Automation of Novel MLC-Based Spatially Fractionated Radiation Therapy Method for Unresectable Bulky Tumors Incorporating Spatial BED Evaluation Tool for Highly Heterogenous Dose Distributions

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Objectives: SFRT treatment delivers highly heterogenous dose distributions to large tumors (> 6 cm) and has been shown to debulk large, deep-seated tumors via direct and indirect cell kill mechanisms while sparing adjacent organs-at-risk (OAR). Recent improvements to this technique have included the utilization of inversely optimized lattice-based IMRT/VMAT and Helical Tomotherapy methods. Other more advanced techniques involve the robotic CyberKnife unit and proton SFRT therapy. However, these techniques are expensive and highly complex in nature, and their access is limited to many SFRT patients on a daily basis. To address this need in our clinic, we have implemented a novel, forward-planned MLC-based 3D-conformal SFRT method that requires minimal physics support and quality assurance (QA) resources. This simple method provides same-day SFRT treatment, with palliative intent for pain relief and therapeutic approach for tumor local control. We propose that automation of our SFRT method allows for an even more efficient clinical workflow. We also developed a novel tool for evaluating the spatial biological equivalent dose (BED) for these highly heterogenous SFRT dose distributions via a voxel-based methodology. Currently, there is no easily accessible tool for physicians to evaluate the spatial BED10 for tumors and maximum dose to OARs for patients undergoing combined therapy (single-dose of SFRT followed by consolidated daily RT dose) with widely different fractionation schemes. Simply summing the doses from the two treatments does not reflect the biological effectiveness, as it doesn't factor in how the spatial BED changes with fractionation.

Methods: Six patients with multiple tumor sites (head and neck, pelvic nodes, mouth, posterior back), and with varying tumor sizes ranging from 134.1–981.5cc treated with a nominal single-dose of 15 Gy SFRT followed by combination RT at our institution were included in our study. These clinical SFRT plans were manually generated by an experienced physicist using our MLC-based 3D-conformal SFRT technique, which creates a 1-cm diameter cylinder with a center-to-center spacing of 2 cm at isocenter. This method uses up to 6 coplanar crossfire gantry angles spaced 60 degrees apart with all collimators set at 90 degrees using 6 or 10MV beams and Acuros-base dose engine. This specific planning geometry has corresponding, matched open and closed MLCs on opposing gantry angles, creating high-dose cylindrical distributions within the bulky GTV target without post-processing the physician drawn GTV contour. This produces a highly heterogenous sieve-like dose distribution. This novel SFRT planning technique was fully-automated using Eclipse Scripting Application Programming Interface (ESAPI, v15.6). The automated script allows the users to choose the treatment machine, energy, prescription dose, and target to automatically generate a site-specific SFRT treatment plan in a few minutes. In addition to the planning automation, we have developed a new

ESAPI script that rapidly calculates the spatial BED10 of the highly heterogenous dose distribution within the SFRT target and surrounding OARs while incorporating the combination therapy. The script does so by using conventional Linear Quadratic (LQ) formulism to calculate BED10 for each individual voxel within the structure. The average of all calculated voxel BED10 is then presented to the user to utilize for the evaluation of the plan sum with consolidated RT.

Results: Using this novel SFRT method, our automation script was successful in creating site-specific plans tested on 6 previously treated patients' data. This automated planning method provided excellent dose parameters with mean GTV(V7.5Gy) and mean GTV dose of 51.5% and 8.6 Gy respectively for the nominal 15-Gy prescriptions, while respecting the maximum dose tolerances to adjacent critical organs, similar to manually generated clinical SFRT plans. The average peak-to-valley-dose-ratio (PVDR) was around 3.0 and the mean beam-on time was 3.5 minutes for TrueBeam Linac (600 MU/min). The ESAPI script was able to generate SFRT plans in < 2 minutes on average in contrast to manually generated plans that took about an hour. There were no egregious errors with any of the scripted plans, and the script didn't violate any of the manual SFRT planning rules used in our clinic. Moreover, our voxel-based BED calculation tool successfully calculated both the spatial BED and EQD2 for SFRT target and dose to OAR contours in the plans, rapidly and clearly displaying them for the physician's review of combined-therapy treatment plan. Utilizing this script on anonymized clinical SFRT plans, we calculated the spatial BED and found that on average, the BED for D90%, D10%, and D50% to be 4.56 Gy, 25.0 Gy, and 11.32 Gy respectively. Additionally, our script calculated the EQD2 for D90%, D10%, and D50% to be 3.80 Gy, 20.84 Gy, and 9.44 Gy respectively. Voxel-based spatial BED proved to be a very clinically useful tool in understanding and predicting the biological response of these targets and adjacent OAR while using SFRT.

Conclusion(s): Automating our MLC-based 3D-conformal SFRT method allows for highly efficient clinical workflow for the management of large, bulky tumors for both palliative and therapeutic intents. This method allows for same-day treatment by eliminating the need for excessive inverse planning, optimization, and patient-specific QA times, which may improve patient start time, comfort, and compliance, while significantly reducing physicist workload. We highly suggest that other cancer centers, particularly community centers with remote and underserved patient cohorts, commission and validate both this MLC-based method and automation scripts for their use. Rapid calculation of BED10 voxel-by-voxel may be essential and beneficial for the treating physician to review SFRT plans that have highly heterogenous dose distributions. From there, the physician may decide which combination therapy prescription is suitable for the patient on a case-by-case basis. This tool may help the physician to enhance the therapeutic ratio of SFRT patients, adequately spare the adjacent OARs, and improve the toxicity profile of these complex and difficult patients. By accurately predicting the spatial BED10 information of SFRT treatment, we may be able to estimate the contribution made by indirect cell-death due to bystander signaling to adjacent tumor cell, enhancing intratumor immune-response, and providing vascular damage to large, bulky, and unresectable tumors, in addition to the direct cell-kill. In the future, this may facilitate improvement in the standard LQ Model by predicting a more accurate radiobiological response to SFRT coinciding with the greater treatment response observed in the clinic.