the treatment time, then some coherence will develop between the two motions – interference. In Fig. 4, this generic solution from Bortfeld *et al* (2002) is used as a way to understand why interference was not observed in this test, as well as other regular motion tests with HT that we have performed. Any particular situation could have more fine structure and be different or more complicated than shown in Fig. 4. However, the basic location of this interference maxima should be robust. The addition of the chest phantom which provided unplanned shifts in heterogeneity as the tumor moved and also the non-uniform dose distribution dose painting plan both did not affect the observed blurring and the lack of interference. The blurring may actually be beneficial. For HT, dose painting will involve a discretization from a PET image (Bowen *et al* 2009), so the blurring, being predictable and easy to calculate, may help provide for a dose delivery pattern closer to the original PET image.

Even without a software change from the vendor, and considering that many HT lung treatments are working very well without any active motion management, some steps that a clinician might consider to improve HT treatments for respiratory motion with or without the TomoTherapy motion management are as follows,

- a. Consider choosing planning parameters to increase the number of breathing cycles averaged into the treatment for each voxel. Note that the pitch primarily controls the gantry period if over 15 s, and the beam width sets the couch speed but also depends the modulation factor that adjusts the average dose rate relative to the maximum. Slower treatments are safer for averaging out a stray breathing cycle or two.
- b. One might attempt to coach the patient for steady shallow breathing and no other body movements on the order of minutes in duration (see Keall *et al* 2006 for a good discussion of coaching) to keep the breathing relatively steady in displacement as low frequencies (variations in breathing period are less of a problem). This can be tested with multiple 4DCT scans if desired to see how well the patient can be coached. One should keep the drifting order of the beam width divided by the couch speed very small, but a single breath being irregular will get averaged out.
- c. If the patient will be more calm, use a motion restraint like the BodyFix™ (Medical Intelligence, Munich, Germany) to make the breathing more shallow, less drifting on the low frequencies (see Keall *et al* 2006 for a good discussion of restraints).
- d. One should do a patient specific motion QA test with a good 4D motion phantom. One should not rely alone of the 5 mm motion criterion mentioned in Keall *et al* 2006 for HT and other dynamic IMRT, since the effects of frequency should also be considered and tested for (Kissick and Mackie 2009).
- e. These steps above are how to deal with not tracking the breathing phase, but they will make motion management with active tracking also perform better on HT.

The above steps should help avoid drifting or low frequency components to the motion (on the order of the beam width divided by the couch speed or larger) that cause interference with the couch: see Chaudhari *et al* (2009). They will help avoid randomness that will spread the motion power spectra into regions of interference with either the couch/jaws at the low frequency side or with the MLC leaves (which has never been observed in our experiments) at the high frequency side (Kissick *et al* 2008). They can also help avoid or detect problems if the motion is very regular at *just the wrong frequency* such that significant dose errors from interference may occur, and they may be related to the gantry rotation as well (Kim *et al* 2009).

The prospect of controlled blurring for dose painting would greatly simplify the delivery analysis, allowing for a linear systems theory approach as is done with imaging (Stern and Kopeika 1999, Zalevsky *et al* 1999). The extent to which the moving compensator approximation used in Bortfeld *et al* (2002) is a valid description for dynamic IMRT with motion, and the extent that one is well away from the interference maxima, is also the extent to which a simple blurring transfer-function of the motion can be used for the whole delivery as was done for HT for the arc motion of a single beamlet about a projection (Kissick *et al* 2007).

V. Conclusion

The ability to use the beneficial averaging of large numbers of rapidly-fired beamlets, particular to HT, in order to avoid noticeable interference with dynamic IMRT was demonstrated in a situation closer to clinical reality than the motivating previous study (Kissick *et al* 2008). That previous study did not consider the 1 cm beam completely, and the ability to perform dose painting and more complex situations will likely require this smaller beam width that is on the

order of typical respiratory motion magnitudes in humans. In addition, an anthropomorphic chest phantom was now used to provide a shifting heterogeneity typical of the clinical situation. Whether the results are clinically acceptable depends on factors beyond the scope of this study such as what errors are acceptable for the margins of a boosted sub-volume.

The study demonstrates that, if active motion management, such as motion tracking, cannot be used, an alternative technique may be to require that the patient be made to breathe as regularly as possible without low frequency drifting of the motion (periods larger than the beam width divided by the couch speed). The tumor needs to be planned and registered to the average displacement of its motion as well. In addition, motion restraint devices and coaching the patient to control the breathing over an average time that any voxel is on the beam (on the order of a few minutes) is advised. Input parameters should be chosen to allow for more breathing cycles to average into the dose, thereby reducing the effects of a single abnormal breath or two. One can also choose a lower modulation factor to allow for smoother sinograms that could also reduce the errors of mixing up beamlets from the motion. If the treatment planning software is not adjusted to estimate potential dose errors from patient motion, then, it seems especially important to do some type of patient motion specific quality assurance check to see if the patient can control their breathing in the modest way suggested and that no unfortunate interference arises. Understanding and checking the effects of frequency with HT delivery allows for a higher quality treatment.

Acknowledgments

The authors are grateful for the new Wisconsin Institutes of Medical Research (WIMR) facility at the University of Wisconsin School of Medicine and Public Health and the cooperation of the staff at the Paul P. Carbone Comprehensive Cancer Center at the University of Wisconsin Hospital and Clinics. The authors wish to express significant gratitude to Prof. Søren Bentzen whose guidance was essential. We thank Scott Johnson for making the Virtual Water™ spherical phantom and arm. Thanks are also extended to Dr. Ryan Flynn whose discussions related to previous works were inspirational here as well. We remain grateful for the continued resource and effort sharing from TomoTherapy, Inc. The author Thomas Rockwell Mackie does have ownership interests in TomoTherapy, Inc. which is commercializing helical tomotherapy. This work is supported by United States National Institutes of Health, National Cancer Institute grants K25 CA119344, P30 CA014520, and T32 CA09206, and also the Susan Komen Grant BCTR0504129 and National Science Foundation grant 0427689.

References

- Adkison JB, Khuntia D, Bentzen SM, Cannon GM, Tomé WA, Jaradat H, Walker W, Traynor AM, Weigel T, Mehta MP. Dose escalated, hypofractionated radiotherapy using helical tomotherapy for inoperable non-small cell lung cancer: preliminary results of a risk-stratified phase I dose escalation study. *Technol Cancer Res Treat* 2008;7:441–7. [PubMed: 19044323]
- Alber M, Paulsen F, Eschmann SM, Machulla HJ. On biologically conformal boost dose optimization. *Phys Med Biol* 2003;48:N31–5. [PubMed: 12587912]
- Bentzen SM. Theragnostic imaging for radiation oncology: dose-painting by numbers. *Lancet Oncol* 2005;6:112–7. [PubMed: 15683820]
- Bortfeld T, Jokivarsi K, Goitein M, Kung J, Jiang SB. Effects of Intra-fraction motion dose delivery: statistical analysis and simulation. *Phys Med Biol* 2002;47:2203–20. [PubMed: 12164582]
- Bowen SR, Flynn RT, Bentzen SM, Jeraj R. On the sensitivity of IMRT dose optimization to the mathematical form of a biological imaging-based prescription function. *Phys Med Biol* 2009;54:1483–501. [PubMed: 19218733]
- Chao KS, Bosch WR, Mutic S, Lewis JS, Dehdashti F, Mintun MA, Dempsey JF, Perez CA, Purdy JA, Welch MJ. A novel approach to overcome hypoxic tumor resistance: Cu-ATSM-guided intensity-modulated radiation therapy. *Int J Radiat Oncol Biol Phys* 2001;49:1171–82. [PubMed: 11240261]
- Chaudhari SR, Goddu SM, Rangaraj D, Pechenaya OL, Lu W, Kintzel E, Malinowski K, Parikh P, Bradley JD, Low DA. Dosimetric variances anticipated from breathing-induced tumor motion during tomotherapy treatment delivery. *Phys Med Biol* 2009;54:2541–2555. [PubMed: 19349658]

- Dehdashti F, Mintun MA, Lewis JS, Bradley J, Govindan R, Laforest R, Welch MJ, Siegel BA. In vivo assessment of tumor hypoxia in lung cancer with ^{60}Cu -ATSM. *Eur J Nucl Med Mol Imaging* 2003;30:844–50. [PubMed: 12692685]
- Flynn RT, Bowen SR, Bentzen SM, Rockwell Mackie T, Jeraj R. Intensity-modulated x-ray (IMXT) versus proton (IMPT) therapy for theragnostic hypoxia-based dose painting. *Phys Med Biol* 2008;53:4153–67. [PubMed: 18635895]
- George R, Vedam SS, Chung TD, Ramakrishnan V, Keall PJ. The application of the sinusoidal model to lung cancer patient respiratory motion. *Med Phys* 2005;32:2850–61. [PubMed: 16266099]
- George R, Chung TD, Vedam SS, Ramakrishnan V, Mohan R, Weiss E, Keall PJ. Audio-visual biofeedback for respiratory-gated radiotherapy: impact of audio instruction and audio-visual biofeedback on respiratory-gated radiotherapy. *Int J Radiat Oncol Biol Phys* 2006;65:924–33. [PubMed: 16751075]
- Keall PJ, Mageras GS, Balter JM, Emery RS, Forster KM, Jiang SB, Kapatoes JM, Low DA, Murphy MJ, Murray BR, Ramsey CR, Van Herk MB, Vedam SS, Wong JW. The management of respiratory motion in radiation oncology report of the AAPM Task Group 76. *Med Phys* 2006;33:3874–900. [PubMed: 17089851]
- Kim B, Chen J, Kron T, Battista J. Motion-induced dose artifacts in helical tomotherapy. *Phys Med Biol* 2009;54:5707–34. [PubMed: 19729710]
- Kissick MW, Mackie TR. Correspondence: Task Group 76 Report on ‘The management of respiratory motion in radiation oncology’ [Med. Phys. 33, 3874–3900 (2006)]. *Med Phys* 2009;36:5721–2. [PubMed: 20095285]
- Kissick MW, Mackie TR, Jeraj R. A Delivery Transfer Function (DTF) analysis for helical tomotherapy. *Phys Med Biol* 2007;52:2355–2365. [PubMed: 17440239]
- Kissick MW, Fenwick J, James JA, Jeraj R, Kapatoes JM, Keller H, Mackie TR, Olivera GH, Soisson ET. The Helical Tomotherapy Thread Effect. *Med Phys* 2005;32:1414–23. [PubMed: 15984692]
- Kissick MW, Flynn RT, Westerly DC, Hoban PW, Mo X, Soisson ET, McCall KC, Mackie TR, Jeraj R. On the impact of longitudinal breathing motion randomness for tomotherapy delivery. *Phys Med Biol* 2008;53:4855–4873. [PubMed: 18711250]
- Lin Z, Mechalakos J, Nehmeh S, Schoder H, Lee N, Humm J, Ling CC. The influence of changes in tumor hypoxia on dose-painting treatment plans based on ^{18}F -FMISO positron emission tomography. *Int J Radiat Oncol Biol Phys* 2008;70:1219–28. [PubMed: 18313529]
- Ling CC, Humm J, Larson S, Amols H, Fuks Z, Leibel S, Koutcher JA. Towards multidimensional radiotherapy (MD-CRT): biological imaging and biological conformality. *Int J Rad Onc Biol Phys* 2000;47:551–60.
- Low DA, Harms WB, Mutic S, Purdy JA. A technique for the quantitative evaluation of dose distributions. *Med Phys* 1998;25:656–61. [PubMed: 9608475]
- Mackie TR, Holmes T, Swerdloff S, Reckwerdt P, Deasy JO, Yang J, Paliwal B, Kinsella T. Tomotherapy: a new concept for the delivery of dynamic conformal radiotherapy. *Med Phys* 1993;20:1709–19. [PubMed: 8309444]
- Malinen E, Søvik Å, Hristov D, Bruland OS, Olsen DR. Adapting radiotherapy to hypoxic tumours. *Phys Med Biol* 2006;51:4903–21. [PubMed: 16985278]
- Malinowski, K.; Noel, C.; Lu, W.; Lechleiter, K.; Hubenschmidt, J.; Low, D.; Parikh, P. Development of the 4D phantom for patient-specific end-to-end Radiation therapy QA. In: Hsieh, J.; Flynn, MJ., editors. proceedings of SPIE– Vol. 6510, Medical Imaging 2007: Physics of Medical Imaging; Mar. 16, 2007; 2007. p. 65100E
- Menegotti L, Delana A, Martignano A. radiochromic film dosimetry with flatbed scanners: a fast and accurate method for dose calibration and uniformity correction with single film exposure. *Med Phys* 2008;35:3078–85. [PubMed: 18697531]
- Olivera, GH.; Shepard, DM.; Ruchala, K.; Aldridge, JS.; Kapatoes, J.; Fitchard, EE.; Reckwerdt, PJ.; Fang, G.; Balog, J.; Zachman, J.; Mackie, TR. Tomotherapy. In: Van Dyk, J., editor. The Modern Technology of Radiation Oncology: A Compendium for Medical Physics and Radiation Oncologist. Vol. chapter 15. Madison, WI: Medical Physics Publishing; 1999. p. 521–87.

- Postema EJ, McEwan AJ, Riauka TA, Kumar P, Richmond DA, Abrams DN, Wiebe LI. Initial results of hypoxia imaging using 1-alpha-D: -(5-deoxy-5-[18F]-fluoroarabinofuranosyl)-2-nitroimidazole (18F-FAZA). *Eur J Nucl Med Mol Imaging* 2009;36:1565–73. [PubMed: 19430784]
- Rasey JS, Koh WJ, Evans ML, Peterson LM, Lewellen TK, Graham MM, Krohn KA. Quantifying regional hypoxia in human tumors with positron emission tomography of [18F]fluoromisonidazole: a pretherapy study of 37 patients. *Int J Radiat Oncol Biol Phys* 1996;36:417–28. [PubMed: 8892467]
- Saur S, Frengen J. Gafchromic EBT film dosimetry with flatbed CCD scanner: a novel background correction method and full dose uncertainty analysis. *Med Phys* 2008;35:3094–101. [PubMed: 18697534]
- Seppenwoolde Y, Shirato H, Kitamura K, Shimizu, Van Herk M, Lebesque JV, Miyasaka K. Precise and real-time measurement of 3D tumor motion in lung due to breathing and heartbeat, measured during radiotherapy. *Int J Rad Onc Biol Phys* 2002;53:822–34.
- Søvik Å, Malinen E, Skogmo HK, Bentzen SM, Bruland OS, Olsen DR. Radiotherapy adapted to spatial and temporal variability in tumor hypoxia. *Int J Radiat Oncol Biol Phys* 2007;68:1496–504. [PubMed: 17674980]
- Stern A, Kopeika NS. Optical transfer function analysis of images blurred by nonharmonic vibrations characterized by their power spectrum density. *J Opt Soc Am A* 1999;16:2200–8.
- Tanderup K, Olsen DR, Grau C. Dose painting: art or science. *Radioth and Onc* 2006;79:245–8.
- Thorwarth D, Eschmann SM, Paulsen F, Alber M. Hypoxia dose painting by numbers: a planning study. *Int J Radiat Oncol Biol Phys* 2007;68:291–300. [PubMed: 17448882]
- Thorwarth D, Soukup M, Alber M. Dose painting with IMPT, helical tomotherapy and IMXT: A dosimetric comparison. *Radiother Oncol* 2008;86:30–4. [PubMed: 18061294]
- Wolthaus JWH, Schneider C, Sonke JJ, van Herk M, Belderbos JSA, Rossi MMG, Lebesque JV, Damen EMF. Med-ventilation CT scan construction from four-dimensional respiration-correlated CT scans for radiotherapy planning of lung cancer patients. *Int J Radiation Oncology Biol Phys* 2006;65:1560–71.
- Yang Y, Xing L. Towards biologically conformal radiation therapy (BCRT): selective IMRT dose escalation under the guidance of spatial biology distribution. *Med Phys* 2005;32:1473–84. [PubMed: 16013703]
- Yu CX, Jaffray DA, Wong JW. The effects of intra-fractional organ motion on the delivery of dynamic intensity modulation. *Phys Med Biol* 1998;43:91–104. [PubMed: 9483625]
- Zalevsky Z, Raveh I, Mendlovic D, Lohmann AW. Image restoration from vibrating photographic systems. *Appl Opt* 1999;38:6205–12. [PubMed: 18324145]

Fig. 1.

(a) The motion trace programmed for the 'lung tumor' sphere shown in (b) inside the anthropomorphic chest phantom. The arm attaches to the Washington University 4D Motion Phantom, and is shown here about to enter the TomoTherapy Hi-Art II™ machine bore (film not yet inserted).

Fig. 2.

Contour plots comparing the film (thin solid lines) to the plan (thick dashed lines) from stationary (a) and motion (d) cases. The transparent gray lines show the profile locations. The stationary profiles (b: lateral) and (c: craniocaudal) are shown comparing the film (red lines) to the plan (blue lines). The corresponding profiles for the motion case are in (e: lateral) and (f: craniocaudal). These figures are derived from TomoTherapy software screenshots: note that the film edges are visible for the red profiles as sharp vertical drops in dose, and the dose values beyond these edges are irrelevant.

Fig. 3.

The gamma maps for the stationary (a) case and the motion (b) case. The colorbar is applicable to both cases. The distance to agreement is 5 mm, and the search radius is 5 mm. The dose tolerance is 5%. The motion blurring dose errors at the edges of the boost regions are evident in (b), but it still is acceptable. These figures are derived from TomoTherapy, Inc. software screenshots.

Fig. 4.

Using the sinusoidal moving compensator approximation for IMRT interference as in T. Bortfeld et al 2002 Phys. Med. Biol. 47, 2203-2220, their Eq. 11 with the phase set to zero for dose errors is plotted versus a quantity proportional to the inverse of the motion period. There will be interference when there is coherence between modulation frequency and tumor motion frequency. When the modulation frequency is much greater than the tumor motion frequency, many motion periods are averaged in and the dose errors reduce. In the opposite limit, only a partial motion cycle is experienced by the treatment. The phase was set to zero such that it would be equivalent to registration to the average of the motion position. An average delivery sinogram value of 1/2 is used for the heavy arrow indication for each beamlet.