Reirradiation using SBRT may be a promising treatment option for locoregional, recurrent head and neck cancers.

Stereotactic Body Radiotherapy for Recurrent Unresectable Head and Neck Cancers

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Background: Treatment of locoregional, recurrent head and neck cancers following definitive radiotherapy has evolved during the past 30 years. Brachytherapy as well as protracted courses of systemic therapy and chemoradiotherapy result in 12-month survival rates of 40% to 50% but have high rates of severe toxicity. Given the advancements in radiotherapy targeting and delivery, stereotactic body radiotherapy (SBRT) has been investigated as an alternative treatment option with the potential advantages of reduced treatment time and rates of toxicity.

Methods: The authors reviewed prospective trials and retrospective reports from the past decade addressing the management of locoregional, recurrent, previously radiated head and neck cancers, focusing on SBRT.

Results: The body of evidence is growing in support of reirradiation using SBRT for the treatment of recurrent head and neck cancers. The 1-year survival rates associated with SBRT are promising and similar to those seen with chemoradiotherapy alone and concurrent, conventionally fractionated radiotherapy and chemotherapy. Treatment-related adverse events of reirradiation using SBRT are also similar to other palliative therapies. Late carotid rupture is a relatively rare but concerning late toxicity associated with reirradiation using SBRT.

Conclusions: SBRT is a promising treatment for locoregional recurrent head and neck cancers. It also offers a logistical advantage over other palliative treatments, as it only requires 1 to 2 weeks of treatment.

Background
In 2016, an estimated 61,760 new head and neck cancer cases were diagnosed and an estimated 13,190 deaths occurred due to head and neck cancers in the United States. Most patients with head and neck cancers present with locoregional advanced disease and require a multimodal approach to treatment, including a combination of surgery, radiation, or systemic therapy. Despite aggressive management, 40% to 50% of patients will experience locoregional recurrence and, of patients who recur, 50% to 60% will die from disease progression. Following recurrence, surgery is the preferred approach, although fewer than 50% of patients are candidates for salvage surgery because of the location, extent of recurrence, or both, as well as medical comorbidities that may preclude surgery. For patients who are not candidates for salvage surgery, few treatment options remain, including reirradiation, supportive care, or palliative systemic therapy.

Systemic Therapy
Palliative systemic therapy results in a 12-month survival rate ranging from 40% to 50%, but it comes at the
cost of high rates of toxicity. A phase 3 trial that included participants with recurrent or metastatic squamous cell carcinoma of the head and neck showed that systemic therapy with cisplatin or carboplatin in combination with fluorouracil and cetuximab, a targeted inhibitor of epidermal growth factor receptor, resulted in a median survival rate of 10 months and an 82% rate of grade 3/4 adverse events. Following this study cetuximab in combination with cisplatin was approved for the treatment of metastatic head and neck squamous cell carcinoma. Pemetrexed, a folate antimetabolite, was also tested in a large, randomized, phase 3 trial in combination with cisplatin for recurrent or metastatic head and neck cancers but did not improve overall or progression-free survival rates when compared with combination cisplatin/placebo. However, on subgroup analysis, an improvement in survival was seen with pemetrexed/cisplatin among patients with a performance status of 0 or 1 (8.4 vs 6.7 months, respectively) and patients with oropharyngeal cancers (9.9 vs 6.1 months, respectively) compared with cisplatin alone.

A phase 2 trial assessed combination cisplatin, cetuximab, and pemetrexed among 66 participants with recurrent or metastatic head and neck cancers and reported an overall survival rate of 9.7 months. Survival outcomes with this triplet therapy were similar to those seen with other systemic therapy alternatives, although treatment-related deaths were higher than expected; therefore, this triplet combination was not recommended for routine use.

Conventionally fractionated radiotherapy in combination with systemic therapy has also been attempted for locoregional control of recurrent head and neck cancers with moderate success. In the early 1990s, Vokes et al first investigated concurrent chemoradiotherapy with 5-fluorouracil and hydroxyurea in study patients who had previously received irradiation for their recurrent head and neck cancers. The researchers reported treatment-related deaths in 5 of 45 study patients (11%) and concluded that reirradiation was feasible but that further research was needed.

Subsequently, the first multi-institutional, phase 2 prospective reirradiation head and neck trial was reported by Spencer et al. This benchmark trial included 79 participants who had previously received radiotherapy for recurrent or new primary head and neck cancers. The study patients were treated with 60 Gy in 1.5 Gy twice-daily fractions concurrently with fluorouracil and hydroxyurea. The rates of median and 1-year survival were 8.5 months and 40.5%, respectively, with 14 participants (17.7%) experiencing grades 4/6 toxicity and 7.6% with grade 5 acute toxicity. Langer et al performed a separate prospective phase 2 trial that enrolled 105 patients who were similarly treated to a total dose of 60 Gy with twice-daily 1.5 Gy fractions, 5 days per week every other week; study participants were also treated with concurrent cisplatin and paclitaxel as radiosensitizers. The median survival rate was 12 months, and the rate of toxicity was similar to previous reirradiation studies; 8 deaths (8%) were also attributed to the treatment, including 2 cases of late carotid hemorrhage. A trial update in 2012 reported a 5-year survival rate of 15% and an estimated 10-year survival rate of 5% with 6 study patients alive. These results were promising, yet room for improvement remains.

One possible explanation for suboptimal outcomes with reirradiation is that cancer cells from previously radiated, recurrent head and neck tumors are radioresistant. To overcome the inherent radioresistance of recurrent head and neck cancers and to limit the rate of toxicity to healthy, surrounding tissues, dose-escalated and focused reirradiation using stereotactic body radiotherapy (SBRT) has been investigated.

**What Is Stereotactic Body Radiotherapy?**

SBRT is the delivery of large daily fractions of highly focal radiotherapy, typically 5 to 30 Gy per fraction in 1 to 5 fractions, using image guidance and other techniques to account for tumor motion. Initial reports of SBRT in early-stage, inoperable lung cancer had local control rates that exceeded 90%. SBRT has also shown good local control rates with 1 to 3 metastatic lesions of the liver, oligometastatic lung cancer, renal cell carcinoma, and metastatic lesions to the spine, as well as when administered after a prior course of SBRT for locally recurrent disease or limited metastatic disease progression. Given that SBRT delivers a high dose of radiation per fraction, the mechanism of tumor cell death was initially hypothesized to be a result of the effects of radiation on the tumor vasculature, thus causing endothelial cell death at doses of more than 7 Gy/fraction. However, new evidence suggests that SBRT maintains the classic pathways of radiation-induced cellular death along with possible enhanced antitumor immunity from high fractional doses.

**Reirradiation**

Experiences with SBRT for the treatment of locally recurrent head and neck cancers following prior radiation are presented in the Table. SBRT provides a potential advantage over other salvage therapies because it requires a shorter treatment course and has potentially fewer systemic adverse events compared with conventional chemoradiotherapy or protracted courses of systemic therapy alone. Heron et al performed the first phase 1 dose-escalation trial with SBRT for recurrent squamous cell carcinoma of the head and neck in the reirradiation setting. A total of 25 study participants received radiation doses starting at 5 Gy that escalated to 8.8 Gy per fractions for 5 fractions over 2 weeks. The researchers initially reported a maxi-
mum tolerated total dose of 44 Gy with no grade 3/4 acute toxicities and an overall response rate of 76%, a median duration of response of 4 months, and a median survival rate of 6 months.29 An update of the report, which included 85 enrolled patients, revealed a radiation dose response with improved local control at reirradiation doses of at least 35 Gy (71% vs 59%, respectively) compared with less than 35 Gy.25 Following this study and reports of improved survival rates with the addition of cetuximab to systemic therapy, another group investigated concurrent cetuximab with SBRT and compared it with SBRT alone (both treatment groups, n = 35); both study arms were given a median radiation dose of 40 Gy (range, 20–44 Gy).4,25,30 The researchers reported improved rates of survival in the combined cetuximab and SBRT group compared with those assigned to SBRT alone (median 24.5 vs 14.8 months, respectively).30 In 2014, the trial data were updated to include more enrollees (132 participants) treated to a median dose of 44 Gy (range, 35–50 Gy) and had a short median follow-up of 6 months.28 The study participants had median and 1-year survival rates of 7 months and 38%, respectively, and acute and late toxicities were relatively mild (16 participants [12%]), although 6 participants (7%) did experience toxicities of at least grade 3.28 The group also assessed predictive factors for recurrence and survival rates and reported improved recurrence-free survival rates, with a treatment duration of fewer than 14 days, but also worse rates of survival and worse incidences of acute — but not late — toxicity with reirradiation in study patients whose tumor volume was more than 25 mL.28 Thus, these prospective studies of reirradiation using SBRT helped to refine the optimal radiation dose and fractionation for reirradiation using SBRT, and the survival results for treatment with concomitant SBRT and cetuximab surpassed previous results with chemoradiation or systemic therapy alone.

Two sites in Europe have also reported outcomes with reirradiation using SBRT. A group in France led by Comet et al22 performed a feasibility study with salvage reirradiation using SBRT with or without cetuximab for the treatment of locally recurrent or new primary head and neck cancers. In this phase 1 trial, 40 study patients with 43 lesions were treated to a total dose of 36 Gy in 6 fractions prescribed to the 85% isodose line, 15 (37.5%) were treated with concurrent cetuximab, and 1 was treated with concurrent cisplatin.22 One-half of the study patients had squamous cell carcinoma histology.22 Rates of median and 1-year survival were 13.6 months and ~50, respectively. Of the 34 study patients who were evaluable for response, 15 (44%) had a complete response, 12 (35%) had a partial response, and 7 (21%) had stable disease.22 Of the 14 evaluable study patients treated with concurrent cetuximab, 75% had an overall objective response.22 Following these results, Lartigau et al23 headed a phase 2 multi-institutional trial to assess reirradiation using SBRT with concurrent cetuximab in 56 patients with recurrent or new primary head and neck cancers. Participants — all with squamous cell carcinoma — were treated with 36 Gy in 6 fractions for 11 to 12 days.23 Use of SBRT resulted in consistent median and 1-year survival rates of 11.8 months and

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**Table. — Select Studies for the Treatment of Locoregional, Recurrent Head and Neck Cancers After Prior RT**
47.5%, respectively.23 Of the 49 evaluable study participants, the objective response rate was 69%, complete response was seen in 24 (49%), partial response in 10 (20%), and stable disease in 11 (23%).23 Eighteen study patients (32%) experienced toxicities of grade 3 or higher and 1 patient died from arterial rupture.23 These results were comparable with those seen in the study conducted by Heron et al.50 Lartigau et al25 attributed the low rate of carotid rupture (ie, 1 occurrence) to the careful selection of patients without tumor encasement of less than one-third of the carotid artery.

Cengiz et al21 also performed a retrospective analysis of 46 study participants with locally recurrent head and neck cancers treated with reirradiation using SBRT to a median dose of 30 Gy (range, 18–35 Gy) for 1 to 5 fractions. Most of those enrolled in the study had squamous cell carcinoma; 16 participants (35%) had nonsquamous histologies.21 The median overall survival rate was similar to other studies, with a 1-year survival rate of 46%.21 A total of 10 of 37 evaluable study patients (27%) had a complete response, 11 (30%) had a partial response, and 10 (27%) had stable disease on imaging.21 Despite these comparable survival outcomes with other studies, the late-grade (≥4) toxicity rate was higher: 8 study patients (17%) experienced late carotid blowout, 7 (15%) of whom died from carotid hemorrhage.21 It has been suggested that the relatively high rate of late toxicity in this study was a result of daily SBRT fractionation, rather than an every-other-day fractionation scheme, as seen in most other studies.28

Two other studies addressing reirradiation using SBRT have provided consistent 1-year survival rates between 40% and 50%, although each has had subtle variations in treatment regimens, patient selection criteria, and treatment regimens.24,27 Unger et al27 reported their experience with 65 study patients treated with palliative reirradiation with SBRT for recurrent head and neck cancers. The study included 27 participants (42%) with metastatic disease or untreated local disease, 11 (17%) with nonsquamous histologies, 19 (29%) treated with surgery prior to reirradiation, and 21 (32%) treated with concurrent chemoradiation; the SBRT doses ranged from 21 to 35 Gy in 2 to 5 fractions.27 The group reported an overall response rate of 80%, a complete response rate of 54%, a partial response rate of 27%, and no response of 27% by laryngopharyngoscopy, biopsy, imaging, or all 3 procedures.27 The median rate of survival was 12 months and the 2-year survival rate for participants with nonmetastatic cancer at the time of treatment was 41%.27 Seven enrollees (11%) experienced late toxicities related to reirradiation, and 1 study patient died due to treatment.27

A Korean trial conducted by Roh et al24 enrolled 36 patients (totalling 44 lesions) who were treated for locally recurrent head and neck cancers using SBRT at 18 to 40 Gy (median, 30 Gy) in 3 to 5 fractions. More than one-half of the lesions were squamous cell carcinoma, although other histologies were included, and a median survival rate of 16 months was reported with a complete response rate of 43%, a partial response rate of 37%, and stable disease in 9%.24 Grade 3 acute complications were reported in 13 participants (36%) and late complications were reported in 3 (8%).23 The median survival rate in this study was 16 months; however, a high rate of late grade (≥ 4) toxicities was seen, which others have suggested were likely the result of daily radiation rather than every-other-day delivery.24,28

Reirradiation experiences with or without cetuximab offer promising and relatively consistent rates of median survival (~12 months) comparable with previously reported, protracted courses of chemoradiation and chemotherapy alone (see Table).4,10 However, despite this, subtle differences in selection criteria and tumor histology exist between studies, along with slightly different radiation doses and fractionations, making it difficult to directly compare each study. As a result, a large, multi-institutional phase 3 trial examining reirradiation using SBRT would be useful, especially to evaluate whether the 24-month rate of median survival reported by Heron et al50 is reproducible in a multi-institutional setting.

**Toxicity**

With reirradiation of normal tissues, it is important to be aware of possible late toxicities and to limit doses to normal tissue in order to minimize late effects. Both carotid blowout syndrome and spinal cord myelopathy are rare, but they are highly morbid conditions that can present as fatal, late complications of reirradiation.31,32 An animal model for studying reirradiation to the spinal cord was performed by Medin et al,55 in which 23 pigs were treated with 30 Gy in 10 fractions to 10 cm of the spinal cord and then stratified into 6 groups, with mean maximum reirradiation doses escalating from 14.9 to 25.4 Gy. The group reported a steep dose-response relationship with no neurological changes when using a maximum spinal cord dose below 18.8 Gy and 100% with neurological changes when using a dose higher than 21.3 Gy; they also found a 50% incidence of paralysis at a dose of 19.7 Gy (ie, median effective dose).53 When compared with other pigs treated with de novo, single-dose spinal cord irradiation, Medin et al34 found a nearly identical median effective dose of 20.0 Gy.

In a feasibility study for reirradiation of the head and neck with concurrent chemotherapy, Balermapas et al35 treated 5 study patients with reirradiation and limited the cumulative spinal cord maximum dose to 67 Gy without observing any late cord toxicities. Other groups have reported successfully limiting the
maximum dose of spinal cord reirradiation to 8 Gy in 1 fraction, 12 Gy in 2 fractions, 8 Gy in 5 fractions, and 6 Gy in 6 fractions without a single reported late case of radiation-induced myelopathy.5,25,29

By contrast, carotid blowout syndrome occurs more frequently with reirradiation of the head and neck, but few risk factors for carotid blowout syndrome have been identified. A Japanese study led by Yamazaki et al26 published the results of a trial of 381 participants who were treated with 484 reirradiation sessions to a median dose of 30 Gy in 5 fractions for recurrent head and neck tumors. Of those participants, 32 (8.4%) experienced carotid blowout syndrome, and the researchers reported a 1-year survival rate of 37.5% among these study patients.36 Tumor invasion of the overlying skin was the single significant risk factor associated with carotid blowout syndrome on multivariate analysis (odds ratio, 1.96; risk factor associated with carotid blowout syndrome.23 A literature review of carotid blowout syndrome following reirradiation of the head and neck reported an increased risk of carotid blowout syndrome with an accelerated hyperfractionated (1.5 Gy twice daily, 5 days per week, alternating weeks) or delayed hyperfractionated radiation regimen, compared with conventional fractionation, although the overall incidence of carotid blowout syndrome remained low (4.5% vs 1.3%, respectively); however, studies of reirradiation using SBRT were not included in the review.29 In an attempt to reduce the risk of carotid blowout syndrome, 1 study of reirradiation using SBRT limited the carotid radiation dose to less than 20 Gy and reported no late cases of carotid blowout syndrome.23 Another study by Yacizi et al37 retrospectively compared daily (n = 43) with every-other-day (n = 32) reirradiation using SBRT for the treatment of head and neck cancers and reported improved survival rates and no incidence of carotid blowout syndrome when irradiation was provided as an every-other-day regimen (23 vs 11 months and 9 vs 23 months, respectively). No events related to carotid blowout syndrome were reported in study patients who received a maximum carotid artery dose (< 34 Gy).57

Conclusions
Stereotactic body radiotherapy is a promising but still evolving strategy for the treatment of locally recurrent, unresectable head and neck cancers following definitive radiotherapy. In general, the 1-year survival rates following treatment are similar to both chemotherapy alone and concurrently, conventionally fractionated radiotherapy and chemotherapy. Treatment-related adverse events of reirradiation using stereotactic body radiotherapy are difficult to compare head-to-head with systemic palliative therapies given the relatively small volume of tissue treated, although it is now known that late carotid rupture is a rare — but concerning — late adverse event. Reirradiation using stereotactic body radiotherapy offers patients a potential logistical advantage compared with other palliative treatments, because it requires 1 to 2 weeks of treatment, rather than up to 18 weeks of maintenance cetuximab or 6 to 7 weeks of daily treatment with conventional chemoradiation. Initial experiences with combined cetuximab and reirradiation also appear to have benefit in the reirradiation setting, although larger, confirmatory studies are needed.

References


