Tumor Volume Variation in Proton Radiotherapy Planning

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Dr. Alexei Chvetsov received his Ph.D. in Nuclear Engineering in 1992 from the Moscow Engineering Physics Institute in Russia. Following his graduation, Dr. Chvetsov held research and academic positions at the Moscow Engineering Physics Institute in Russia, Ruhr-University of Bochum in Germany, Tom Baker Cancer Center in Canada and Case Western Reserve University in USA. His clinical training and work experience began at the Tom Baker Cancer Center in Calgary, Canada. Dr. Chvetsov is certified in radiotherapy physics by American Board of Radiology and Canadian College of Physicists in Medicine. His research interests include optimization problems for cancer radiotherapy, inverse problems in treatment planning and numerical transport theory. Since November 2006 Dr. Chvetsov has been working as Assistant Professor in the Department of Radiation Oncology of the University of Florida. In this article he describes a problem of *a priori* prediction of physiological changes in tumor volume and developing an understanding of its implications in fractionated radiotherapy with proton beams. Dr. Chvetsov believes solving this problem may lead to improved patient treatment with proton therapy, which is prone to large uncertainties in dose delivery with physiological changes in tumor and normal tissue.

I. Measurements of tumor volume variation during fractionated radiotherapy

The accuracy of 3D conformal dose calculation and radiation delivery to static tumors is rapidly approaching its theoretical limit. The advent of image-guided radiation therapy (IGRT) and our ability to observe patient motion in real time has brought on a realization that a patient's geometry, including the tumor and normal tissue changes with time. Time-dependent target definition and tracking have become priorities in radiation therapy. A significant amount of research is being devoted to set-up-uncertainties, breathing motion and image-guided radiation therapy.

During the last few years, several clinical studies have been published on *in-vivo* tumor-volume variation during fractionated X-ray radiotherapy. The data are obtained using integrated 3D-imaging techniques like CT/linear accelerator systems, Tomotherapy or cone-beam computed tomography (1-5). Similar studies have been done using conventional CT scanners for proton therapy (6) and photon therapy (7). The acquired data indicate that the physiological geometry changes in tumors and normal tissues between dose fractions can affect dose distributions during fractionated radiotherapy, with an apparent maximum effect for the lung as well as head-and-neck cancers. Tumor volume variation, specifically volume-based dose planning and sharp dose fall-off around the tumor, is becoming increasingly important as intensity-modulated radiation therapy becomes a widespread technology (8, 9). For head-and-neck and lung cancers, tumor shrinkage can shift high

dose volumes into critical structures and change tumor dose for both X-ray and proton therapy. Proton therapy is even more sensitive to the physiological changes because of its limited range in patient and sharp dose fall-off (10, 11). There is also evidence of the relationship of tumor volume and treatment outcome (12, 13). The most recent studies of tumor volume during radiotherapy are summarized in Table 1.

Table.1. Experimental data on in-vivo tumor-volume measurements during radiotherapy

#	Site	Imaging system	Institution	Publ., Red Jou
1	Head-and-Neck	CT/Linac system	MD Anderson cancer center, Houston, TX	Barker et at 20
2	Lung	Tomotherapy	MD Anderson Cancer Center, Orlando, FL Thompson Cancer Survival Center, Knoxville, TN	Kupelian et al
3	Lung	Tomotherapy,	University of Wisconsin, Wisconsin, MD	Siker et al 200
4	Lung	Tomotherapy	London Regional Cancer, London, Canada	Woodford et al
5	Lung	4DCT	MD Anderson Cancer Center, Houston, TX	Bucci et al 200
6	Lung	Cone-beam CT	University of Florida, Gainesville, FL	Newlin et al 20
7	Cervical cancer	MRI	Princess Margaret Hospital, Toronto, Canada	Lim et al 2008
8	Lung	4DCT	Johns Hopkins University, Baltimore, MD	Fox et al 2009
9	Cervical cancer	MRI	Ohio State University, Columbus, OH	Mayr et al 200

II. Impact of tumor volume variation on proton radiotherapy planning

Proton therapy is an emerging radiotherapy technology that has significant theoretical advantage over high-energy X-rays and electron beams, which are commonly used for cancer treatment with high radiation doses (14-16). The dose distribution from proton beams is characterized by a rapid dose fall-off laterally that is similar to X-ray beams and a limited range of penetration. In addition to these advanced characteristics, dose deposition from a proton beam has a relatively lower dose at shallow depths which increases towards the end of its range producing the effect called the Bragg peak. These advantages make proton beams an ideal treatment modality for radiation therapy cases for which high doses should be delivered to the deep-seated tumors while sparing normal tissue surrounding the tumor (18, 19). Each disease site that has been treated with proton beams has been shown to have local control as good as or better than photon beams and, in most cases, reduced late effects (15, 16). Therefore, radiotherapy with proton

beams is gaining significant interest and there is substantial growth in the number of proton therapy facilities. At the present time, about 25 facilities around the world are treating patients with proton beams and over 43,000 patients have been treated (14). Five of these facilities are located in the United States: Northeast Proton Therapy Center, Loma Linda University Medical Center, Midwest Proton Radiation Institute, M.D. Anderson Proton Therapy Center, and University of Florida Proton Therapy Institute.

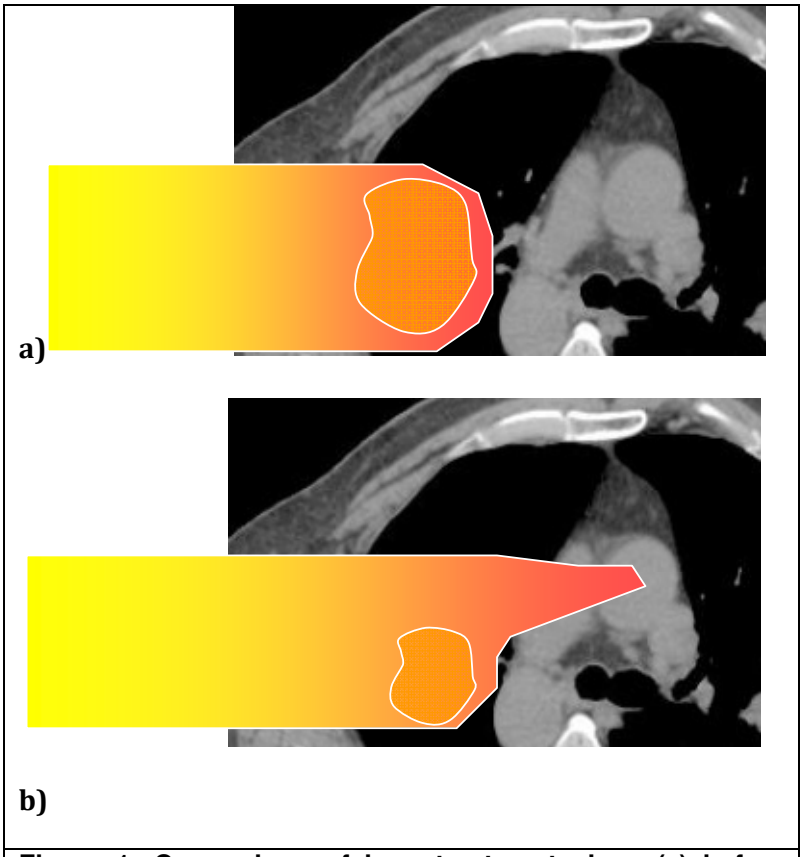

Figure 1: Comparison of lung treatment plans (a) before treatment and (b) in the middle of treatment.

Finite range of proton beam makes the dose distributions in proton therapy extremely sensitive to any density variation in the human body (19). Therefore, the dose distribution from proton beams with steep dose fall-off in the lateral and longitudinal directions may put more emphasis on robustness and accuracy in the definition of computational geometry. Tumor shrinkage during radiotherapy results in the replacement of relatively high-density tumor tissue within low-density lung tissue. This may change a proton range significantly, thus leading to significant variation in the planned treatment. The treatment plan at the beginning of the treatment and in the middle of the treatment is shown in Fig. 1(a) and (b). The dose distribution has changed significantly for the shrunken tumor. The deviation from the initial treatment plan can cause radiation damage of the cord or other critical organs in the path of the beam.

III. Radiobiological tumor-volume modeling during fractionated radiotherapy

Tumor-volume modeling can address these problems and improve the quality and accuracy of 4D radiation therapy treatment planning. For instance, the tumor-volume model can be used to optimize image-guidance protocols and treatment 4D simulations.

Many radiobiological models have been proposed for the tumor regression during RT. These models span from simple tumor-volume models similar to that proposed by Fischer (20,21) to more complicated computer implementations which are based on 3-dimensional individual cell simulations using random processes simulated by Monte Carlo methods (22,23). Other new approaches for tumor-volume simulation during fractionated RT have been developed to address the tumor-volume measurements using on-board imaging (24, 25). These models are based on mathematical regression models or prior data from a patient database; therefore, they do not utilize

underlying radiobiological mechanisms. Therefore, these models can not explain many phenomena which have been observed in tumor volume variation measurements.

Although radiobiological tumor regression models have been studied, there has been no practical application of these models in RT treatment planning. The previous research has been primarily dedicated to the development of effective dose fractionation schedules, models for tumor control probability (TCP), and normal-tissue-complication probability (NTCP) (26, 27). Tumor volume was also studied, but only as a predictor of TCP (28, 29). Less attention has been paid to the models for tumor-volume changes during RT probably because it was assumed that these changes could not significantly affect the dose distributions in highly conformal radiotherapy. Another reason is that the 3D integrated imaging technologies that are capable of monitoring tumor volume variation *in vivo* during RT treatment have not been available for accurate verification of these models till recently.

The most accurate tumor volume simulations during RT can be performed using Monte Carlo individual cell simulation techniques (22, 23). However, it would be difficult to accurately define the initial and boundary conditions necessary to simulate individual tumors. These initial conditions can include vascular structure and nutrition supply, which may differ among individual patients. As a result, we think that simpler practical approaches for radiobiological modeling of tumor mass-volumetric response are needed. Integrated radiobiological phenomena can be described by simple mathematical functions despite the complexity of the underling radiobiological processes at the cellular level. The examples are the linear-quadratic (LQ) survival model or exponential tumor-control probably (TCP) model. For instance, the 4-level cell population model proposed by Fischer (20, 21) can be used for tumor volume modeling.

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IV. Potential practical and scientific impact of the tumor-volume models

We think the accuracy and effectiveness of proton therapy could be improved without resorting to frequent volumetric imaging if a radiation oncologist has a tool to predict the volumetric radiobiological changes, even if with limited uncertainties. We believe that practical models for a radiobiological tumor volumetric response are needed (30, 31). These models can utilize CT, PET and MRI imaging technologies as much as possible for verification and derivation of computing parameters (32-34) and should be fast enough for real-time treatment planning

Lung cancer patients treated with proton beams are at risk of increased healthy tissue damage because of disappearance of tumor shielding effect during tumor shrinkage**.** Similar situation can be in the head-and-neck cancer treatment. Repeat CT imaging and re-planning after each fraction is costly and time-consuming and it increases dose to the patient from imaging studies. Therefore, any treatment optimization which would reduce the number of repeat CT images and generate treatment plans which are less sensitive to the tumor shielding effect would be useful in clinical practice. A tumor volume model can be used to optimize time intervals of repeat CT imaging. The potential impact is reduced treatment cost and less CT dose to patients.

Other potential practical applications may include the following:

1) *In-vivo* verification of proton RBE (relative biological effectiveness), which is assumed to be 1.1 by comparing the tumor-volume regression rates in proton and photon beam therapy.

2) Establishing relationship between tumor-volume regression and treatment outcome. This has been the focus of recent publications (12, 13).

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