Presenting Clinical Outcome Modeling of 3D MLC-Based SFRT Treatments for Large and Unresectable Tumors

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ABSTRACT

Purpose:
This study models clinical outcomes of SFRT treatments delivered using the 3D MLC-based Crossfire technique.

Methods and Materials:
A total of 131 SFRT patients (median tumor volume = 477.55 cc) with follow-up data (median interval 4 months) ranging from tumor control, pain relief, toxicity, and overall survival (OS). Median SFRT prescription was 15Gy/1fx. The linear-quadratic model was used to calculate biological effective dose (BED) metrics (D10%, D50%, D90%, D95%) and equivalent dose in 2Gy-per-fraction (EQD2) from the combined effective dose of SFRT plus follow-up treatments using an α/β of 10 and 3 Gy for tumors and normal tissues, respectively. Follow-up treatments were either palliative (median: 30Gy/10fx) or curative (median: 70Gy/35fx) depending on histopathology. Multivariable logistic regression was used to model tumor control probability (TCP) and pain relief using BED metrics. OS was modeled with an univariable Cox hazard model using BED metrics. Toxicity was modeled with univariable logistic regression using maximum EQD2.

Results:
The TCP model (75/98 tumors reported clinical benefit) had no dose metrics be independently associated with local control (p>0.05). The pain relief model (59/82 reported benefit) again had no statistically significant metrics. In the Cox model, increases in all BED metrics were associated with improved OS (p<0.05). Toxicities were reported in 28/95 patients, including seven grade 3+ events. The skin's max EQD2 was associated with skin toxicity (p=0.014), and the parotid's max EQD2 was associated with xerostomia (p=0.002).

Conclusions:
These models provide a framework for identifying key metrics that may improve SFRT planning and delivery. Results should be interpreted cautiously given the limited number of adverse events (toxicity and tumor growth) and the heterogeneity of the patient cohort.

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INTRODUCTION

Spatially Fractionated Radiotherapy (SFRT) is the use of a highly heterogenous dose distributions consisting of an alternating pattern of high and low dose. This technique has demonstrated excellent debulking capabilities while maintaining normal tissue toxicity.[1] The major knowledge gap with this technique is the lack of a protocol/guideline for implementing this technique.[2]
We modeled our clinical outcome data to provide guidelines for treatment planning using this SFRT method for unresectable bulky tumors. The outcomes modeled in this study was tumor control, pain relief, normal tissue toxicities, and overall survival rates

METHODS AND MATERIALS

- 137 large tumors with different histopathologies were treated with the 3D MLC-based SFRT method using MLC-fitting for a 1 cm cylindrical high-dose and a 2 cm center-to-center distance at the isocenter. An example case is shown **Figure 1.**
- Physical and biological equivalent dose metrics for the SFRT target were reported, as were the maximum EQD2 to nearby critical organs.
- Clinical follow-up data included tumor local control evaluated on post-treatment CT scans, pain relief, toxicity profiles, and overall survival (OS).
- Tumor control probability (TCP) and pain relief probability were modeled using multivariable logistic regression, while normal tissue complication probability was modeled using univariable logistic regression. OS was modeled with a univariable Cox hazard model.

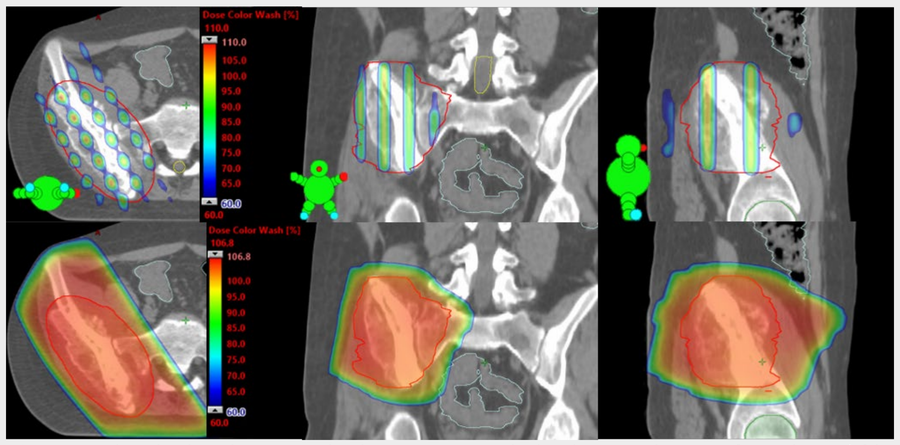

Figure 1: A clinical right pelvis case with a large mass, prescribed with an initial course of SFRT (15 Gy/1fx) followed up with a palliative course (37.5 Gy/15fx)

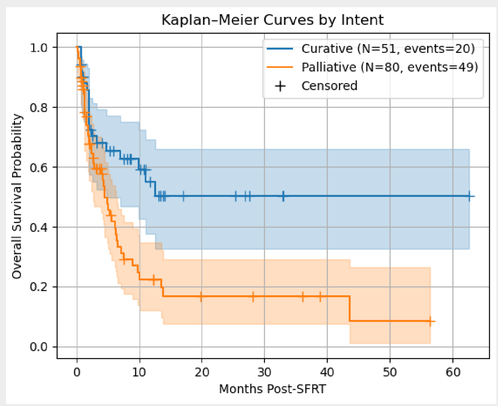

Figure 4: The Kaplan-Meier curves for our SFRT patient cohort, stratified by treatment intent. The shaded bands represent the 95% confidence interval.

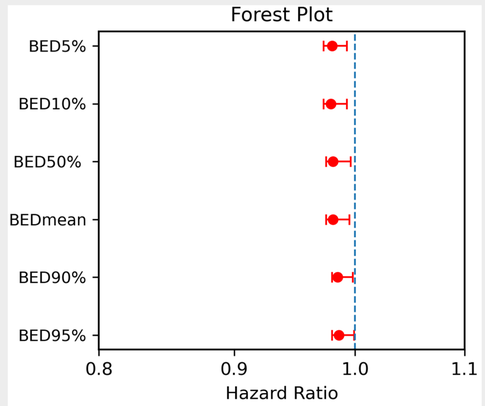

Figure 5: Resulting Hazard Ratios (HR) when modeling OS with a Cox Hazard Model using total GTV BED metrics. Red indicates statistically significant HR.

RESULTS

- This cohort had a median tumor volume of 477.55 cc (range, 121.47-7879.87 cc).

1. A tumor local control rate of **76.5%** (75/98), and a pain relief rate of **72.0%** (59/82) was found. None of the extracted dose metrics were statistically significantly correlated with predicting tumor control or pain relief. **Figure 2** shows the resulting ROC curves when fitting these outcomes using multivariable logistic regression. Using the cumulative treatment's BED metrics showed to have little increase in AUC when predicting tumor control and a decrease in AUC when predicting pain relief when compared to using just the SFRT dose metrics.
2. In total, 95 SFRT patients were available for toxicity assessment, with 65 (**68.4%**) reporting no toxicities and 7 (**7.4%**) reporting grade 3+ events. Skin toxicity and xerostomia were statistically significantly correlated with maximum EQD2 values to the skin (**p = 0.022**) and parotid glands (**p = 0.038**) as shown in **Figure 3**. Mean EQD2 to the parotids was not statistically significantly correlated with xerostomia.
3. The Cox hazard model showed that increases in cumulative treatment's BED metrics were statistically significantly associated with longer OS (Figure 5); however, increases in SFRT dose metrics were not. We reported OS rates of **51.8%**, **36.3**%, and **30.3%** at 6, 12, and 18 months, respectively. Moreover, we found differences in OS between patients who received a combination palliative treatment to those who received a curative treatment (**p = 0.002**). Resulting K-M curves of these outcomes is shown in **Figure 4.**

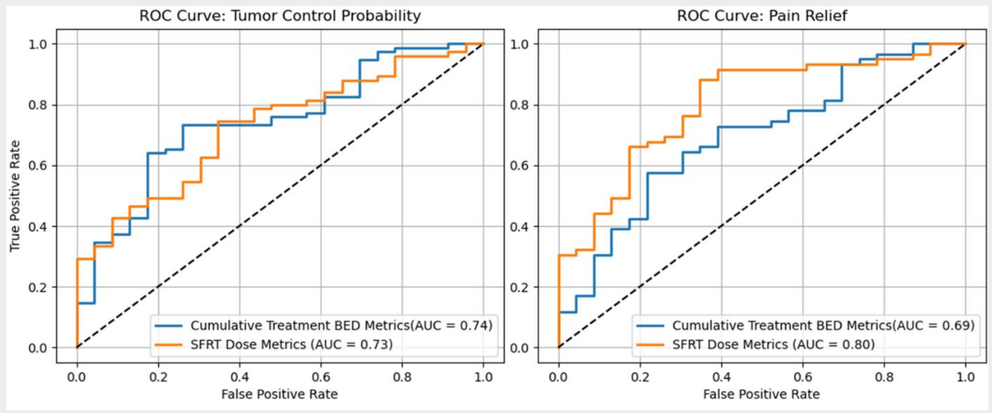

Figure 2: ROC curves from the multivariable logistic models to predict either tumor control (left) or pain relief (right). For each outcome prediction, two models were produced: one fitted to the cumulative treatment's BED metrics (blue), and one fitted to the SFRT plan's dose metrics (orange).

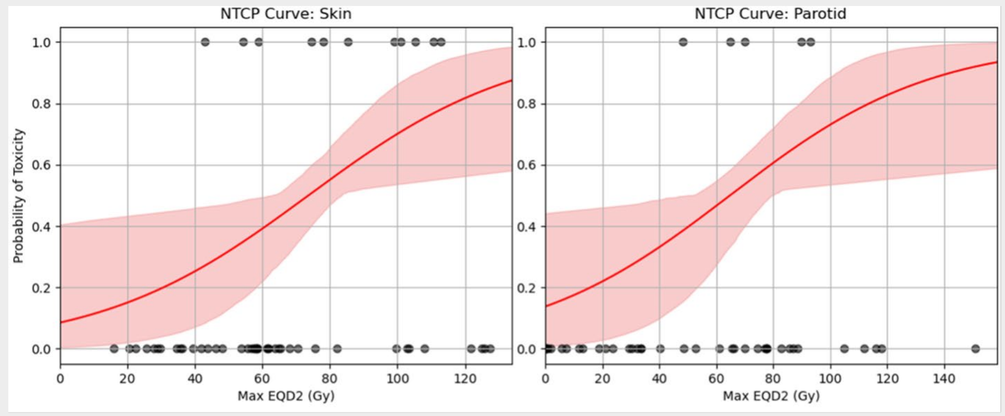

Figure 3: The resulting univariable logistic regression models for skin toxicity (left) and xerostomia (right) for SFRT patients. Black dots represent the individual data points, the red line represents the logistic model, and the light red band represents the 95% confidence interval.

CONCLUSIONS

This work has reported our single-institution results using the 3D-MLC-based crossfire technique for SFRT treatment and the resulting outcome models. We have found that there wasn't a statistically significant metric with predicting TCP or pain relief. However, the cumulative BED metrics were statistically significantly correlated OS rates. We have reported our TCP, pain relief, and toxicity rates in addition to the OS. Further refinement of this predictive model for SFRT in a larger, more diverse cohort is ongoing to validate our findings.

REFERENCES

1. Knight JA, et al. Reported Early Clinical Outcomes of Forward-Planned Multileaf Collimator-Based 3-Dimensional Conformal Spatially Fractionated Radiation Therapy Technique for Large and Bulky Tumors. International Journal of Radiation Oncology*Biology*Physics. doi:10.1016/j.ijrobp.2025.04.016
2. Zhang H, et al. Photon GRID Radiation Therapy: A Physics and Dosimetry White Paper from the Radiosurgery Society (RSS) GRID/LATTICE, Microbeam and FLASH Radiotherapy Working Group. Radiation Research. 2020;194(6). doi:10.1667/RADE-20-00047.1