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A Prospective, Randomized Phase II Study of Surgery with or without Adjuvant Stereotactic Body Radiotherapy (SBRT) in Patients with Previously-Irradiated Head and Neck Cancer

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Abstract
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Abstract

Objective: Recurrence after definitive chemoradiation for head and neck squamous cell carcinoma (HNSCC) is associated with a poor prognosis with limited treatment options. Surgical resection represents the currently accepted standard of care. The only phase III experience evaluating adjuvant therapy after surgical salvage is from the Institute Gustave-Roussy where the addition of adjuvant concurrent chemotherapy and re-irradiation was compared to observation. They found that disease-free survival was improved, but not overall survival. However, this regimen was associated with grade 3 or 4 acute mucositis in 28% of patients. Late grade 3 or 4 toxicity was 39% in the treatment arm versus 10% in the observation arm. The potential advantages of stereotactic body radiation therapy (SBRT) in the setting of re-treatment of high-risk patients with HNSCC are a highly conformal treatment volume that affords a small number of fractions, decreased overall treatment time, and radiobiological advantages (where acute responding tissue is better spared with higher doses per fraction/lower overall dose to minimize acute toxicity).

Methods: In 2013-2014, we developed a single institutional Phase II clinical trial where patients after salvage surgery with high-risk features (ECE or close/positive surgical margins) were randomized to observation or 40-50 Gy in 5 fractions SBRT. Inclusion criteria included patients who had undergone curative intent macroscopic complete salvage surgery with R0 or R1 resection and high-risk pathological features (compromised/positive surgical margins [⩽ 2mm] or extra-nodal extension), prior radiotherapy dose ⩾ 50Gy, no evidence of distant metastasis, and KPS ⩾60. Exclusion criteria included patients with distant metastases, gross residual disease following salvage surgery, and/or any co-morbidity or condition of sufficient severity to limit full compliance with protocol. Primary objective was 1-year local control. Secondary objectives were local, regional, and distant progression-free survival (PFS), overall survival, and acute and late toxicities of adjuvant SBRT.

Results: The trial was closed in 2021 after failing to meet its accrual goal of 42 patients. From 2015-2018, nine patients were screened, and seven patients were enrolled. Median re-irradiation interval was 5 months (interquartile range [IQR] 4-8). Median KPS at enrollment was 80% (IQR 80.0-80.0). Median follow-up for all patients was 41 months (IQR 8-44). Four patients were randomized to observation and three patients were randomized to SBRT. Two patients had loco-regional failure at 2 and 8 months, and subsequently succumbed to their disease at 27 months and 12 months, respectively. Both patients were in the observation arm. No new acute grade 3 toxicity above pre-treatment baseline was note in the SBRT arm. In the SBRT arm, late grade ⩾3 toxicities included one patient with dysphagia requiring PEG tube placement 2 years after randomization and one patient with pneumonia possibly related to aspiration and 4 months after randomization.

Conclusion: The limited accrual and closure of this trial demonstrated the difficulty of a randomized clinical trial to validate the role of SBRT in this setting. The 50% locoregional failure rate noted in the observation

arm, and prior retrospective data would continue to support a potential role for post-operative SBRT in this patient population that may prove elusive to validate in a prospective setting.