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# Patient-Reported Clinical Outcomes of MLC-Based Spatially Fractionated Radiotherapy Following Offline Adaptive Radiotherapy for Large and Bulky Unresectable Head and Neck Tumors

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Damodar Pokhrel [1], James A. Knight [2, 3], Joshua Misa [4], Mahesh Kudrimoti [5]

1. Physics, University of Kentucky, Lexington, USA 2. Department of Radiation Medicine, University of Kentucky, Lexington, USA 3. Radiation Medicine, University of Kentucky, Lexington, USA 4. Department of Radiation Oncology, University of Kentucky, Lexington, USA 5. Radiation Oncology, University of Kentucky, Lexington, USA

**Corresponding author:** Damodar Pokhrel, damodar.pokhrel@uky.edu

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## Abstract

Objectives:

Delivery of spatially fractionated radiation therapy (SFRT) via traditional single-field Cerrobend GRID blocks has historically been hampered by significant challenges in managing skin toxicity and delivering prescribed dose to greater depths within large, bulky (⩾ 6 cm) tumors. At our institution, we have recently implemented a novel forward-planned, multi-field MLC-based 3D-conformal spatially fractionated radiation therapy (SFRT) method via image-guidance (J Appl Clin Med Phys. 2022; 23: e13608) for the management of bulky head and neck tumors with definitive intent. In addition to direct cell-kill, SFRT enhances indirect cell-kill mechanisms via radiation-induced bystander signaling to adjacent tumor cells, damaging the intratumor micro-vasculature, and upregulating various immunostimulatory cytokines that contribute to dramatic tumor shrinkage. Recently, many advanced methods for SFRT have been developed for use in selected patients, including inversely optimized IMRT/VMAT lattice therapy, Helical TomoGRID, robotic CyberKnife, microbeam, and proton GRID therapy. However, these modalities require a substantially long clinical workflow time–contributing factors include third-party software requirements to generate lattice structures, time to delineate critical organs, inverse-treatment planning time, and additional patient-specific physics quality-assurance (QA). Consequently, these modern SFRT methods may not enable same-day treatment of bulky head and neck masses, resulting in delayed progression to systematic therapy and detrimental outcomes for head and neck cancers patients. Furthermore, the accessibility of these treatment options may be hindered by treatment expenses, and cancer care cost and limited availability of these modalities in many clinics including community practices. Forward-planned 3D-conformal MLC-based SFRT avoids those issues, enabling immediate same-day SFRT treatment and rapid initiation of concurrent chemoradiation in head and neck patients. To appropriately account for rapid tumor response/mass reduction to SFRT in this cohort, we have implemented an offline adaptive radiotherapy (ART) strategy during combination therapy, based on daily pre-treatment cone beam CT (CBCT) imaging information and physician's discretion. Herein, we present the patient-reported clinical outcomes of our first three patients with advanced head and neck cancers treated with SFRT treatment, followed by ART with definitive intent.

Methods:

We credentialed our clinic for MLC-based SFRT method via head and neck phantom irradiation from the IROC MD Anderson's Houston QA Center. First three SFRT head and neck cancer patients with large stage IV(A-B) squamous cell carcinoma bulky tumors in the left piriform sinus (980 cc, patient #1), larynx (605 cc, patient #2) and hypopharynx (97 cc, patient #3) were evaluated. These patients were treated via same-day MLC-based 3D-conformal SFRT method (15 Gy in 1 fraction), followed by combination therapy of 70 Gy in 35 fractions (via 6 MV photons with highly conformal VMAT plans) with concurrent platinum-based chemotherapy (cisplatin 80 mg/m2 q21d for patient #1, cisplatin 40 mg/m2 q7d for patient #2, and carboplatin for patient #3, respectively). Evaluated dosimetric parameters for MLC-based SFRT plans included peak-to-valley-dose-ratio (PVDR = GTVD10%¬ ÷ GTVD90%) ~3.5; mean GTV dose > 7.8 Gy, GTV(V7.5Gy) > 50% and maximum dose achieved to adjacent organs-at-risk (OAR). Dose constraints to OAR were met per NRG-RTOG 0915 trial (Arm 1, single fraction scheme) and AAPM Task Group 101 protocol recommendations. Advanced Acuros-based dose engine was used to generate MLC-fitted sieve-like, highly heterogenous dose tunnels automatically, within an hour of CT simulation, allowing for same-day image-guided SFRT delivery. Maximum dose to spinal cord in each SFRT plan was kept below 3 Gy. These SFRT treatments were delivered on C-arm Linac (6 MV photons) with Millennium 120MLC via CBCT guided patient set up verification with 6DOF PerfectPitch couch corrections. Time interval from SFRT delivery to start of consolidated combination VMAT radiotherapy was 3 days, 2 days and 1 day for patient #1, #2, and #3,

respectively. Due to the rapid tumor response and mass reduction after SFRT, the initial combination radiotherapy plan was adapted offline twice for patient #1, and once for patient #2 and #3 per treating physician's discretion, while evaluating the pre-treatment CBCT images at the treatment console. The new offline ART plan(s) were generated on a new set of CT images co-registered with the original planning CT images and dose-sum was created via image/dose registration. Offline adaptation of VMAT plan was done on weekends to prevent disruption to ongoing chemoradiation plans. After completion of SFRT and highly conformal VMAT chemoradiotherapy with offline ART, the patients underwent post-treatment CT imaging follow-up. Reported treatment outcomes included tumor response, pain control, and radiation-associated toxicity.

Results:

All patients tolerated SFRT treatment well. Beam-on time for the SFRT plans was < 3.5 minutes. Overall treatment time, including patient setup, pre-treatment verification and CBCT image-guidance, and beam-on time, was < 15 minutes. Response Evaluation Criteria in Solid Tumors (RECIST, v1.1) was used to determine the objective radiographic tumor response and mass reduction on follow up CT images. Acute radiation-associated toxicity was graded according to the Common Terminology Criteria for Adverse Events (v 4.03). The clinical follow up interval for the head and neck patient #1, #2 and #3 was 50 months, 6 months, and 10 months, respectively. Patient #1 demonstrated complete tumor response, but with this excessively large tumor, the patient experienced grade-3 skin reaction requiring debridement, that was performed without complication. Patients #2 and #3 presented with partial tumor response with pain control. Clinical benefit rate was 100%, all patients still surviving. Patient #2 had grade-1 skin reaction but patient #3 experienced no radiation-associated toxicities. No other treatment related radiation induce toxicity profile was reported.

Conclusion(s):

The same-day MLC-based 3D-conformal SFRT method with offline ART strategy offered a fast, safe, and effective treatment against large, bulky, unresectable head and neck tumors, with rapid tumor response and refinement of treatment delivery. This simple, yet clinically useful SFRT technique with offline ART provided effective disease control by debulking large tumor masses and enabling faster initiation of definitive chemoradiation, while improving patient comfort and compliance. This method required minimal physics support and patient-specific QA resources, allowing for fast, safe, and effective clinical workflow without delaying systemic therapy. The concurrent use of offline ART in highly conformal VMAT chemoradiation plans further minimized maximum dose to critical organs, enabled patient-specific decision-making by the physician, and facilitated longitudinal assessment of tumor control. Going forward, we plan to adapt the combination therapy on a weekly basis. That will allow for even more accurate assessment of the tumor mass reduction and further sparing the adjacent OAR. We suggest other academic institutions and community practices adopt, validate, and clinically implement this simple yet clinically valuable SFRT technique with offline ART strategy for the management of their complex and difficult head and neck bulky tumors in their clinics. We believe implementing this cost-effective method could provide adequate treatment response to underserved, resource-limited patient populations in the future. Using SFRT with offline ART as neoadjuvant radiotherapy, or in combination with immunotherapy, against large, bulky tumors in the lungs, abdomen, and pelvis, warrants further investigation.