Comparison of treatment planning approaches for spatially fractionated irradiation of deep tumors

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Abstract

Purpose: The purpose of this work was to compare the dosimetry and delivery times of 3D-conformal (3DCRT)-, volumetric modulated arc therapy (VMAT)-, and tomotherapy-based approaches for spatially fractionated radiation therapy for deep tumor targets.

Methods: Two virtual GRID phantoms were created consisting of 7 “target” cylinders (1-cm diameter) aligned longitudinally along the tumor in a honey-comb pattern, mimicking a conventional GRID block, with 2-cm center-to-center spacing (GRID2 cm) and 3-cm center-to-center spacing (GRID3 cm), all contained within a larger cylinder (8 and 10 cm in diameter for the GRID2 cm and GRID3 cm, respectively). In a single patient, a GRID3 cm structure was created within the gross tumor volume (GTV). Tomotherapy, VMAT (6 MV + 6 MV-flattening-filter-free) and multi-leaf collimator segment 3DCRT (6 MV) plans were created using commercially available software. Two tomotherapy plans were created with field widths (TOMO2.5 cm) 2.5 cm and (TOMO5 cm) 5 cm. Prescriptions for all plans were set to deliver a mean dose of 15 Gy to the GRID targets in one fraction. The mean dose to the GRID target and the heterogeneity of the dose distribution (peak-to-valley and peak-to-edge dose ratios) inside the GRID target were obtained. The volume of normal tissue receiving 7.5 Gy was determined.

Results: The peak-to-valley ratios for GRID2 cm/GRID3 cm/Patient were 2.1/2.3/2.8, 1.7/1.5/2.8, 1.7/1.9/2.4, and 1.8/2.0/2.8 for the 3DCRT, VMAT, TOMO5 cm, and TOMO2.5 cm plans, respectively. The peak-to-edge ratios for GRID2 cm/GRID3 cm/Patient were 2.8/3.2/5.4, 2.1/1.8/5.4, 2.0/2.2/3.9, 2.1/2.7/5.2 and for the 3DCRT, VMAT, TOMO5 cm and TOMO2.5 cm plans, respectively. The volume of normal tissue receiving 7.5 Gy was lowest in the TOMO2.5 cm plan (GRID2 cm/GRID3 cm/Patient = 54 cm³/19 cm³/10 cm³). The VMAT plans had the lowest delivery times (GRID2 cm/GRID3 cm/Patient = 17 min/8 min/9 min).

Conclusion: Our results present, for the first time, preliminary evidence comparing IMRT-GRID approaches which result in high-dose “islands” within a target, mimicking what is achieved with a conventional GRID block but without high-dose “tail”
regions outside of the target. These approaches differ modestly in their ability to achieve high peak-to-edge ratios and also differ in delivery times.

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KEY WORDS
deep-seated tumors, grid therapy, spatially fractionated radiotherapy

1 | INTRODUCTION

Spatially fractionated radiotherapy was initially used in the era of low energy x-rays to allow for safe delivery of radiation to internal tumors while allowing for skin and superficial tissue sparing.\textsuperscript{1,2} The radiation beam, often delivered through a single field, was spatially fractionated into small beamlets by sieve-like blocking to form a grid pattern (GRID therapy). Tissues, such as skin, in the blocked portion of the treatment field were thought to promote healing/repair of normal tissues irradiated to high dose in the beamlet paths. In the era of skin-sparing megavoltage photon irradiation, GRID therapy has continued to play a role in radiation oncology, mostly in the treatment of bulky tumors.\textsuperscript{1,2} The GRID treatment has typically been delivered in one high-dose (15–20 Gy) fraction, often followed by conventionally fractionated treatment courses which target the entire tumor. The radiation field is partitioned by commercially available blocks or by MLC leaf patterns which reproduce the effect of these blocks.\textsuperscript{3} The treatments are often delivered in a single field. Many studies have shown excellent tumor response results with this approach and there is a great deal of interest in the radiobiology of GRID treatments.\textsuperscript{1–5} Upfront treatment with GRID may influence oxygenation in tumors as well as induce bystander effects.\textsuperscript{4,5}

Despite the successes with conventional GRID therapy, it has dosimetric limitations in the treatment of very deep-seated tumors.

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{figure1.png}
\caption{(a) Target arrangement for two virtual GRID phantoms consisting of seven cylinders (1-cm diameter) aligned longitudinally along the GTV in a honeycomb pattern, mimicking a conventional GRID block with 2-cm center-to-center spacing (GRID\textsubscript{2 cm}) and 3-cm center-to-center spacing (GRID\textsubscript{3 cm}), all contained within a larger cylinder. The larger cylinder is 8 and 10 cm in diameter for the GRID\textsubscript{2 cm} and GRID\textsubscript{3 cm} arrangements, respectively. Inline and crossline profiles are identified by the arrows. (b) Schematic of quantities evaluated for plan assessment. GTV is defined by the purple outline, valley (which is the GTV minus the GRID target) is defined by the light purple, and the GRID target is defined by the purple filled circles within the GTV. The ring is the 2-mm ring around the GTV. The peak-to-edge dose ratio (PEDR) is defined as the ratio of the mean dose to the GRID target to the mean dose of the valley. The peak-to-valley dose ratio (PVDR) is defined as the ratio of the mean dose to the GRID target to the mean dose to the 2-mm edge. The solid black line is the volume of the normal tissue.}
\end{figure}
Due to attenuation characteristics, the maximum dose from a single photon beam is delivered to a shallow depth, with decreasing dose as the deep tumor is reached. Some investigators have tried to mitigate this dosimetric problem with the use of parallel opposed fields. Another solution, which maintains the unique geometry of high-dose “islands” within tumors inherent with GRID and takes advantage of high-energy x-ray attenuation features, is to paint three-dimensional target structures throughout the tumor which mimic conventional two-dimensional GRID blocks and then use conformal or intensity-modulated planning with the goal to deliver high doses to these areas (instead of the entire tumor). This approach has previously been studied using tomotherapy. In this report, we compare a tomotherapy-based approach with two other approaches: volumetric modulated arc therapy (VMAT) and a simple 3D conformal (3DCRT)-based planning technique using cylindrical target structures.

2 | MATERIALS AND METHODS

2.A | GRID structures

The virtual GRID structures were generated by DICOMan which is an open source software (University of Arkansas, Little Rock, Arkansas). DICOMan allows for a GRID target to be created within the target volume. The diameter of the cylinders and the center-to-center distance between the cylinders can be configured to the patient’s anatomy. To mimic an ideal geometry, two virtual GRID phantoms were created consisting of seven cylinders (1-cm diameter) aligned longitudinally within a larger cylinder (the “GTV”) in a honey-comb pattern, mimicking a conventional GRID block, with 2 cm (GRID2 cm) and 3 cm (GRID3 cm) center-to-center spacing [Fig. 1(a)]. The larger cylinders (GTV) were 8 and 10 cm in diameter for the GRID2 cm and GRID3 cm arrangements, respectively. The “normal tissue” outside of the GTV was defined as a 5-cm ring around the GTV. In the dosimetric analysis, we defined the “peak” dose as the mean dose of the GRID target. We defined the “edge” as a 2-mm ring just outside of the GTV, and the edge dose as the mean dose to this structure.

2.B | Phantom treatment planning

All treatment plans were generated using the Pinnacle v. 9.10 treatment planning system (TPS) (Philips Amsterdam DE) or the tomotherapy TPS (Accuray, Sunnyvale, California). All 3DCRT, VMAT, and GRID-block plans were planned to be delivered by an Elekta linac equipped with Agility MLC (Versa HD, Elekta Inc., Stockholm, Sweden). Three treatment techniques were used for comparison: 3DCRT, VMAT, and tomotherapy. For the GRID2 cm arrangement, the 3DCRT plans used six beams with gantry angles ranging from 30 to 330° (at 60° increments) intended to align beam paths with groups of individual cylinders. For each gantry angle, three equally weighted segments were created where the field shape corresponded to the outline of a single cylinder. For the GRID3 cm arrangement, the 3DCRT plan used the same gantry angles as the GRID2 cm plan, with six additional beams at gantry angles 0°, 120°, 180°, 240°, and 300°. For these additional gantry angles, a single segment with the field shape corresponding to the central cylinder, with lower weight, was used.

The VMAT plans for GRID2 cm used four full arcs with collimator rotated at 90° (for arcs 180°–270°) and 270° (for arcs 180°–180°). These collimator angles were selected to minimize the creation of “dose islands” between grid targets at varying gantry angles. The VMAT GRID3 cm arrangement used two full arcs with the collimator rotated at 90° (for the 180°–180° arc) and 270° (for the 182°–180° arc). For tomotherapy, two plans were created with field widths of 5.01 cm (TOMO5 cm) and 2.5 cm (TOMO2.5 cm) with the same pitch of 0.43. Table 1 shows a list of target and planning structure objectives used for the VMAT and tomotherapy plans. We used 6 MV energy for all plans.

| Table 1 | List of target and planning structures for VMAT and Tomotherapy plans. |
| Structures | Objectives | Weights |
| GRID2 cm VMAT | | |
| Target | $D_{\text{min}} = 15 \text{ Gy}$ | 50 |
| Valley | $D_{\text{max}} = 2 \text{ Gy}$ | 0.01 |
| Rings | $D_{\text{max}} = 12 \text{ Gy}$ | 5 |
| GRID2 cm Tomotherapy | | |
| Target | $D_{\text{min}} = 15 \text{ Gy}$ | 1000 |
| Valley | $D_{\text{max}} = 9.5 \text{ Gy}$ | 100 |
| Valley | $D_{\text{10}} = 9 \text{ Gy}$ | 100 |
| Valley | $D_{\text{20}} = 8 \text{ Gy}$ | 100 |
| Rings | $D_{\text{max}} = 12 \text{ Gy}$ | 200 |
| GRID3 cm VMAT | | |
| Target | $D_{\text{min}} = 15 \text{ Gy}$ | 50 |
| Valley | $D_{\text{max}} = 2 \text{ Gy}$ | 0.001 |
| Rings | $D_{\text{max}} = 8 \text{ Gy}$ | 0.008 |
| GRID3 cm Tomotherapy | | |
| Target | $D_{\text{min}} = 15 \text{ Gy}$ | 1000 |
| Valley | $D_{\text{max}} = 8.5 \text{ Gy}$ | 50 |
| Valley | $D_{\text{10}} = 8 \text{ Gy}$ | 50 |
| Valley | $D_{\text{20}} = 7 \text{ Gy}$ | 50 |
| Rings | $D_{\text{max}} = 12 \text{ Gy}$ | 100 |

For patient VMAT and Tomotherapy plans:

| Structures | Objectives | Weights |
| Target | $D_{\text{min}} = 15 \text{ Gy}$ | $\frac{1}{1000}$ |
| Valley | $D_{\text{max}} = 9.5 \text{ Gy}$ | 0.3/50 |
| Valley | $D_{\text{10}} = 9 \text{ Gy}$ | 0.3/50 |
| Valley | $D_{\text{20}} = 8 \text{ Gy}$ | 0.3/50 |
| Rings | $D_{\text{max}} = 10 \text{ Gy}$ | 0.05/100 |
| Large ring | $D_{\text{max}} = 3 \text{ Gy}$ | 0.05/150 |

$D_{\text{min}}$, minimum dose; $D_{\text{max}}$, maximum dose; $D_{\text{10}}$, dose to 10% of the volume; $D_{\text{20}}$, dose to 20% of the volume; weights of the patient plan are expressed as VMAT/Tomotherapy.
2.C | Patient treatment planning

For a single patient with recurrent cervical cancer, a waiver of consent was obtained through the Johns Hopkins Hospital institutional review board. Images were acquired using a Brilliance Big Bore CT simulator (Philips, Amsterdam DE) and transferred to the Pinnacle TPS for contouring and planning. Patient GTV and organs-at-risk were contoured by the attending physician.

The same patient CT image datasets and same contours generated from Pinnacle TPS were transferred to DICOMan to generate a virtual GRID2 cm arrangement.

The prescription for the GRIDblock was at a point at the depth of maximum dose ($d_{max}$) along the central axis. Five treatment plans were created for comparison: 3DCRT with and without optimized segment weighting (6 MV), VMAT (6 MV with and without FFF), and tomotherapy. The 3DCRT plans used six beams with the following gantry angles: 20°, 70°, 90°, 110°, 270°, and 340°, again selected to align the beam path with groups of grid targets. Each beam had three to five segments where each segment had a field shape associated with a cylinder. The weighted 3DCRT plan had lower weights to the posterior beams to lower dose to the cauda equina. The VMAT plans for both the GRID2 cm and GRID3 cm arrangements used two full arcs with the collimator rotated at 90°. Three millimeter wide rings were created around the GRID structures. Surrounding the PTV, a 5-cm wide ring was created to limit dose to the normal tissue. For tomotherapy, two plans were created with field widths of 5.01 cm (TOMO5 cm) and 2.5 cm (TOMO2.5 cm) with the same pitch of 0.43. Table 1 shows the objectives for the VMAT and tomotherapy plans.

To illustrate the difference between the IMRT and 3DCRT GRID approaches and a conventional single field GRID-block approach, a conventional GRID-block treatment plan was also produced for this patient. We used an in-house compensator model for a commercially available GRID block (.decimal inc., Sanford FL) commissioned for use in our clinic. The compensator models the geometry, material, and thickness of the brass GRID block, enabling the analysis of resultant 3D dose distributions in Pinnacle plan was produced using a single angle. Prescribed dose for phantom and patient was set to a mean 15 Gy to the GRID target in a single fraction. Patient plans were delivered on a MapCHECK phantom for patient-specific quality assurance. Using the $\gamma$ index tolerance criteria of 3%/3 mm, all plans passed at a threshold of $\geq 95$%.

2.D | Dosimetry analysis

The peak-to-valley dose ratio (PVDR) was defined as the ratio of the mean dose to the GRID target to the mean dose of the valley. The peak-to-edge dose ratio (PEDR) was defined as the ratio of the mean dose to the GRID target to the mean dose to the 2-mm ring [Fig. 1(b)]. The volume of the normal tissue receiving 7.5 Gy ($V_{7.5 Gy}$) and 5 Gy ($V_{5 Gy}$) was quantified. To evaluate superficial tissue sparing, we evaluated the dosimetric differences for 0.03 cc ($D_{0.03 cc}$) and 10 cc ($D_{10 cc}$) of skin for the patient data.

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**Fig. 2.** 3D conformal (3DCRT), VMAT, and Tomotherapy (with field width 5 cm [TOMO5 cm] and 2.5 cm [TOMO2.5 cm]), plans forming the grid pattern using GRID2 cm. The GRID2 cm target is indicated by the cyan and the GTV is shown in purple color wash. The distance from the GRID2 cm target to the edge of the GTV is 2 cm. Mean dose of 15 Gy was prescribed to the GRID2 cm target.
3 DCRT, three-dimensional conformal radiotherapy; TOMO5 cm, tomotherapy plans with 5 cm field width; TOMO2.5 cm, tomotherapy plans with 2.5 cm field width; D\text{mean}, mean dose of structure; D\text{max}, maximum dose to structure; PEDR, peak-to-edge dose ratio; PVDR, peak-to-valley dose ratio; Normal Tissue V7.5, volume of normal tissue receiving 7.5 Gy; Normal Tissue V5, volume of normal tissue receiving 5 Gy.

### Table 2: Comparison of delivery time, peak-to-edge dose and peak-to-valley dose ratios for 3D conformal, VMAT, and Tomotherapy plans across the GRID2 cm and GRID3 cm cylinder arrangements.

|                      | 3D CRT | VMAT | TOMO5 cm | TOMO2.5 cm |
|----------------------|--------|------|----------|------------|
| 2-cm separation      |        |      |          |            |
| Delivery time (min)  | 15     | 17   | 37       | 56         |
| GRID D\text{mean} (Gy) | 15 | 15 | 15       | 15         |
| GTV edge D\text{mean} (Gy) | 5.3 | 7.3 | 7.6      | 7.1        |
| GTV valley D\text{mean} (Gy) | 7.2 | 8.7 | 8.8      | 8.4        |
| PEDR                 | 2.8    | 2.1  | 2.0      | 2.1        |
| PVDR                 | 2.1    | 1.7  | 1.7      | 1.8        |
| Normal tissue V7.5 Gy (cc) | 3  | 30  | 110      | 54         |
| Normal tissue V5 Gy (cc) | 334  | 363 | 461      | 222        |
| 3 cm separation      |        |      |          |            |
| Delivery time (min)  | 21     | 8    | 24       | 45         |
| GRID D\text{mean} (Gy) | 15 | 15 | 15       | 15         |
| GTV edge D\text{mean} (Gy) | 4.7 | 8.3 | 6.7      | 5.5        |
| GTV valley D\text{mean} (Gy) | 6.5 | 10  | 7.9      | 7.6        |
| PEDR                 | 3.2    | 1.8  | 2.2      | 2.7        |
| PVDR                 | 2.3    | 1.5  | 1.9      | 2.0        |
| Normal tissue V7.5 Gy (cc) | 30 | 108 | 43       | 19         |
| Normal tissue V5 Gy (cc) | 291  | 647 | 767      | 178        |

Figure 2 shows a comparison of the 3DCRT, VMAT, and tomotherapy plans across the GRID2 cm arrangement. The coronal, axial, and sagittal planes are shown. In the axial slice, it is visually apparent that the dose to edge of the GTV is highest in the 3DCRT plan in the left-right and anterior-posterior directions. However, the dose outside the GTV in the superior-inferior direction and the dose to the valley appear to be the lowest in the 3DCRT plan. In the coronal and sagittal planes, it appears that the TOMO5 cm has the highest dose outside the GTV in the superior-inferior and left-right directions. Quantitatively, the 3DCRT plan had the lowest normal tissue V7.5 Gy and TOMO2.5 cm plan had the lowest normal tissue V5 Gy for the GRID2 cm arrangement (Table 2). Compared to the 3DCRT and VMAT plans, both TOMO5 cm and TOMO2.5 cm plans had the longer delivery times.

The treatment plans for the GRID3 cm cylinder arrangement are shown in Fig. 3. Similar to the GRID2 cm arrangement, it is visually apparent that the dose to edge of the GTV is highest in the 3D conformal plan in the left-right and anterior-posterior directions. Given the greater spacing between the GRID targets, the points at which the beams intersected coincide with the edge of the GTV. In the coronal and sagittal planes, it again appears that the TOMO5 cm has the highest dose outside the GTV in the superior-inferior and left-right directions. For the GRID3 cm arrangement, TOMO2.5 cm had the lowest normal tissue volumes receiving 7.5 and 5 Gy (Table 2). Similar to the plans for the GRID2 cm arrangement, the TOMO5 cm and TOMO2.5 cm plans had the longest delivery times.

Figure 3: 3DCRT, VMAT, and Tomotherapy (with field width 5 cm [TOMO5 cm] and 2.5 cm [TOMO2.5 cm]), plans forming the grid pattern using GRID3 cm. The GRID3 cm target is indicated by the cyan and the GTV is shown in purple color wash. The distance from the GRID3 cm target to the edge of the GTV is 2 cm in the anterior-posterior and superior-inferior direction. Mean dose of 15 Gy was prescribed to the GRID3 cm target.
Figure 4 shows the inline and crossline profiles for both GRID2 cm and GRID3 cm cylinder arrangements along the central axis. The shaded region identifies the limits of the GTV. The profiles affiliated with the GRID3 cm arrangement had the lowest doses to the valleys. The mean delivery times were consistently lower for the GRID3 cm arrangement for all plans (Table 2). The 3DCRT had the greatest PEDR and PVDR values, relative to the VMAT and TOMO5 cm and TOMO2.5 cm plans. However, the TOMO2.5 cm plan had the lowest fraction of normal tissue receiving 7.5 Gy for both the GRID2 cm and GRID3 cm arrangements.

For a representative patient, a single axial slice is shown for the six treatment plans in Fig. 5. Visually, it can be seen that the VMAT and tomotherapy plans resulted in the lowest dose surrounding the PTV. Similar to the phantom plans, the 3DCRT plans had the highest PEDR and PVDR (Table 2 and Table 3). However, when looking at the percentage of normal tissue receiving 7.5 and 5.0 Gy, these values were lowest with the VMAT and tomotherapy plans (Table 3). Specifically, the TOMO2.5 cm plan had the lowest Dmax to the cauda (6.8 Gy) and liver (5.4 Gy), whereas the 3DCRT plan had the highest (cauda Dmax = 13.4 Gy and liver Dmax = 10.3 Gy). As expected, the 3DCRT plans had the highest dose to the skin (D0.03cc > 9 Gy and D10cc = 5.6 Gy). We created a VMAT plan using the 10MV-FFF; however, it was not deliverable due to the dose rate variability. We were able to deliver a 6 MV-FFF plan. Out of the deliverable plans, the VMAT plan using 6FFF energy had the lowest dose to skin (D0.03cc = 4.5 Gy and D10cc = 3.1 Gy) and bowel (Dmax = 8.8 Gy). It should be noted that the TOMO2.5 cm field width had the highest delivery time (34min). The overall lowest doses to the critical
Fig. 5. 3DCRT, VMAT, Tomotherapy, and GRID-block plans across the GRID3 cm cylinder arrangement and corresponding dose volume histograms for a representative subject. Axial slices are shown where the teal contour represents the PTV and the cyan represents the GRID3 cm.
structures were observed in the VMAT-6FFF plan, which also had the lowest delivery time (5 min). Figure 5 also shows the treatment plan utilizing the GRID block. As expected, the dose to the deep-seated targets is visually lower than that of the other treatment plans. The dose to the normal tissues outside the GTV is visually higher compared to the other plans.

4 | DISCUSSION

In this study, we used tomotherapy-, VMAT-, and 3DCRT-based approaches to generate spatially fractionated radiation treatment patterns in deep-seated tumors. We painted cylindrical targets throughout tumor volumes as a template to guide treatment planning. These cylinders were a 3D representation of the 2D circular patterns seen with conventional GRID blocks. In the initial phantom studies, the simple 3DCRT approach for the GRID2 cm and GRID3 cm arrangements had the highest PEDR and PVDR values, relative to the results seen with the VMAT and tomotherapy plans. With the selected gantry angles and blocking technique, much of the valley could be directly blocked with the 3D planning approach.

Although the 3D conformal demonstrated high PEDR and PVDR values in the example patient plan, these metrics do not quantify the extent of dose that is delivered outside the GTV. We characterized dose spillage in normal tissues by evaluating V7.5 Gy, and V5Gy values. These values were the lowest in the TOMO2.5 cm plan for both phantom and patient plans. Overall, for the patient plan, we found that the 3DCRT was inferior to the tomotherapy and VMAT approaches for these same measures. It should be noted that segment weights were distributed uniformly in the phantom due to the radial symmetry of the phantom and target, leading to minimum low dose spread in normal tissue. Asymmetric target geometry, heterogeneous density, and asymmetric avoidance structures in the patient required variable segment weights, which led to an increase in low-dose spread in normal tissue compared to the phantom. This difference illustrates that, in relatively homogeneous media with simple target shapes a simple 3DCRT approach may provide competitive PEDR, PVDR and dose spillage results, but in practice, more

| Target volumes | 3DCRT | 3DCRT WT | VMAT 6MV | VMAT 6FFF | VMAT 10FFF | TOMO5cm | TOMO2.5cm |
|----------------|-------|----------|----------|----------|------------|---------|-----------|
| GRID Dmean (Gy) | 15 | 15 | 15 | 15 | 15 | 15 | 15 |
| GRID Dmax (Gy) | 20.1 | 21.1 | 17.9 | 18.4 | 18.5 | 17 | 18.4 |
| GRID D95 (Gy) | 11.2 | 10.2 | 12.9 | 12.2 | 12.6 | 13.6 | 12.7 |
| GTV Dmean (Gy) | 5.6 | 5.1 | 5.8 | 5.4 | 5.4 | 6.5 | 5.6 |
| GTV Edge Dmean (Gy) | 2.8 | 2.5 | 2.9 | 2.6 | 2.5 | 3.8 | 2.9 |
| GTV Edge Dmax(Gy) | 13.6 | 12.6 | 8.6 | 7.7 | 7.6 | 10.9 | 8.7 |
| GTV Valley Dmean (Gy) | 5.3 | 4.7 | 5.5 | 5.0 | 5.0 | 6.3 | 5.3 |
| GTV Valley Dmax (Gy) | 23.4 | 18.6 | 15.8 | 15.7 | 16.3 | 15.7 | 17.1 |
| PEDR | 5.4 | 6.0 | 5.4 | 5.8 | 6.0 | 3.9 | 5.2 |
| PVDR | 2.8 | 3.1 | 2.8 | 3.0 | 3.0 | 2.4 | 2.8 |
| Normal tissue | | | | | | | |
| Liver Dmax (Gy) | 9.8 | 10.3 | 7.5 | 5.6 | 5.5 | 6.5 | 5.4 |
| Liver Dmean (Gy) | 0.3 | 0.2 | 0.3 | 0.2 | 0.2 | 0.4 | 0.3 |
| Cauda Dmax (Gy) | 13.4 | 9.7 | 7.8 | 7.6 | 7.5 | 7.4 | 6.8 |
| Cauda Dmean (Gy) | 2.3 | 1.5 | 2.5 | 2.0 | 1.5 | 3.4 | 2.5 |
| Bowel Dmax (Gy) | 15.7 | 9.8 | 9.4 | 8.8 | 8.9 | 11.3 | 9.1 |
| Bowel Dmean (Gy) | 1.4 | 1.2 | 1.3 | 1.2 | 1.2 | 1.6 | 1.3 |
| Skin D0.03cc (Gy) | 9.5 | 9.4 | 4.9 | 4.5 | 4.6 | 5.0 | 4.6 |
| Skin D5cc (Gy) | 5.6 | 5.6 | 3.3 | 3.1 | 3.8 | 4.1 | 3.4 |
| Normal tissue V7.5 Gy (cc) | 124 | 79 | 17 | 9 | 7 | 51 | 10 |
| Normal tissue V5 Gy (cc) | 777 | 625 | 321 | 194 | 164 | 479 | 211 |

3DCRT: 3-dimensional conformal radiotherapy; 3DCRT WT: 3-dimensional conformal radiotherapy plan with unequal weighted beams; FFF: flattening filter free; TOMO5cm: tomotherapy plans with 5cm field width; TOMO2.5cm: tomotherapy plans with 2.5cm field width; Dmean: mean dose of structure; Dmax: maximum dose to structure; D95: dose to 95% of the volume; PEDR: peak-to-edge dose ratio; PVDR: peak-to-valley dose ratio; Normal Tissue V7.5: volume of normal tissue receiving 7.5 Gy; Normal Tissue V5: volume of normal tissue receiving 5 Gy.
advanced IMRT techniques may be required to handle complex geometries and fluctuating densities.

For the GRID2 cm and GRID3 cm phantom arrangements, the PEDR achieved with tomotherapy was intermediate between the 3D conformal and VMAT approaches. In the patient example, however, the PEDR was lowest with both TOMO2 cm and TOMO2.5 cm plans. Visually, the regions with the greatest dose to the edge of the GTV were in the cranial-caudal direction. This is consistent with the notion that in tomotherapy, the beam width remains fixed for the duration of the treatment, thus a complete field width is irradiated at the cranial and caudal end of the target, leading to higher doses at the edge relative to the 3DCRT and VMAT plans. To mitigate this, a smaller field width (2.5 cm) was also used for planning. This improved results relative to the 5-cm field width plans, but at the consequence of a greater delivery time. Alternatively, TomoEdge technology can be used where the superior and inferior jaw opens and closes independently at the start and end of a target in order to reduce the longitudinal penumbra. This technology is not available at our institution and was not modeled. A third approach to this problem would be to truncate the GRID target volumes at their extremes near the edge of the GTV. This would lower the PEDR, as well as lower the V5 Gy and V7.5 Gy normal tissue values, at the expense of lowering the volume of tumor receiving high-dose irradiation.

A key clinical issue moving forward is to determine the appropriate number and spacing of "high-dose islands" targets within tumors. Although the value of a high PEDR result seems clear, the relevance of high PVDR values is less clear. It should be noted that the optimal PVDR and PEDR have not been extensively explored in previous work. studies have reported valley to peak ratios ranging from 0.0008 to 2.510,11 and PEDRs ranging from 5 to 20.11 Our approach in this work was to construct, in three-dimensions, the two-dimensional pattern achieved with a conventional GRID-block based on the historical successes with this approach. However, it should also be noted that in conventional GRID irradiation that, for a given slice perpendicular to the axis of the beam, the dose homogeneity in the tumor increases with depth. Thus, at the 2D level, the PVDR approaches 1 at depth. Finally, we should also acknowledge that the treatment planning time required for a GRID-block treatment is substantially less than approaches proposed in this study. This may limit our technique to patients who do not need to be treated immediately.

In summary, we demonstrated that all of the studied approaches are capable of delivering high-dose radiation to cylindrical structures within large tumors, yielding spatially fractionated radiation dose distributions over the length of the tumor. Selection of one approach over another may depend on the shape and depth of the GTV in the patient and the type and extent of surrounding critical structures. To evaluate the efficacy of these approaches in patients, clinical trials are required.

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CONFLICT OF INTEREST

Authors have nothing to declare.

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