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Original article

Spatiotemporal fractionation schemes for liver stereotactic body radiotherapy

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ABSTRACT

Background and purpose: Dose prescription in stereotactic body radiotherapy (SBRT) for liver tumors is often limited by the mean liver dose. We explore the concept of spatiotemporal fractionation as an approach to facilitate further dose escalation in liver SBRT.

Materials and methods: Spatiotemporal fractionation schemes aim at partial hypofractionation in the tumor along with near-uniform fractionation in normal tissues. This is achieved by delivering distinct dose distributions in different fractions, which are designed such that each fraction delivers a high single fraction dose to complementary parts of the tumor while creating a similar dose bath in the surrounding noninvolved liver. Thereby, higher biologically effective doses (BED) can be delivered to the tumor without increasing the mean BED in the liver. Planning of such treatments is performed by simultaneously optimizing multiple dose distributions based on their cumulative BED. We study this concept for five liver cancer patients with different tumor geometries.

Results: Spatiotemporal fractionation presents a method of increasing the ratio of prescribed tumor BED to mean BED in the noninvolved liver by approximately 10–20%, compared to conventional SBRT using identical fractions.

Conclusions: Spatiotemporal fractionation may reduce the risk of liver toxicity or facilitate dose escalation in liver SBRT in circumstances where the mean dose to the non-involved liver is the prescription-limiting factor.

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Clinical motivation

Liver stereotactic body radiotherapy (SBRT) has become an established treatment option for primary and metastatic liver cancer [1–9]. For large tumors, the prescription dose is often limited by the mean dose delivered to the noninvolved liver. This reduces the chance of loco-regional tumor control and warrants the exploration of novel concepts to allow for further dose escalation [4,8].

Spatiotemporal fractionation

Fractionated treatments face a tradeoff. Increasing the number of fractions is desirable to protect normal tissues. However, the total dose must be increased to maintain tumor control [10]. In that sense, the ideal treatment would simultaneously facilitate hypofractionation in tumors along with near-uniform fractionation in normal tissues. Recently, it has been shown that this goal can be achieved to some degree by delivering distinct dose distributions in different fractions. The concept has been named spatiotemporal fractionation [11–14].

The concept was initially demonstrated for proton therapy [13,14] and subsequently for conventional photon beams [11,12]. The rationale can be understood in the context of rotation therapy delivered with tomotherapy or volumetric-modulated arc therapy (VMAT). Distinct VMAT plans for different fractions can be designed in such a way that each fraction delivers a similar dose bath to the normal tissue surrounding the tumor (i.e. exploits the fractionation effect). However, each fraction delivers a high single-fraction dose to different parts of the target volume. Thereby, some degree of hypofractionation is achieved in the tumor along with near-uniform fractionation in normal tissues. Spatiotemporal fractionation was outlined as an approach to

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improve fractionated radiosurgery for large cerebral arteriovenous malformations [12].

In this report, we investigate the potential of spatiotemporal fractionation to improve the ratio of tumor BED to mean liver BED in liver SBRT. Thereby, the approach may reduce the risk of radiation-induced side effects in the liver. Alternatively, spatiotemporal fractionation may facilitate dose escalation in liver SBRT in circumstances where the mean dose to the non-involved liver is the prescription-limiting factor.

Methods

Patients

We demonstrate spatiotemporal fractionation for 5 liver cancer patients shown in Fig. 1. These patients were selected as to represent a spectrum of tumor geometries, locations and sizes. Patient 1 has 4 metastases of varying size located throughout the right lobe of the liver and is discussed in detail in the results section. The total GTV volume is 391 cc and the mean liver dose is the dose-limiting constraint. Characteristics of patients 2–5 are described in the Supplementary materials, Appendix A.

Modeling of fractionation effects

We consider SBRT treatments with 5 fractions and assume that the fractionation schemes summarized in Table 1 are isoeffective. These fractionation effects can be modeled via the BED model [10,15] using generic values for the α/β-ratio, i.e. $\alpha/\beta = 10$ in the tumor and $\alpha/\beta = 4$ in all normal tissues. For example, 50 Gy delivered to the tumor in 5 fractions is equivalent to 27 Gy in a single fraction, and both regimens correspond to a BED_{10} of 100 Gy.

For spatiotemporal fractionation, we assume that the BED model can be extended to non-stationary fractionation schemes, in which the dose varies from fraction to fraction. In voxel i, the cumulative BED b_i of all fractions is given by

$$b_i = \sum_{t=1}^{n} \left(d_{it} + \frac{d_{it}^2}{(\alpha/\beta)_i} \right)$$

where d_{it} is the dose delivered in fraction t, n is the number of fractions, and $(\alpha/\beta)_i$ is the α/β-ratio of the structure that voxel i belongs to.

For visualization and quantitative interpretation, the BED can be scaled by a factor $1/[1 + X/(\alpha/\beta)]$, where X is a reference dose level [16]. In this report, we set X to 8 Gy, i.e. to the prescribed dose per fraction in the PTV. This yields the equieffective dose

$$EQD8 = \frac{b}{\left[1 + \frac{8}{(\alpha/\beta)}\right]}$$

$EQD8$ can be interpreted as the total physical dose that needs to be delivered in a uniformly fractionated treatment with a dose of 8 Gy per fraction to achieve the BED b.

Treatment plan optimization

We simultaneously optimize multiple IMRT plans based on their cumulative BED distribution. Traditional treatment plan optimization for IMRT is performed using objective and constraint functions evaluated for physical dose. Here, we apply the same functions with the difference that these are evaluated for cumulative BED rather than physical dose. To derive BED constraints for normal tissues and BED prescriptions for the target volume, typical constraints and prescriptions for 5-fraction liver SBRT were converted into BED[1]. We consider the following treatment planning problem:

Constraints

1. The maximum BED_4 to the bowel, duodenum and stomach is constrained to 75 Gy, corresponding to 30 Gy physical dose in 5 fractions.

Objectives

1. A BED_{10} of 100 Gy is prescribed to the GTV (implemented via quadratic penalty functions). This corresponds to 50 Gy physical dose delivered in 5 fractions.
2. A BED_{10} of 72 Gy is prescribed to the PTV, corresponding to 40 Gy physical dose in 5 fractions. A BED_{10} exceeding 100 Gy is penalized quadratically.
3. A BED_4 to the chest wall exceeding 120 Gy, corresponding to 40 Gy physical dose in 5 fractions, is penalized quadratically.
4. The plan is to be conformal (implemented via quadratic penalty functions where the allowed dose decreases linearly with distance from the PTV). A dose falloff to half the PTV prescription dose at 1 cm distance from the PTV is aimed for.
5. The mean BED_4 to the healthy tissue excluding the PTV and the liver is minimized.
6. The mean BED_4 to the liver excluding the GTV is minimized.

We first optimize a treatment plan that delivers the same dose in each fraction, which we call the *reference plan*. This is done based on a weighted sum of the 6 objectives. Second, we optimize two spatiotemporal plans:

1. Spatiotemporal plan 1 is obtained for optimizing the same objective function as for the reference plan, i.e. the same relative weighting of the 6 objectives. Hence, the benefit of spatiotemporal fractionation is distributed over all objectives.
2. Spatiotemporal plan 2 is obtained by minimizing the mean liver BED, subject to the constraints that the plan is no worse that the reference plan for each of the other 5 objectives. Hence, the entire benefit of spatiotemporal fractionation is concentrated on reducing mean liver BED.

Details of treatment plan optimization are described in the Supplementary materials, Appendix B. We consider IMRT plans consisting of 19 equispaced coplanar beams, which approximates the best coplanar rotation therapy plan, which could be delivered with tomotherapy or VMAT [17]. We use a beamlet resolution of 5×5 mm.

Results

Fig. 2g shows the dose distribution for patient 1 for the reference plan that delivers the same dose distribution in all 5 fractions. The plan achieves a mean liver dose of 18.3 Gy, which is near or exceeding the tolerance for 5-fraction treatments [9,18]. Hence, the mean liver dose represents the dose-limiting constraint. Fig. 2a-e shows the spatiotemporal treatment plan 2. Each fraction delivers a high single-fraction dose to complementary parts of the tumor. In some places, single fraction doses exceeding 25 Gy are delivered. Note that a single-fraction dose of 27 Gy delivers the

[1] Prescription doses and normal tissue constraints are based on a Phase III trial to evaluate the efficacy of proton therapy against photon therapy conducted at Massachusetts General Hospital (www.clinicaltrials.gov; Study title: Radiation Therapy with Protons or Photons in Treating Patients with Liver Cancer). These parameters also reflect institutional practice at University Hospital Zürich.

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