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Robust optimization in intensity-modulated proton therapy to account for anatomy changes in lung cancer patients

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ABSTRACT

Background and purpose: Robust optimization for IMPT takes setup and range uncertainties into account during plan optimization. However, anatomical changes were not prospectively included. The purpose of this study was to examine robustness and dose variation due to setup uncertainty and anatomical change in IMPT of lung cancer.

Material and methods: Plans were generated with multi-field optimization based on planning target volume (MFO-PTV) and worst-case robust optimization (MFO-RO) on simulation computed tomography scans (CT0) for nine patients. Robustness was evaluated on the CT0 by computing the standard deviation of DVH (SD-DVH). Dose variations calculated on weekly CTs were compared with SD-DVH. Equivalent uniform dose (EUD) change from the original plan on weekly dose was also calculated for both plans.

Results: SD-DVH and dose variation on weekly CTs were both significantly lower in the MFO-RO plans than in the MFO-PTV plans for targets, lungs, and the esophagus ($p < 0.05$). When comparing EUD for ITV between weekly and planned dose distributions, three patients and 28% of repeated CTs for MFO-RO plans, and six patients and 44% of repeated CTs for MFO-PTV plans, respectively, showed an EUD change of >5%.

Conclusions: RO in IMPT reduces the dose variation due to setup uncertainty and anatomy changes during treatment compared with PTV-based planning. However, dose variation could still be substantial; repeated imaging and adaptive planning as needed are highly recommended for IMPT of lung tumors.

Introduction

Intensity-modulated proton therapy (IMPT), which simultaneously optimizes the intensity and energy of proton beamlets using constraints for both targets and normal structures (similar to intensity-modulated photon radiotherapy), could reduce doses of radiation to normal tissues [1–5]. However, IMPT is sensitive to setup and range uncertainties and patient anatomy changes [6–9]. In recent years, robust optimization techniques have been developed to account for setup and range uncertainties [10]. Robustness in IMPT could be loosely viewed as the sensitivity of dose distribution to variations such as setup uncertainty, range uncertainty, and patient anatomy changes. In essence, robust optimization techniques employ extra criteria or constraints in conjunction with the normal objective functions during spot weight optimization to find the spot weight configuration that is least sensitive to the change in patient setup location or change in proton range inside of the patient. The ability of robustly optimized plans to retain intended dose distribution despite setup and range uncertainty has been validated for various cancer sites via planning studies [11–15].

However, unlike setup and range uncertainties, anatomy changes such as tumor shrinkage or patient weight loss are not usually prospectively taken into consideration in the planning process. In practice, repeated imaging and adaptive planning are used to account for anatomy changes in the patient [16–18], and clinically, the robustness of a treatment plan could be evaluated and quantified by the change of dose distribution and the need of adaptive planning through the course of treatment, i.e. a robust treatment plan will maintain the dose distribution in the patient throughout the course of the treatment. Even though the robust optimization method does not directly account for anatomy changes, it can be anticipated that the resulting spot weight configuration is in essence less sensitive to the change in the proton

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beam range along the ray lines regardless of what causes such a change. In this study, we hypothesized that, in addition to the anticipated robustness against setup and range errors, robustly optimized plans can minimize the re-planning required to meet clinical goals.

The purpose of this study was to understand the relationship between robustness and the magnitude of dose variation through the course of patient treatment. Although the robust optimization technique incorporates only setup and range uncertainty, we also evaluated its effectiveness in making IMPT plans resilient to inter-fractional anatomical changes, in terms of the need for adaptive planning based on repeated computed tomography (CT) scans.

Material and methods

Simulation and treatment planning

The records of nine consecutive lung cancer patients from an institutional review board-approved protocol who underwent IMPT at our institution between August 2012 and July 2013 were selected for this retrospective study. Table s1 in the supplement summarizes the pretreatment characteristics of the patients. Each patient underwent 4-dimensional (4D) CT simulation on a GE Lightspeed 16-slice CT scanner (GE Healthcare, Waukesha, WI). Each 4DCT dataset consisted of ten 3-dimensional image sets corresponding to the ten respiratory phases, along with maximum-intensity projection (MIP) and averaged-intensity projection (AVIP) datasets generated for planning purposes. To account for tumor motion, the internal gross tumor volume (IGTV) was contoured using either the union of the GTV on an individual phase or the contour of the GTV on MIP as verified through different breathing phases. The internal target volume (ITV) was defined as an 8 mm isotropic expansion of the IGTV and edited clinically. The planning target volume (PTV) was defined as an expansion of the ITV by 5 mm.

Respiratory motion is one of the major concerns in IMPT for patients with lung cancer. At our institution, currently only patients with minimum motion (<5 mm) are considered for IMPT [19], and a separate study to minimize the dosimetric impact of respiratory motion is being performed [20]. For each patient in our study, motion analysis was performed on the acquired 4DCT before proceeding with IMPT planning, and an IGTV override technique was used for all patient planning [21]. Multi-field optimization (MFO) based on PTV (MFO-PTV) and robust optimization with respect to setup and range uncertainties (MFO-RO) were developed on a simulation averaged-intensity projection CT (CT0). The MFO-PTV plans were developed using a commercialized planning system (Eclipse v8.9, Varian Medical Systems, Palo Alto, CA), using PTV to account for setup uncertainties. The MFO-RO plans were developed using an in-house optimization system [14] with the dose calculated in Eclipse. The MFO-RO used ITV as the target volume of worst-case robust optimization, assuming ±3 mm setup uncertainties and ±3.5% range uncertainties [14,15].

Three matched beam angles and similar planning constraints were used for the MFO-PTV and MFO-RO plans, with the exception of PTV, which was only used in MFO-PTV. Both plans were reviewed by the treating radiation oncologist, and the MFO-RO plans were used for patient treatment.

Robustness evaluation with setup and range uncertainties

Owing to the steep dose gradient of the proton beam, IMPT plans can be sensitive to both setup and range errors [7,8] and can lead to a distorted dose distribution in the patient. Therefore, the robustness evaluation of an IMPT plan against setup and range uncertainty is an important component in the treatment planning process. Evaluation of the robustness of an IMPT plan is not straightforward. The conventionally used plan evaluation method based on enlarged volume (i.e. coverage of PTV in relation to true clinical target volume coverage) does not work well for proton therapy because of the non-static nature of dose distribution in and out of the volume being evaluated. The "worst-case scenario" method [15], in which the worst-case dose distribution is calculated as the voxel-by-voxel worst-case dose value that can occur when setup and range errors are introduced, was developed to evaluate the robustness of IMPT plans. Although the worst-case scenario evaluation has been shown to be a conservative bound on the real worst-case dose distribution [22], for our study the worst-case technique could be biased because the same technique was used in optimization. Therefore, we used a recently developed statistical technique [23] to evaluate the robustness of the IMPT plans. In this statistical technique, 600 combinations of setup and range uncertainties were introduced to the planning CT (CT0), and a fast dose calculation technique was used to calculate the dose distribution with the introduced uncertainties [24]. Dose-volume histograms (DVHs) of the target volumes and critical structures for each dose distribution were calculated. The mean DVH (E[DVH]) and the standard deviation of the DVH (SD-DVH), which represents the robustness of the plan under setup and range uncertainties, were calculated from the collection of the DVHs as follows:

$$E[\mathrm{DVH}(d)] = \sum_{i=1}^{n} P[d_i \geqslant d]\, v_i \tag{1}$$

where d is the dose in Gy, i indexes the voxels in a given ROI, n is the total number of voxels in the ROI, v_i is the volume of voxel i, and d_i is the dose to voxel i.

$$\mathrm{SD}[\mathrm{DVH}(d)] = \sqrt{\frac{1}{N-1}\sum_{j=1}^{N}\left(\mathrm{DVH}_j(d) - E[\mathrm{DVH}(d)]\right)^2} \tag{2}$$

where j indexes the sampled setup and range uncertainties, and N is the total number of dose distributions sampled. The total dose variation (DV) of the plan for a structure was quantified using $\pm 2\sigma$ (or 4σ) as in:

$$\mathrm{DV}_{\text{SD-DVH}} = \int_d 4 * \mathrm{SD}[\mathrm{DVH}(d)] \tag{3}$$

where the integral over dose (d) was calculated numerically by making 1000 equal spacing samples over 0 to the maximum dose among all scenarios. $\mathrm{DV}_{\text{SD-DVH}}$ could be visualized as the area of a DVH band with width of 2SD on each side of the E-DVH at dose level d, with a unit of dose * volume (Gy * cc). All DV data presented in the manuscript were normalized by the organ volume and prescription dose.

Robustness evaluation based on repeated CTs

CTs were taken approximately weekly during the course of treatment. For each patient, two to seven CTs were acquired, resulting in a total of 39 repeated CTs. Each repeated CT was registered with the planning CT using rigid registration of the bony anatomy to determine the isocenter. A new dose distribution was then calculated using the original MFO-PTV and MFO-RO plans' beam data using this isocenter. The original contours were deformed from the planning CT to the repeated weekly CTs using a commercial system (Velocity, Velocity Medical Solutions, Atlanta, GA). The accuracy and integrity of the newly deformed structures were visually assessed and approved by the treating physicians. Based on the newly created dose distribution and DVHs, adaptive planning was performed for selected patients as needed per the

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