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Integral dose based inverse optimization objective function promises lower toxicity in head-and-neck

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ABSTRACT

Purpose: The voxels in a CT data sets contain density information. Besides its use in dose calculation density has no other application in modern radiotherapy treatment planning. This work introduces the use of density information by integral dose minimization in radiotherapy treatment planning for head-and-neck squamous cell carcinoma (HNSCC).

Materials and methods: Eighteen HNSCC cases were studied. For each case two intensity modulated radiotherapy (IMRT) plans were created: one based on dose-volume (DV) optimization, and one based on integral dose minimization (Energy hereafter) inverse optimization. The target objective functions in both optimization schemes were specified in terms of minimum, maximum, and uniform doses, while the organs at risk (OAR) objectives were specified in terms of DV- and Energy-objectives respectively. Commonly used dosimetric measures were applied to assess the performance of Energy-based optimization. In addition, generalized equivalent uniform doses (gEUDs) were evaluated. Statistical analyses were performed to estimate the performance of this novel inverse optimization paradigm.

Results: Energy-based inverse optimization resulted in lower OAR doses for equivalent target doses and isodose coverage. The statistical tests showed dose reduction to the OARs with Energy-based optimization ranging from ~2% to ~15%.

Conclusions: Integral dose minimization based inverse optimization for HNSCC promises lower doses to nearby OARs. For comparable therapeutic effect the incorporation of density information into the optimization cost function allows reduction in the normal tissue doses and possibly in the risk and the severity of treatment related toxicities.

1. Introduction

Head-and-neck squamous cell carcinoma (HNSCC) cases represent a challenging group of cancer patients. Radiotherapy and concurrent chemotherapy is considered to be the nonsurgical standard of care both for locally advanced HNSCC and for postoperative therapy in patients with a high risk of recurrence [1]. Various meta-analyses studies have clearly shown that delivering chemotherapy and radiotherapy concomitantly (chemoradiation) significantly boosts the effects of radiation alone [2–6]. However, with the increasing use of aggressive combined modality therapy and with altered radiation techniques the acute and late effects of treatment have become an area of intensive interest and investigation [7]. This combined multimodality approach raises a number of practical challenges, most of them resulting from poor treatment tolerance and reduced compliance to the prescribed dose levels of chemoradiation [8]. Most HNSCC patients receiving high-dose radiotherapy are affected by severe acute side effects, including mucositis (stomatitis), dysphagia, and skin toxicity (radiation dermatitis). Chemoradiation is associated with an even higher incidence of severe (grade 3/4) acute adverse events [9,10], indicating the detrimental effects of chemo-radiotherapy combination for this treatment site [11].

Intensity modulated radiotherapy (IMRT) is normal tissue sparing irradiation technique commonly used for HNSCC [12,13]. Compared with conventional techniques IMRT allows better sparing of unaffected tissues. The subsequent reduction in radiation-induced mucositis and xerostomia may help to decrease the morbidity of intensive concomitant chemoradiotherapy [2,14]. The purpose of this work is to present the incorporation of tissue density information, derived from planning computed tomography (CT) imaging studies, into the inverse optimization objective function. The incorporation is achieved via

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integral dose, where the integral dose is defined as an integral of the product between dose and mass over the volume of interest. It has been shown in phantom studies that this integral dose (or Energy hereafter), minimization is superior than most commonly used dose-volume-based inverse optimization, thereby holding a potential for increased tissue sparing in the complicated heterogeneous head-and-neck anatomy [15].

2. Materials and methods

2.1. Patient data

Eighteen locally advanced HNSCC cases, planned with simultaneous integrated boost technique [16], were used in this study. The targets included planning target volume (PTV) and nodal volumes, where different doses were prescribed. In addition to the targets, organs at risk (OARs) surrounding the targets were outlined for planning and treatment purposes. Those OARs included spinal cord, brainstem, parotid glands, and larynx. The close proximity (and sometimes the overlap) of the OARs to the targets makes the HNSCC site very challenging for modern inverse optimization IMRT planning.

2.2. Optimization functions

Dose-volume (DV) optimization is based on Eq. (1), where $F^{k,j}$ is the objective

$$F^{k,j} = \sum_{i \in V} \left(\frac{d_i - d^{k,j}}{d^{k,j}} \right)^2 v_i \tag{1}$$

function for jth fractional volume of organ k. d_i is the dose in voxel (3D volume element) i of the volume V, $d^{k,j}$ is the desired dose in each voxel for the jth fractional volume of the kth organ, v_i is the normalized voxel volume with respect to the total organ volume V, and V denotes the volume of the anatomical structure k. The volume V encompasses all of the voxels in the organ k where d_i is greater than $d^{k,j}$ [15,17,18]. Therefore, an optimization function $F^{k,j}$ is created for each optimization objective j (jth fractional volume) specified for the organ of interest k.

As it was mentioned above, the integral dose used in this work is a quantity represented by integration of the product between dose and mass over the volume of the irradiated objects. Since the CT imaging data used in radiotherapy is discrete, i.e. represented by voxels with finite spatial dimensions, the integral dose for all practical purposes would be represented by a sum over the voxels where the mass of each voxel is multiplied by the imparted dose to this voxel. Tissue mass in each voxel is computed from the raw CT data (Hounsfield number) through CT-to-density calibration procedure routinely used in radiotherapy dose calculations. The explicit form of the integral dose objective function is

$$F^k = \frac{1}{E_{0,k}} \sum_{i \in V} d_i m_i = \frac{1}{E_{0,k}} \sum_{i \in V} d_i \rho_i v_i \tag{2}$$

presented in Eq. (2) [15]. d_i, m_i, ρ_i, and v_i are the dose, mass, density and volume of dose voxel i respectively. The summation is over all dose voxels contained in the volume of the organ of interest V. The quantity $E_{0,k}$ is the desired integral dose to be imparted on the organ of interest k. Its determination is explained in detail in the next section. This optimization type is termed Energy hereafter.

In both Eqs. (1) and (2) there are normalization factors involved. In Eq. (1) it is the normalization to the total organ volume V, while in Eq. (2) the normalization is with respect to the desired integral dose E_0. The purpose of this normalization is that all of the objective functions F^k (in Energy optimization) and $F^{k,j}$ (in DV optimization) should have comparable values such that a combined objective function F

$$F = \sum_{k=1}^{N} \sum_{j=1}^{M} F^{k,j} \tag{3}$$

(cf. Eq. (3)) can be constructed, where N is the number of the organs of interests and M is the number of objectives per organ (in the case of Energy-based optimization the summation is only over the organs of interest because there is only one objective function per organ). Without normalization the individual functions F^k (Energy) and $F^{k,j}$ (DV) would have vastly different values and therefore the composite objective function from Eq. (3) would be dominated by a single (or very few) large objectives values. The optimization algorithm would work very hard on the minimization of the objective with the largest absolute value while the other objectives would be unaffected. Thereby the normalization is used to equalize the contribution of all individual objectives to the composite objective function such that a global solution can be found.

2.3. Treatment planning

For each of the eighteen cases two step-and-shoot IMRT plans were generated [19,20]. In either of those plans the target objectives were specified in terms of minimum, maximum, and uniform doses, while the objectives for the OARs were either DV [17,18], or Energy-minimization based [15]. The treatment plans consisted of 9 co-planar 6 MV beams, where beam-splitting was allowed. The beam splitting was due to the large treated nodal volumes, thereby allowing better target coverage and lower OAR doses. All of the planning parameters in terms of number of segments, minimum segment area, and minimum monitor units per segment were set the same for DV and Energy optimizations. Both optimization schemes utilized dose grids with size of $0.3 \times 0.3 \times 0.3\,\text{cm}^3$. All plans were optimized such that 95% of the PTV received 6600 cGy, while 90% of the nodal volumes received 5600 cGy. At the same time dose to all OARs were lowered until standard deviation of the dose across the PTV in each plan became 4%. It has been shown that this level of inhomogeneity does not affect the clinical applicability of the plans from radiobiological (based on tumor control probabilities) stand point [21]. The optimization scheme is in essence step-wise reduction of the OAR doses, and it is outlined on Fig. 1. In the first stage only doses to the targets and the auxiliary (ring regions of interest used to constrain the doses) structures are optimized, while there are no optimization objectives for the OARs. The target objectives were set as PTV minimum, maximum, and uniform dose of 6600, 6620, and 6610 cGy respectively. The nodal doses were set to minimum and maximum doses of 5600 and 6300 cGy respectively. Three rings, 1 cm thick, were defined around the nodal volumes. The first ring was 0.5 cm away, the second was 3 cm away, and the third was 5 cm away. The objectives for those rings were set to maximum and average doses of 5600 and 4000 cGy, 3600 and 1000 cGy, and 1900 and 500 cGy respectively. They were identical for both DV- and Energy-based optimization schemes. The aim of this stage is solely to achieve the prescription doses for the targets. The targets and the ring objective doses are not altered or adjusted anymore in the subsequent optimization stages. After completion of the first stage the number and the type of the OAR objectives is set, as outlined in stage 2 of the figure. The underlying dosimetric metric is evaluated for all OARs. In the case of DV optimization the dose-volume histograms (DVHs) for all OARs used as dose-limiting structures are generated, and five equally spaced points for fractional volumes from 1% to 80% for each OAR are evaluated for those DVHs. OAR doses from these initial DVH points are used as the base for the determination of the OAR dose-volume objectives for the next step in the optimization process. The OAR objective doses $d^{k,j}$ from Eq. (1) for the five preset fractional volumes are adjusted such that the OAR optimization objective values $F^{k,j}$ (DV) are slightly larger (by ~5%) than the largest objective value for the targets. The doses $d^{k,j}$ in the DV optimization can be regarded as commonly used clinical objectives such as dose to 50% of the parotid gland being less than