International Journal of Radiation Oncology biology • physics

www.redjournal.org

Clinical Investigation: Gastrointestinal Cancer

Accumulated Dose in Liver Stereotactic Body Radiotherapy: Positioning, Breathing, and Deformation Effects

Michael Velec, B.Sc.,[*,‡] Joanne L. Moseley, B.Math.,[*] Tim Craig, Ph.D.,[*,†] Laura A. Dawson, M.D.,[*,†,‡] and Kristy K. Brock, Ph.D.[*,†,‡]

**Radiation Medicine Program, Princess Margaret Hospital, University Health Network, Toronto, ON, Canada; and Department of [†]Radiation Oncology and the [‡]Institute of Medical Science, University of Toronto, Toronto, ON, Canada*

Received Mar 25, 2011, and in revised form Sep 13, 2011. Accepted for publication Sep 22, 2011

Summary

Deformable image registration was used to accumulate the delivered dose in 6-fraction SBRT, on the basis of the four-dimensional (4D) cone-beam CT (CBCT) acquired daily for 30 liver cancer patients. The majority of patients had accumulated dose deviations of at least 5% to the minimum tumor or maximum normal tissue dose, relative to the breathing dose distribution predicted on the planning 4D CT. Residual setup errors were most commonly the

Purpose: To investigate the accumulated dose deviations to tumors and normal tissues in liver stereotactic body radiotherapy (SBRT) and investigate their geometric causes.

Methods and Materials: Thirty previously treated liver cancer patients were retrospectively evaluated. Stereotactic body radiotherapy was planned on the static exhale CT for 27−60 Gy in 6 fractions, and patients were treated in free-breathing with daily cone-beam CT guidance. Biomechanical model-based deformable image registration accumulated dose over both the planning four-dimensional (4D) CT (predicted breathing dose) and also over each fraction's respiratory-correlated cone-beam CT (accumulated treatment dose). The contribution of different geometric errors to changes between the accumulated and predicted breathing dose were quantified.

Results: Twenty-one patients (70%) had accumulated dose deviations relative to the *planned static prescription dose* >5%, ranging from −15% to 5% in tumors and −42% to 8% in normal tissues. Sixteen patients (53%) still had deviations relative to the *4D CT−predicted dose*, which were similar in magnitude. Thirty-two tissues in these 16 patients had deviations >5% relative to the 4D CT−predicted dose, and residual setup errors ($n = 17$) were most often the largest cause of the deviations, followed by deformations ($n = 8$) and breathing variations ($n = 7$).

Conclusion: The majority of patients had accumulated dose deviations >5% relative to the static plan. Significant deviations relative to the predicted breathing dose still occurred in more than half the patients, commonly owing to residual setup errors. Accumulated SBRT dose may be warranted to pursue further dose escalation, adaptive SBRT, and aid in correlation with clinical outcomes. © 2012 Elsevier Inc.

Reprint requests to: Michael Velec, B.Sc., M.R.T.(T.), Princess Margaret Hospital, Radiation Medicine Program, 610 University Ave., Toronto, ON, Canada M5G 2M9. Tel: (416) 946-4501; Fax: (416) 946-6521; E-mail: michael.velec@rmp.uhn.on.ca

Presented in part at the 51st Annual Meeting of the American Society for Radiation Oncology, November 1−5, 2009, Chicago, IL.

This work is supported by Grant No. 5RO1CA124714-02 from the U.S. National Institutes of Health. Clinical trials were supported by Grant 18207 from the National Cancer Institute of Canada and Elekta Oncology Systems. K.K.B. is supported as a Cancer Care Ontario Research Chair.

Conflict of interest: K.K.B. serves on the IMPAC Physics Advisory Board and receives grant funding from Philips Medical Systems, RaySearch Laboratories, and Elekta Oncology Systems. L.A.D. receives grant funding from Bayer. K.K.B. and L.A.D. have a financial interest in the Morfeus technologies reported.

Acknowledgment—The authors thank Jan-Jakob Sonke and Marcel van Herk (The Netherlands Cancer Institute) for help with the four-dimensional cone-beam CT, and Graham Wilson and Michael Sharpe for valuable assistance with this research.

Int J Radiation Oncol Biol Phys, Vol. 83, No. 4, pp. 1132−1140, 2012
0360-3016/$ - see front matter
doi:10.1016/j.ijrobp.2011.09.045

cause of these dose deviations, followed by abdominal deformation and changes in breathing motion between the 4D CT and the 4D CBCT.

Keywords: Deformable registration, Dose accumulation, Image-guided radiotherapy, Stereotactic body radiotherapy, Liver cancer

Introduction

Stereotactic body radiotherapy (SBRT) is a promising treatment for primary and metastatic liver cancer patients ineligible for other localized treatment. Stereotactic body radiotherapy planning uses individualized, highly conformal dose distributions aimed at reducing treatment margins and sparing normal tissue dose and related toxicity. Liver normal tissue complication probability (NTCP) models can help estimate SBRT toxicity and allocate or escalate dose (1, 2). Trials have shown high local control rates with acceptable toxicity (3–5), whereas lower doses have been associated with poorer survival or disease control (1, 4), suggesting that further dose escalation may be beneficial provided toxicity rates remain low.

Minimizing geometric uncertainties is necessary for SBRT. Respiratory motion can be negated using active breathing control devices allowing gated beam delivery during breath holds (6) or reduced with an abdominal compression plate (7). These may allow for smaller margins, normal tissue sparing, and higher tumor doses, but many patients are ineligible and are treated in free-breathing. Incorporating breathing motion into liver SBRT dose calculations can potentially impact tumor and normal tissue doses and margin design (8–10). Whether these techniques actually estimate the delivered dose better than static dose calculations is presently unknown. Image-guided radiotherapy (IGRT) can potentially identify and correct baseline shifts in liver position (relative to bone), breathing motion, or deformation before treatment (6, 11, 12). Direct tumor visualization is typically not possible, so IGRT methods for liver SBRT involve imaging fiducial markers (13) or the liver and diaphragm as soft-tissue surrogates using two-dimensional fluoroscopy or three-dimensional (3D) CBCT in the presence of breathing motion (7, 14).

Mendez Romero *et al.* (15) estimated daily dose deviations in a liver SBRT trial using rigidly registered repeat CT, finding that IGRT did not on average improve the daily dose to normal tissues, owing to anatomic deformations. Rigid registration is unable to accumulate dose over multiple fractions in the presence of these changes. Deformable image registration (DIR) applies spatially variable transformations during registration to more accurately track tissues between two or more imaging sessions (*i.e.*, SBRT fractions). Janssens *et al.* (16) found that intensity-based DIR significantly improved interfraction dose accumulation on deforming phantoms over rigid registration, noting that its accuracy is highly dependent on both image quality and contrast. They also reported that sharp dose gradients, required by liver SBRT plans to spare normal tissue, can exacerbate dose accumulation errors caused by DIR errors. Soft-tissue contrast is generally poor on CBCT, making IGRT and DIR challenging. Brock *et al.* (11) applied a biomechanical model-based DIR algorithm on the daily CBCT of liver SBRT patients, revealing residual errors in the tumor position that exceeded the setup tolerance in 15% of fractions. The dosimetric impact of these uncertainties is not well understood.

Our previous work (9) indicated that performing deformable dose accumulation incorporating breathing motion from the 4D CT resulted in substantial deviations in the estimated dose to the tumor and normal tissues compared with the static plan. The work presented here expands on this, evaluating how well the planning 4D CT predicts for the best estimate of delivered dose, using deformable dose accumulation over each fraction's 4D CBCT. The aim was to accumulate dose using DIR of CBCT over 6-fraction SBRT in free-breathing liver patients. This was compared with both the static dose on the planning CT and the breathing dose predicted from the planning 4D CT, to assess which method better predicts the accumulated dose. The second aim was to investigate the effect of different geometric uncertainties on dose deviations. Characterizing uncertainties in current SBRT techniques may enable robust planning development, enable safe escalation of SBRT doses in future trials, and improve interpretation of clinical outcomes.

Methods and Materials

Patients and SBRT planning

Thirty patients previously treated on institutional review board–approved Phase I and II trials of dose-escalated, hypofractionated liver SBRT from February 2006 to April 2010 were investigated. Patient and planning details are summarized in Table 1. All were ineligible for active breathing control treatment owing to intolerance or small breathing amplitudes (<5 mm), and thus were treated in free-breathing (with or without abdominal compression). Planning was done on end-exhale 4D CT. Inhale 4D CT liver motion, diaphragm fluoroscopy motion, and cine-MRI tumor motion aided in breathing motion characterization for designing individualized planning target volumes (PTVs). Delineation and static plan optimization was done on exhale CT in a commercial treatment planning system (Pinnacle^3 v7.6–8.0; Philips Medical Systems, Madison WI). Asymmetric PTVs were designed to account for the patient-specific breathing motion observed on the imaging studies, with a minimum PTV of 5 mm required. Dose was individually prescribed for 6 fractions in 2 weeks by determining the risk of radiation-inducted liver disease from a Lyman-NTCP model (2). The primary planning goal was that the minimum dose to the GTV and PTV received a minimum of 95% of the prescribed dose to 0.5 cm^3, while respecting normal tissue constraints. The maximum allowable doses to the luminal gastrointestinal organs ranged from 30 to 36 Gy to 0.5 cm^3. Volume, margin generation, and NTCP calculations have been detailed by Dawson *et al.* (2).