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Toxicities Following Stereotactic Ablative Radiotherapy Treatment of Locally-Recurrent and Previously Irradiated Head and Neck Squamous Cell Carcinoma

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Stereotactic ablative radiotherapy (SABR) with concomitant cetuximab is an effective treatment option for previously irradiated, locally recurrent squamous cell carcinoma of the head and neck. Its local control and overall survival are similar to those of other available treatment options. Each retreatment depends heavily on the prior treatment and every patient is a special case. Based on the experience of our institution and previously published studies, for patients who receive concomitant cetuximab with a median prior radiation therapy dose of 70 Gy, we recommend a total dose of 40-44 Gy delivered in 5 fractions on alternating days over 1-2 weeks. However, Grade 2 or 3 toxicities are not uncommon. Therefore, in this review, we also report a pilot study that applies a normal tissue complication probability dose-response model to estimate the probability of toxicities in locally recurrent squamous cell carcinoma of the head and neck reirradiated with SABR. Although this dose-response model includes concurrent targeted therapy and no comparable model yet exists for SABR without it, complication rates without concurrent biological therapy or chemotherapy should be no higher than those described here.

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The locoregional recurrence rate in squamous cell carcinoma of the head and neck (SCCHN) following definitive and adjuvant chemoradiation therapy remains substantial at approximately 20%-30%,[1,2] despite major improvements in the multimodality treatment of SCCHN. Radiation Therapy Oncology Group protocols reported locoregional recurrences as first failure sites in 50%-60% of both human papillomavirus-positive and human papillomavirus-negative subsets.[3] An additional problem is the development of second primary head and neck cancers. The concept of field cancerization was first coined by Slaughter in 1953, who noticed the presence of histologically abnormal tissue surrounding oral squamous cell carcinoma. He proposed that the entire mucosa undergoes histological changes when exposed to environmental carcinogens such as tobacco and alcohol and is therefore susceptible to developing multiple primary malignancies.[4] Based on this concept, the risk of a second primary malignancy for successfully treated SCCHN associated with tobacco and alcohol use is at least 1% per year.[5] As locoregional progression is the most common cause of death,[6] achieving local control in previously irradiated, locally recurrent disease may have a potentially significant effect on survival. Good local control also improves quality of life as uncontrolled tumor growth is associated with significant pain, bleeding, and impairment of essential functions such as swallowing, speaking, and breathing.

For patients with resectable SCCHN recurrence, surgical salvage is the standard treatment.[6] Unfortunately, many patients with previously irradiated locally recurrent SCCHN (rSCCHN) have tumors that are unresectable and reirradiation with or without chemotherapy becomes the only potentially

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curative salvage option. However, prospective randomized clinical trials studying conventional reirradiation techniques with chemotherapy reported significant toxicities with Grade 3 or higher acute toxicity rates of 64%-78% and Grade 3 or higher late toxicity rates of 22%-38%.[7,8] Even modern intensity-modulated radiation therapy (IMRT) is associated with high rates of mucosal and soft tissue toxicities.[9,10]

Stereotactic ablative radiotherapy (SABR), owing to its great conformity and precision in dose delivery, has been associated with fewer normal tissue toxicities than conventional radiotherapy and IMRT. Furthermore, SABR requires much shorter treatment time (around 1-2 weeks) compared with IMRT, which can take 6-7 weeks. Since 2003, patients with previously irradiated rSCCHN have been treated on protocols with SABR ± cetuximab at our institution.[11-13] Although the treatment was in general well tolerated, we did observe some Grade 2-3 toxicities and occasional Grade 4 toxicities. The purpose of this review is to evaluate the toxicities of SABR in treating locally rSCCHN with previous irradiation and report results of a pilot study that applies the normal tissue complication probability (NTCP) dose-response model to study the dose-volume relationship to toxicities in previously irradiated, locally rSCCHN treated with SABR.

Toxicities of SABR in Reirradiating Locally rSCCHN

Prospective Clinical Trials

Several randomized, prospective clinical trials have investigated the use of SABR in reirradiating locally rSCCHN, as summarized in Table 1. Heron et al[14] reported the first Phase I dose-escalation trial of reirradiating with SABR. Overall, 25 patients with locally rSCCHN, median tumor volume = 44.8 (4.2-217) cm^3, were retreated using SABR in 5 fractions with a total dose of 25-44 Gy, in 5 dose groups. The mean prior dose in each escalated dose group ranged from 66.0-69.6 Gy in 30-36 fractions.[14] Nobody received concurrent cetuximab or chemotherapy. The median time to disease progression after completion of SABR was 4 months and the median overall survival (OS) after completion of SABR was 6 months. No Grade 3 or 4 or dose-limiting toxicities occurred. In all, 2 patients experienced Grade 1 mucositis, 1 patient with Grade 2 dysphagia and 1 patient with Grade 1 hyperpigmentation. Self-reported quality of life was not significantly affected by SABR treatment.

In 2012, Comet et al[15] conducted a prospective study that included 40 patients with inoperable or new primary head and neck cancer in a previously irradiated area. Overall, 50% of these tumors were squamous cell carcinoma. The median prior RT dose was 66 Gy and median tumor diameter was 29 mm. Overall, 70% had previous surgery and 57% had received chemotherapy during their initial treatment. SABR was delivered in 6 fractions to the 85% isodose line with a total dose of 36 Gy. In this study, 15 patients received concurrent cetuximab and 1 received concurrent cisplatin. The median progression-free survival was 8.8 months (95% CI: 5.2-11.7 months) and the median OS was 13.6 months. The median follow-up was 25.6 months. No Grade 4 toxicity was observed. Of all, 4 (10.3%) patients developed Grade 3 toxicities including mucositis, dysphagia, induration and fibrosis, 3 of whom received concurrent cetuximab. In all, 8 (20.6%) patients experienced Grade 2 toxicities and 10 (25.6%) experienced Grade 1 toxicities.

Iwata et al[16] reported a prospective protocol-based study that included 51 patients with previously irradiated recurrent nasal or paranasal carcinoma. Most patients were reirradiated with a total dose of 30 Gy in 3 fractions or 35 Gy in 5 fractions. The median prior RT dose was 60 Gy (range: 40-70 Gy). The median interval between initial radiation and reirradiation was 18 months (range: 2.5-132 months). The median time-to-local progression after completion of SABR was 9.5 months and the median OS after completion of SABR was 14.5 months. Grade 3 or higher adverse events were observed in 23% of patients. A total of 2 patients developed Grade 4 dermatitis and 1 patient developed Grade 4 soft tissue necrosis. Of all, 2 brain necrosis patients presented with clinical symptoms.

Lartigau et al[17] reported a multiinstitution Phase II study that included 56 patients with previously irradiated, locally rSCCHN. SABR was delivered in 6 fractions to the 85% isodose line with a total dose of 36 Gy. All patients received concomitant cetuximab. The median prior RT dose was not reported. The median progression-free survival after completion of SABR was 7.1 months (95% CI: 5.5-8.9 months) and the median OS after completion of SABR was 11.8 months with a 1-year OS rate of 47.5% (95% CI: 30.8%-62.4%). The median follow-up was 11.4 months. A total of 18 patients developed Grade 3 toxicities including mucositis, dysphagia, induration, and fibrosis.

More recently, Vargo et al[18] reported a prospective Phase II trial of 50 patients with inoperable locally rSCCHN with a previous RT dose ≥60 Gy and tumor volumes of 3.6-209.2 (median = 36.5) cm^3. The median time from initial radiation to reirradiation was 18 months (range: 3-423 months). The median prior RT dose was 70 Gy (range: 52.5-118.2 Gy). All patients received concomitant cetuximab. SABR delivered a total dose of 40-44 Gy in 5 fractions on alternating days over 1-2 weeks. The median OS was 10 months (95% CI: 7-16 months) with a 1-year local progression-free survival rate of 60% (95% CI: 44%-75%). The median follow-up was 18 months (range: 10-70 months). Of all, 6% of patients developed Grade 3 acute toxicities including 1 mucositis, 1 dysphagia and 1 skin rash. A total of 6% of patients developed Grade 3 late toxicities including 1 dysphagia (45 cm^3 tonsil tumor), and 2 aerodigestive fistulae (45 cm^3 stoma/submental and 135 cm^3 base of tongue). There was no Grade 4 or greater toxicity.

In summary, SABR is a feasible option to re-irradiate locally rSCCHN. It is associated with a reasonable local control rate, OS and toxicity profile. However, Grade 2 or 3 toxicities are not uncommon after treatment. Most commonly seen toxicities include mucositis, dysphagia, and dermatitis.