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Research article

Spatially fractionated radiotherapy (SFRT) targeting the hypoxic tumor segment for the intentional induction of non-targeted effects: An *in silico* study to exploit a new treatment paradigm

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ABSTRACT

Introduction: The possibility of intentionally triggering non targeted effects (NTEs) using spatially fractionated radiotherapy (SFRT) alone or combined with immunotherapy is an intriguing and fascinating area of research. Among different techniques for SFRT, stereotactic body radiotherapy targeting exclusively the central hypoxic segment of bulky tumors, (SBRT-PATHY) might trigger immunogenic cell death more efficiently. This in silico study aims to identify the best possible dosimetric trade-off for prescribing SFRT with volumetric modulated arc (VMAT) based stereotactic radiotherapy (SRT).

Material and methods: Eight spherical volumes defined "Gross Tumor Volumes" (GTVs) were generated with diameters of 3–10 cm (with incremental steps of 1 cm), simulating tumor lesions. The inner third part of each GTV ($GTV_{central}$) was selected to simulate the central hypoxic area and a ring structure was derived around it to simulate the tumor periphery ($GTV_{peripheral}$). Volumetric modulated arc radiation treatment (VMAT) plans were calculated to deliver a single fraction of 10 Gy to each $GTV_{central}$ with different dose prescription methods: target mean and isodose driven (40, 50, 60, 70, 80 and 90%).

The volume of $GTV_{peripheral}$ receiving less than 2 Gy was recorded as dosimetric performance indicator.

Results: 56 possible dosimetric scenarios were analyzed. The largest percentage of $GTV_{peripheral}$ spared from the dose of 2 Gy was achieved with dose prescription methods to the 70% isodose line for lesions smaller than 6 cm (range 42.9–48.4%) and to the target mean for larger ones (range 52.9–64.5%).

Conclusions: Optimizing the dose prescription method may reduce the dose to tumor periphery in VMAT-based SFRT, thus potentially sparing tumor infiltrating immune cells. The optimal method may vary according to the size of the lesion. This should be taken into account when designing prospective trials using SFRT.

Introduction

Spatially fractionated radiation therapy (SFRT) consists of the delivery of a single high dose fraction intentionally heterogeneous with high doses within the target but also areas of underdosing, to a large treatment area. SFRT in the form of grid or, more recently, lattice radiation therapy is clearly associated with dramatic responses, often exceeding those expected with homogenous dosing [1].

Another form of SFRT is the one proposed by Tubin and colleagues. Based on the preclinical finding that irradiating the hypoxic fraction of the tumor may intentionally induce non targeted effects, they proposed a new irradiation technique that consists of stereotactic body radiotherapy for partial irradiation of bulky tumors (larger than 6 cm), targeting exclusively their central hypoxic segment (SBRT-PATHY) with high dose (10 Gy). With SBRT-PATHY, they recently observed impressive results in a small retrospective clinical series with local and abscopal response rate of more than 90 and 50%, respectively [2,3].

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The radiation induced abscopal (from Latin "ab scopo", away from the target) effect (RIAE) is a term used to describe radiotherapy-induced tumor regression in lesions distant from the targeted site. Abscopal effect is more likely to occur when immune checkpoint inhibitors are used in addition to radiotherapy, providing a proof of principle for the active involvement of the immune system. Although the exact mechanisms through which radiotherapy exerts its immunomodulating effect are still not completely understood, the induction of immunogenic cell death, wherein dying tumors cells release tumor-associated antigens (TAAs) that stimulate antitumor immunity, seems to play a major role [4].

In murine models, Markovsky and colleagues recently reported that partial irradiation using a single dose of 10 Gy led to tumor responses similar to those of fully exposed tumors in the immunocompetent but not in nude mice. A significant abscopal effect was observed and they found that CD8+ T cells infiltrated the tumor coming from the hemi-irradiated tumors or tumor periphery, after partial irradiation with a single dose of 10 Gy [5].

It can be hypothesized that delivering high dose of radiation to the central hypoxic tumor segment while sparing lymphocytes at the tumor periphery, might trigger immunogenic cell death more efficiently.

Owing to its very steep dose gradients SBRT may represent the ideal delivery technique for this kind of treatments. Optimization of SBRT plan quality is critical to reduce the dose to the peritumoral tissue. In particular, optimizing the prescription isodose with VMAT may offer the potential of dose de–escalation for surrounding tissues while increasing the dose to the tumor simultaneously [6,7].

Tubin and colleagues used VMAT to deliver 1–3 fractions each of 10–12 Gy of SBRT-PATHY in lesions of more than 6 cm, with the aim of keeping the dose within the peritumoral tissue as low as reasonably achievable. The dose was prescribed to the 70% isodose-line, however there is no particular mention that this prescription method has been chosen to reduce the dose to the tumor periphery [2,3].

This in silico study aims to identify the best possible dosimetric trade-off for prescribing SFRT with VMAT based SRT to the hypoxic core of bulky (>6 cm) and small (<6 cm) lesions.

Materials and methods

Eight spherical volumes defined "Gross Tumor Volumes" (GTVs) were generated with diameters of 3–10 cm, by incremental steps of 1 cm, as phantom tumor lesions.

The GTVs were placed in the center of a squared water-equivalent phantom, which side measured 40 cm. The spherical inner third part of each GTV was then delineated to simulate the central hypoxic tumor segment ($GTV_{central}$). Therefore eight $GTVs_{central}$ with increasing diameter of 1–3.3 cm were created.

Lastly, external ring structures ($GTV_{peripheral}$) were created to simulate the tumor peripheral tissue by subtracting each $GTV_{central}$ from the corresponding GTV.

Fig. 1 represents the aforementioned volumes.

Volumetric modulated arc radiation treatment (VMAT) plans were performed with the Eclipse™ planning software (14.6 version) to deliver a single fraction of 10 Gy to each $GTV_{central}$ with the Edge™ linear accelerator (Varian Medical System). Different dose prescription methods were used: to target mean and dose to 100% (with acceptable tolerance of 98–100%), and having $GTV_{central}$ margin covered by the 40–90% isodose line (dose gradient within the $GTV_{central}$ of 60–10%, respectively). The treatment plans isocenter were placed in the center of each $GTV_{central}$. Six MV flattening filter free photon beams were used.

The only planning dosimetric objective was to deliver a near minimum dose (D98%) of 10 Gy to the $GTV_{central}$.

The volume of $GTV_{peripheral}$ receiving less than 2 Gy was reported, as dosimetric performance indicator.

The mean (D_{mean}), and near maximum (D2%) dose to $GTV_{central}$ were also recorded.

Results

A total of 56 possible dosimetric scenarios were analyzed *in silico*.

$Gtv_{central}$

All plans met the dosimetric goal (D98% to the $GTV_{central}$ = 10 Gy).

D_{mean} and D2% to $GTV_{central}$ ranged between 10.0 and 18.6 Gy, and 10.2 and 26.2 Gy, respectively.

The highest values were reported with dose prescription to the 40% isodose line.

$Gtv_{peripheral}$

The volume of $GTV_{peripheral}$ receiving less than 2 Gy ranged between 1.9 and 324.9 cc, accounting for different percentages of $GTV_{peripheral}$ (13.5–64.4%).

The largest percentage of $GTV_{peripheral}$ spared from the dose of 2 Gy was achieved with dose prescription methods to the 70% isodose line for lesions smaller than 6 cm (range 42.9–48.4%) and to the target mean for larger ones (range 52.9–64.5%).

All the dosimetric results are detailed in Table 1.

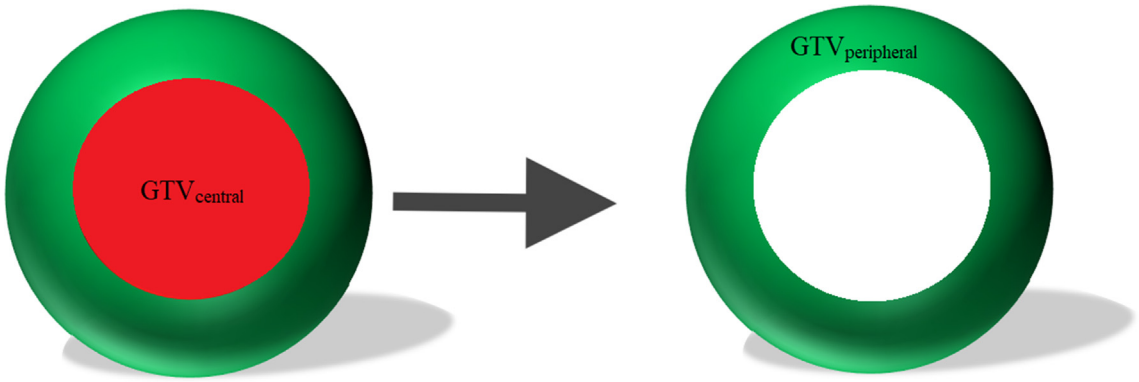

Fig. 1. Gross Tumor Volume (GTV) composed by the internal red volume and the peripheral green volume represent the $GTV_{central}$ and the $GTV_{peripheral}$ respectively.

Table 1
Dosimetric results showing mean and near maximum dose to the $GTV_{central}$ and volume of GTV receiving less than 2 Gy, according to GTV size (highest values in bold font) and the dose prescription method.

GTV diameter (cm)	Dose prescription method	$GTV_{central}$		$GTV_{peripheral}$	
		Mean dose (Gy)	Near maximum dose (Gy)	Volume receiving less than 2 Gy (cc)	Volume receiving less than 2 Gy (% of $GTV_{peripheral}$)
3	Target mean	10	10.2	2.3	16.5
	40% isodose line	17.4	24	4.6	32.9
	50% isodose line	15.3	20.1	1.9	13.6
	60% isodose line	13.4	16.3	3.2	22.9
	70% isodose line	12.5	14.4	**6.0**	**42.9**
	80% isodose line	11.7	12.7	5.3	37.9
	90% isodose line	11.1	11.7	5.0	35.8
4	Target mean	10	10.2	11.3	35.1
	40% isodose line	18	25.7	9.1	28.2
	50% isodose line	15.4	20.1	9.3	28.9
	60% isodose line	13.6	16.8	9.4	29.2
	70% isodose line	12.3	14.1	**15.2**	**47.2**
	80% isodose line	11.6	12.5	14.9	46.2
	90% isodose line	11.1	11.4	13.4	41.6
5	Target mean	10	10.2	29.5	46.8
	40% isodose line	17.8	25.2	25.5	40.5
	50% isodose line	15.8	20.6	24.2	38.4
	60% isodose line	13.5	16.6	27.3	43.3
	70% isodose line	12.5	14.2	**30.5**	**48.4**
	80% isodose line	11.7	12.7	30.3	48.1
	90% isodose line	11.3	11.6	28.8	45.7
6	Target mean	10	10.3	**58.6**	**53.8**
	40% isodose line	18.4	26.1	50.9	46.8
	50% isodose line	16.1	20.6	51.7	47.5
	60% isodose line	14.3	17.5	53.3	49.0
	70% isodose line	12.9	14.8	56.7	52.1
	80% isodose line	12.1	12.9	54.9	50.4
	90% isodose line	11.4	11.7	57.0	52.4
7	Target mean	10	10.3	**91.5**	**52.9**
	40% isodose line	18.4	26	84.6	48.9
	50% isodose line	16	20.4	78.6	45.5
	60% isodose line	14.3	17.1	86.7	50.2
	70% isodose line	12.6	14.3	89.8	51.9
	80% isodose line	11.9	12.6	81.4	47.1
	90% isodose line	11.3	11.7	89.0	51.5
8	Target mean	10	10.2	**141.5**	**54.8**
	40% isodose line	18.6	26.2	127.2	49.3
	50% isodose line	16.1	20.5	132.1	51.2
	60% isodose line	14.1	17.1	137.2	53.2
	70% isodose line	12.6	14.2	138.9	53.8
	80% isodose line	11.6	12.5	138.3	53.6
	90% isodose line	11.1	11.7	140.9	54.6
9	Target mean	10	10.3	**212.5**	**57.8**
	40% isodose line	18.4	25.9	203.5	55.4
	50% isodose line	16.1	20.9	197.3	53.7
	60% isodose line	14.3	17.3	207.1	56.4
	70% isodose line	13.1	14.9	208.5	56.8
	80% isodose line	12.3	13.1	208.2	56.7
	90% isodose line	11.3	11.7	206.4	56.2
10	Target mean	10	10.6	**324.9**	**64.5**
	40% isodose line	18.2	25.4	283.0	56.2
	50% isodose line	16	21	284.5	56.5
	60% isodose line	14.5	17.6	290.8	57.7
	70% isodose line	12.9	14.6	286.4	56.8
	80% isodose line	12	12.8	286.2	56.8
	90% isodose line	11.3	11.7	285.5	56.7

Discussion

SBRT-PATHY is a particular form of SFRT which has been proposed as a new method for intentional induction of RIAE in patient with bulky tumor lesions. The radiobiological mechanism is not completely understood, however one hypothesis is that SBRT-PATHY might potentiate the radiation induced immunogenic cell death by delivering high radiation doses to the central hypoxic part of the tumor while sparing infiltrating lymphocytes at the tumor periphery. This *in silico* study suggests that optimizing the dose prescription method SBRT-PATHY may successfully reduce the dose to tumor periphery, thus potentially sparing tumor infiltrating immune cells which in turn can foster radiation induced immunogenic cell death. It has been observed that the optimal dose prescription method of SBRT-PATHY may vary according to the size of the lesion and its hypoxic segment, and that the prescription to the target mean might be the most convenient method for lesion larger than 6 cm. Furthermore, it has been shown that

SBRT-PATHY may be technically feasible also in lesions smaller than 6 cm.

The principal limitation of this study is its *in silico* nature, that can only approximate on targets with regular shapes what actually occurs in most real life scenarios.

As an example, we selected the inner third part of the GTV to simulate the hypoxic volume, resulting in an isotropic ring structure for the $GTV_{peripheral}$. This was done according to Tubin and colleagues, who observed that the mean hypoxic volume roughly corresponded to one third of the whole bulky lesion [3]. However, not all malignant lesions have round shape, the amount of hypoxic volume may vary and be not homogeneous and also its position within the tumor may be erratic and hardly predictable.

Moreover, it still remains unclear what are the best radiation fractionation protocols to maximize the therapeutic benefits in this innovative setting.

Model simulations based on published experimental data suggest that the optimal radiation doses per fraction, maximizing anti-tumor immunity, are between 10 and 13 Gy [8]. Therefore doses higher than 13 Gy might be may be unnecessary or even more toxic.

In this study, the mean dose to the $GTV_{central}$ ranged between 10 and 18.6 Gy and dose prescriptions to isodoses lower than 60% resulted in mean doses to the $GTV_{central}$ higher than 13 Gy in all the evaluated phantom lesions.

Furthermore, the cells of the immune system are considered to be among the most highly radiosensitive cells of the human body and the immunosuppressive effects of radiotherapy are well known and described: with massive killing of blood cells, such as lymphocytes, resulting from exposures higher than 2 Gy [9].

In this study, the dose prescription method to the 70% isodose line was the best to spare from potential lymphotoxic doses the peripheral portion of lesions smaller than 6 cm. For larger lesions, the dose prescription to target mean performed only slightly better. Interestingly, our methodological *in silico* findings support the choice by Tubin and colleagues to deliver 10–12 Gy to 70% isodose-line with SBRT-PATHY in lesions larger than 6 cm. Results of our study also suggests that even smaller lesions might be treated with SBRT-PATHY, since a large part of the tumor can actually be spared from lymphotoxic doses.

The authors believe that the reported evidence may enhance planning quality in this setting and should be taken into account when designing future trials using SFRT.

Declaration of Competing Interest

No one has conflict of interest.

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