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Escalating Spatially Fractionated Radiotherapy Prescription Dose via Differential Hole-Sizes and Hole-Spacing in the Management of Large and Bulky Deep-Seated Tumors

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Joshua Misa [1], Damodar Pokhrel [2]

1. Physics, University of Arizona, Arizona, USA 2. Physics, University of Kentucky, Lexington, USA

Corresponding author: Joshua Misa, joshua.a.misa@gmail.com

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Abstract

Objectives:

Spatially Fractionated Radiotherapy (SFRT) treatments delivers a highly heterogenous spatial dose distribution to large tumors (⩾ 6 cm) and has been shown to greatly debulk large tumors including deep-seated large tumor masses. The effectiveness of this treatment is due to the direct cell kill in addition to the enhanced indirect cell-death mechanisms via bystander signaling, intra-tumor response, and microvasculature damage within the tumor volume. Traditionally and still now, to generate a highly heterogeneous dose pattern for SFRT treatments, the same hole-size and hole-spacing throughout the tumor is used. We sought to investigate other implementations of SFRT that could enhance both the direct/indirect cell-kill mechanisms via differential hole-size and hole-spacing within the tumor mass. We have investigated the feasibility of using an in-house scripting method to generate a differential hole-size and spacing for SFRT pattern, where a larger diameter high dose sphere is placed in the center of the tumor with smaller diameter high dose spheres are deployed in the periphery of the tumor. We hypothesize that by using differential hole-sizes and hole-spacing for the highly irregular bulky deep-seated masses, we should be able to further enhance the therapeutic gain by escalating tumor core dose and enhance the bystander signaling while adequately sparing immediately adjacent organs-at-risk (OAR).

Methods:

Twenty previously treated SFRT patients were included in this study cohort (10 head and neck (HN) cases and 10 abdominal/pelvis cases). These 20 patients had their clinical SFRT plans generated using an MLC-based 3D-conformal SFRT method. This planning technique generates 1 cm diameter cylinders with a center-to-center spacing of 2 cm at the plane of isocenter using up to 6 coplanar crossfire gantry angles spaced 60o apart. This cohort had an average tumor diameter of 10.17 cm (6.5 – 16 cm) and an average tumor volume of 633.8 cc (172.8 – 2150.9 cc). Eleven lattice patterns were generated and investigated that consisted of core sphere diameters (C) of 4 cm, 3 cm, and 2 cm; periphery sphere diameters (P) of 1 cm to C/2; and spheres center-to-center spacing (S) of 2 cm to C. All patterns were inversely planned with 4 full arcs VMAT plans all with 6MV-FFF beam to be delivered on the TrueBeam LINAC equipped with Millennium 120MLCs. All replans were calculated using the advanced AcurosXB dose model. All plans were prescribed for the tumor to receive a nominal single dose of 15 Gy, then all replans were normalized so the maximum dose within the tumor was 125% of the prescription dose, similar to SBRT treatment planning approach. Dose metrics used to evaluate dose delivered to the tumor was D50%, Dmean, and V50%. Evaluation of OAR doses were done using maximum dose delivered to nearby OARs and maximum dose 2 cm away from the GTV in any direction (D2cm). For HN cases, the spinal cord, esophagus, and larynx was evaluated. For abdominal/pelvis cases, the bowel, bladder, and rectum were evaluated. Lastly, indirect cell kill was evaluated based on peak-to-valley- dose ratio (PVDR) = (D10%/D90%).

Results:

Evaluating metrics concerning dose being delivered to the tumor (D50%, Dmean, V50%), the pattern of a C = 3 cm, P = 1.5 cm, and S = 2 cm ranked the best for both the HN site (930.1 cGy ± 167.3 cGy, 933.8 cGy ± 129.3 cGy, 66.9% ± 15.3%) and abdominal/pelvis sites (950.7 cGy ± 181.9 cGy, 963.3 cGy ± 145.4 cGy, 68.9% ± 15.8%). The tradeoff was that it performed the worst out of the 11 patterns when evaluating the maximum dose to all critical organs. No single pattern outperformed the others when just evaluating the maximum dose to critical organs or when evaluating D2cm, this was the situation for both HN and abdominal/pelvis cases.
Clinical SFRT plans saw an average D50%, Dmean, V50% of 733.1 cGy ± 75.6 cGy, 768.6 cGy ± 81.8 cGy,

45.2% ± 5.7% (HN) and 745.9 cGy ± 54.0 cGy, 788.9 cGy ± 70.9 cGy, 52.3% ± 5.3% (abdominal/pelvis). When comparing against the clinically delivered SFRT plans, all patterns on average gave a decrease in maximum dose to OARs and D2cm for both sites. For HN cases, C = 3 cm, S = 2 cm, and P = 1.5 cm pattern outperformed clinical plans in terms of D50% (930.1 cGy vs 733.1 cGy, $p < 0.01$), Dmean (933.8 cGy vs 768.6 cGy, $p < 0.01$), and V50% (66.9% vs 45.2%, $p < 0.01$). For abdominal/pelvis cases, again the C = 3 cm, P = 1.5 cm, and S = 2 cm pattern outperformed when evaluating D50% (950.7 cGy vs 745.9 cGy, p = 0.015), Dmean (963.3 cGy vs 788.9 cGy, p = 0.021), and V50% (68.9% vs 52.3%, $p < 0.01$). Evaluating PVDR, all patterns on average outperformed clinical SFRT plans. These differential hole-size patterns produced a PVDR > 4 while clinical SFRT plans had PVDR of around 3.
Furthermore, we aggregated these results based on if the tumor had diameter smaller or larger than 10 cm. This was chosen due to SFRT plans on tumors with a diameter less than 10 cm had difficulties in packing more than 1 lattice sphere within the tumor when S = 4 cm. Aggregating these results yields similar trends and results as before. For HN cases larger than 10 cm in diameter, in addition to the pattern C = 3 cm, S = 2 cm, and P = 1.5 cm, when P = 1 cm this yielded superior plan metrics compared to clinical SFRT plans. However, the results weren't statistically significant when comparing D50% (851.1 cGy vs 741.7 cGy, p = 0.12), Dmean (859.5 cGy vs 773.9 cGy, $p < 0.11$), except for V50% (61.0% vs 48.3%, $p < 0.01$). For abdominal/pelvis cases both larger and smaller than 10 cm in diameter, only the pattern C = 3 cm, S = 2 cm, and P = 1.5 cm yielded superior plan metrics compared to clinical SFRT plans.

Conclusion(s):

Herein we present a novel and automatic lattice pattern generation, within the planning system, for SFRT treatments which consists of a large high dose core sphere surrounded by smaller peripheral dose spheres. This avoids exporting/importing planning CT data and structures to the 3rd party contouring system for SFRT lattice contouring. Based on this work, all patterns provided clinically acceptable SFRT plans. However, only certain patterns emerged advantageous when comparing against clinical SFRT plan. For cases where the tumor diameter was greater than 10 cm, patterns with C = 3 cm, S = 2 cm, and P = 1.5 cm or 1 cm gave superior dose metrics depending on the treatment site. For HN and abdominal/pelvis cases with tumor diameter less than 10 cm, only tje C = 3 cm, S = 2 cm, and P = 1.5 cm lattice pattern was superior compared to clinical SFRT plans. We suggest utilizing those patterns in the appropriate scenarios when implementing this novel SFRT technique. This novel application of SFRT could allow for enhanced dose to the tumor core or in the hypoxic area of the bulky tumor (as found in multimodality imaging) while still maintaining dose to nearby critical organs potentially improving patient outcomes in the future. Future work will investigate optimal pattern(s) to use based on tumor size, sphericity, site, and nearby critical organs and its clinical implementation.