Austin Head & Neck Oncology

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Mini Review

Stereotactic Radiotherapy and Proton Therapy for Locally Recurrent Head and Neck Cancer

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Received: May 22, 2017; **Accepted:** July 24, 2017; **Published:** July 31, 2017

Abstract

Re-irradiation in patients with locally recurrent head and neck cancer frequently pose significant radiation treatment planning challenge. This subgroup of patients have potentially curable disease with salvage treatment, however, the delivery of definitive high dose radiation is limited by the dose tolerance of surrounding normal structures which are frequently in close proximity in the head and neck region. The delivery of radiation dose in the re-irradiation setting is largely limited by total dose by normal structures previously and the lag time since previous irradiation course. With recent advances in radiation treatment planning and delivery, there is increasing interest in the use of Stereotactic Body Radiotherapy (SBRT) and proton therapy in the management of patients with recurrent head and neck cancer. Both SBRT and proton therapy have potential advantage in terms of limiting dose to surrounding normal tissues either via increasing conformality and steep dose gradients. Here we review the emerging role and outcomes of SBRT and proton therapy in the re-irradiation setting.

Keywords: Stereotactic; Proton radiotherapy; Recurrence

Introduction

Local and regional relapse in previously irradiated patients with Head and Neck Cancer (HNC) can pose a significant challenge in radiation treatment planning. In a patient who does not have significant burden of distant disease, achieving local control either via surgical resection and/or re-irradiation is of utmost importance as progression of local disease will significantly increase patient's morbidity and quality of life. Although surgery is preferred for patients who recurred after radiotherapy, the majority of patients are not suitable surgical candidates. Mabanta et al [1] reported that only 80% of patients with loco regional recurrence were unsuitable for surgery due to comorbidities, local disease extent (unresectable) and/or performance status. Re-irradiation remained an option for this subgroup of patients. Historically, re-irradiation was largely considered as a palliative treatment. With improvement in treatment planning and more conformal radiation delivery such as Intensity Modulated Radiation Therapy (IMRT), a small cohort of patients has been demonstrated long term disease control and survival with irradiation. However, the toxicity of reirradiation remain high with the literature reporting up to 20% risk of severe late toxicity including carotid blowout, osteoradionecrosis, esophageal stricture, xerostomia and skin ulceration/ necrosis [2-6]. There is increasing interest in the use of Stereotactic Body Radiotherapy (SBRT) and proton therapy in the management of patients with recurrent HNC. Both SBRT and proton therapy are gaining interest in the re-irradiation setting as both techniques have potential advantage in terms of limiting dose to surrounding normal tissues either via increasing conformality and steep dose gradients. Here we aim to discuss the emerging role and outcomes of SBRT and proton therapy in the re-irradiation setting.

Stereotactic Body Radiotherapy (SBRT)

SBRT employs highly conformal radiation dose distribution and enables precise and focused delivery of ablative dose of radiation in a few fractions of radiation. Given the steep dose gradient in SBRT, image guidance is of utmost importance to ensure precise radiation targeting – high dose to the tumor whilst limiting dose to surrounding normal tissues. SBRT studies in other sites including lung, spine, kidney and liver have demonstrated promising results in terms of good local control and possible anti-tumor/ enhanced immune effects on distant sites (abscopal phenomenon). It has been challenging to establish the role of SBRT in recurrent cancer within head and neck region given variability of location of recurrence and the close proximity to radiosensitive critical normal structures.

The literature on SBRT in recurrent head and neck disease remained limited with the majority of publications being retrospective single institution experiences. Table 1 summarizes the current literature. These SBRT studies showed that the treatment is generally well tolerated with less than 15% of late Grade 3 toxicity and reasonable rate of local control achieved.

Radiobiological reasoning for SBRT

The optimal dose/ fractionation required to ablate the recurrent tumor whilst respecting the normal tissue dose tolerance in a previously irradiated region remained unknown. Typically, for irradiated normal tissue, previous dose received by the structure and time lapsed since last treatment are taken into consideration. Radio biologically, it is assumed that the normal tissue can recover from radiation damage over time and begin to 'forget' some dose previously received. Therefore, the treating radiation oncologist tend to be more comfortable re-irradiating a patient who had completed treatment years ago rather than 'weeks' or 'months' ago. Furthermore, if a tumor recurred within weeks or months after a definitive dose of radiotherapy (66 – 70 Gy), it is theorized that the tumor cell(s) which survived the first course of treatment are relatively radio resistant, provided the recurrence did not occur at a low dose region.

Citation: Ng S P and Phan J. Stereotactic Radiotherapy and Proton Therapy for Locally Recurrent Head and Neck Cancer. Austin Head Neck Oncol. 2017; 1(1): 1002.

Table 1: Summary of re-irradiation studies in head and neck cancer utilizing SBRT.

Study	Nature of study	Number of patients	Dose	Prescription Isodose Line	Locoregional control	Overall survival	Late toxicity (≥ Grade 3)
Rwigema et al. [27] 2010	Retrospective	85	Median: 35 Gy		1 year : 51.2% 2 year: 30.7%	1 year: 48.5% 2 year: 16.1%	No Grade 4 or 5
Voynov et al. [35] 2006	Retrospective	22	Median: 24 Gy		2 year: 26%	2 year: 22%	No data
Roh et al. [36] 2009	Retrospective	36	18 – 40Gy	75%			Grade 5 soft tissue necrosis (1), Grade 4 osteonecrosis (2), Grade 4 trismus (1), Grade 4 ulcer (2), Grade 3 trismus (1)
Heron et al. [15] 2009	Prospective, Phase 1	25	25 – 44 Gy	80%	Median: 3 months	Median: 6 months	None
Siddiqui et al. [37] 2009	Retrospective	44	13 – 18 Gy (single fraction) 36 – 48 Gy (multiple fractions)		1 year: 60.6% 2 year: 40.4%	1 year: 38.1% 2 year: 14.3%	Grade 4 fistula (3), Grade 4 dysphagia (1), Grade 3 osteonecrosis (1), Grade 3 dysphagia (1)
Rwigema et al. [38] 2015	Retrospective	27	35 – 44 Gy	95%	2 year: 39.2%	Median: 12 months	Grade 3 osteonecrosis (1), Grade 3 dysphagia (1)
Vargo et al. [18] 2011	Retrospective	34	36 – 50 Gy	77 – 92%	Median: 5 months	1 year: 58%	Grade 3 pain (1), Grade 3 osteonecrosis (1)
Rwigema et al. [19] 2011	Retrospective	96	15 – 50 Gy		Median: 16 months	1 year: 58.9% 2 year: 28.4%	Grade 3 dysphagia (2), Grade 3 fibrosis (1)
Unger et al. [39] 2010	Retrospective	65	21 - 35 Gy		2 year: 30%	2 year: 41%	Death (1), Grade 4 soft tissue necrosis (2), Grade 4 dysphagia (2), Grade 4 arterial bleeding (2)
Yacizi et al. [30] 2013	Retrospective	75			Median: 13 months	Median: 14 months	Carotid blowout syndrome (11) resulting in deaths (7)
Cengiz et al. [28] 2011	Retrospective	46	18 – 35 Gy	Median: 76.5%		1 year: 47%	Soft tissue necrosis (1), osteonecrosis (1), Grade 3 dysphagia (2), carotid blowout syndrome resulting in deaths (7)
Kodani et al. [40] 2011	Retrospective	34	19.5 – 42 Gy			1 year: 70.6% 2 year: 58.3%	Death due to haemorrhage (2), skin necrosis (1), dysphagia (1)
Khan et al. [41] 2015	Retrospective	21	35 – 48 Gy	D90	1 year: 50%	1 year: 60%	No data
Lartigau et al. [17] 2013	Prospective, Phase II	60	36 Gy	85%	3 month: 91.7%	1 year: 47.5%	Death due to haemorrhage (1), Grade 3 xerostomia (2), Grade 3 fibrosis (1), Grade 3 fistula (1)
Kress et al. [6] 2015	Retrospective	85	16 – 41 Gy	Median: 73% Range: 60 – 85%	1 year: 57.8% 2 year: 28%	1 year: 51.1% 2 year: 24%	Grade 3 ulcer (2), Grade 3 soft tissue necrosis (1), Grade 4 toxicity unspecified (1)
Comet et al. [16] 2012	Prospective	40	36 Gy	85%		1 year: 58% 2 year: 24%	4 patients with Grade 3 toxicities: mucositis, dysphagia, induration and fibrosis.

Therefore, retreating these patients with higher dose per fraction may be more efficacious than conventional 2Gy per fraction. In addition, in a cohort of patients with relatively poor prognosis, SBRT remained an appealing option due to the short treatment time, typically 1 – 2 weeks.

As depicted in Table 1, total dose delivered ranges from 16 – 50 Gy. Majority of the studies in Table 1 deliver such doses in 3 – 5 fractions. Hypo fractionation is usually utilized in SBRT, taking advantage of the rapid dose falloff, to deliver higher dose per fraction than conventional fractionation (1.8 – 2 Gy per fraction) to the target with the aim of maximizing therapeutic ratio while limiting normal tissue complications. Although the linear quadratic model [7] for radiation cell killing is thought to be less reliable for very high dose per fraction [8-10], several investigators have attempted to model tumor control probability for SBRT [11]. Whilst the delivery of a very high dose of radiation in a single fraction will be ideal in terms of convenience for the patient, it has been theorized that multiple fractions may produce better clinical outcomes as a higher total dose or BED can be achieved with fractionation, and tumor cells are 'hit' multiple times generating numerous DNA damage (sub lethal or lethal) reducing the possibility of tumor cell recovery or repair [10]. As always, other confounding factors such as tumor hypoxia [12] and tumor actual alpha/beta ratio [13]. Should be considered when modelling tumor cell kill for hypo fractionated regimens. The advantage of fractionated therapy is that it allows time for normal tissues to repopulate and recover [14]. Although on a whole, as a discipline, we agree that higher dose per fraction increases cell killing, however the optimal dose per fraction, number of fractions and tumor cell kill modeling remained debatable.

Dose/ fractionation for SBRT and toxicities

Various institutional dose/fractionation has been reported in the literature (Table 1). Early phase I dose-escalation trial by Heron et al [15]. Investigated reirradiation using SBRT with doses up to 44Gy delivered in 5 fractions over 2 weeks in 25 patients with recurrent head and neck squamous cell carcinoma. The study demonstrated that treatment was well tolerated with no Grade 3 or higher toxicities reported and twelve patients had radiological stable disease after treatment [15]. Comet et al [16] evaluated the feasibility of SBRT using Cyber Knife (Accuray) to deliver 36Gy in 6 fractions with concurrent cetuximab, and showed an overall response rate of 79.4%. Out of 40 patients treated, 4 (10%) patients reported Grade 3 toxicities: dysphagia, mucositis, induration and fibrosis at 9-month follow up [16]. Following that, a multi-institutional phase II study examined SBRT (36Gy/ 6 fractions) with concurrent cetuximab in 60 patients and with a median follow up of 11.4 months, the 1-year overall survival was 46.5% and median progression-free survival was 7.1 months [17]. Eighteen patients had Grade 3 toxicities and one died from haemorrhage and malnutrition [17]. Similarly, another phase II trial delivered SBRT (40 – 44 Gy in 5 fractions) with concurrent cetuximab to 50 patients resulted in a 1-year overall survival of 40%, local progression-free survival of 60%, and disease progression-free survival of 33%. Grade 3 toxicity was low at 6% [18].

A volumetric and dose-response study performed in 96 patients who received SBRT showed that both total dose and tumor volume are independent predictors of treatment outcomes [19]. Patients with tumor volume of > 25cc had poorer 2-year loco regional control after SBRT than those with ≤ 25cc (18.6% *vs.* 67.4%, p = 0.007) [19]. Similarly those who had high SBRT dose (40 – 50 Gy) had better loco regional control rates than those who had lower doses (15 – 36 Gy) (2-year 57.8% *vs.* 31.7%, p = 0.02) [19]. Interestingly, there was no significant association between toxicity rates and total SBRT dose.

Potential SBRT toxicities

Although SBRT delivers high dose radiation to the tumor with a tight margin and SBRT treatment plans have a steep dose gradient, thereby reducing dose to adjacent/ surrounding normal tissues, the potential of severe toxicities should not be disregarded. As this subgroup of patients has had previous high dose irradiation to the head and neck region, even a small volume of reirradiation dose could potentially exceed normal tissue tolerance and significantly increase the risk of late toxicity. Some series have reported radiation-related late toxicities in up to 20% of re-irradiated patients in general [20].

Complications such as dysphagia, osteonecrosis of the mandible, and soft tissue necrosis can cause significant patient morbidity although there are medical management options for these complications. In some instances, these risks are acceptable to both patient and physician as there are further management should the complication arises and the morbidity from local tumor progression can be even more devastating. However, toxicities such as carotid blowout syndrome and neuropathy, while are rare irreversible, highly morbid and potentially fatal complications of re-irradiation.

Whilst peripheral nerves are relatively radio resistant, the spinal cord can be less forgiving. In a radiation-naïve patient, the tolerance dose for spinal cord is usually set at 45 – 50 Gy giving the patient an estimated 0.2% risk of spinal cord injury after receiving tolerance dose to the spinal cord [21]. It is important to note that the tolerance dose is a maximum point dose to the spinal cord rather than an average dose. In retreatment of patients with HNC, the tolerance dose of the cervical spinal cord will depend on time lapse since last radiation course, previous dose/ fractionation and total dose previously delivered to the cord. Generally it is accepted that if a patient has had more than 6 months since their last radiation course, the 'forgotten dose' will be 25 - 50% of received dose [22,23]. For example, if a patient received a maximum dose of 40 Gy to the spinal cord 6 months ago, their spinal cord would have recovered from 20Gy of the dose, allowing a delivery of 25Gy maximum to spinal cord in the re-irradiation plan. It should be noted that the majority of dose response studies in spinal cord were performed in animals and have been extrapolated to humans [24]. Nieder et al [25] performed a combined analysis of reirradiation doses to patients who developed radiation myelopathy and found that patients who received a total dose of ≥102Gy2 or retreatment within 2 months were at higher risk of radiation myelopathy. Hence, one should be careful to limit the dose to the spinal cord to as low as possible. For SBRT series, limiting the spinal cord dose to 8Gy/1 fraction, 12Gy/2 fractions, and 8Gy/5 fractions appear safe without an incident of radiation-related spinal cord myelopathy [15,17,26,27].

Carotid blowout syndrome is potentially a fatal complication of head and neck reirradiation. The dose tolerance of the carotid artery remained largely unknown. Cengiz et al [28] reported a rate of 17.8% of carotid blowout in a cohort of 46 patients who received SBRT to a median prescribed dose of 30Gy. In a large study of 381 patients who were re-irradiated using SBRT technique (median prescribed dose of 30Gy), Yamazaki et al [29] demonstrated that tumor skin invasion was an independent risk factor for subsequent carotid blowout syndrome. Skin invasion may reflect the aggressive behavior of the tumor, potentially invading underlying structures including the carotid artery, and/or weakening of arterial wall and surrounding normal tissue due to previous surgical intervention. The relationship of tumor to the carotid vessel should be taken into account as the risk of carotid blowout increased significantly when the tumor-vessel interface was >270 degrees. Yacizi et al [30] explored the option of second daily fractionation to reduce the risk of carotid blowout in patients who had SBRT. Seven (16%) patients who had daily treatment and 4 (12.5%) who had every other day treatment developed carotid blowout syndrome. On dosimetric analysis, there was no incidence of carotid blowout syndrome in those who received a maximum carotid artery dose of <34Gy or cumulative Biological Equivalent Dose (BED) of 198Gy [30].

Proton Therapy

The proton beam has the advantage of depositing majority of its energy/ dose at the intended tumor region (Bragg peak) with very low doses released in the beam path after the intended treatment area, thus sparing surrounding normal tissues. In recent years, proton therapy is increasingly considered as a reirradiation option for patients with HNC due to its inherent physical properties and ability to spare adjacent normal tissues, such as critical neural structures and oral cavity [31,32]. The decreased low dose scatter with protons may translate to less toxicity.

Being a relatively new technology, evidence for the use of proton therapy in reirradiation is very limited. Romesser et al [33] retreated a

cohort of 92 patients with proton therapy to a median dose of 60.6Gy and demonstrated that proton therapy was well tolerated with only 6 patients who had severe acute toxicities. The 1-year loco regional control and overall survival was 74.9% and 65.2%, respectively. With regards to late toxicity, 2 patients had mucocutaneous fistulas, 1 had chronic neck wound requiring hyperbaric oxygen treatment, 2 had pharyngeal soft tissue necrosis requiring surgical repair, and 1 had osteonecrosis of the mandible requiring surgery. Two patients had treatment-related deaths subsequent to haemorrhage or carotid blowout.

Phan et al [34] retrospectively reviewed 60 patients who received proton therapy re-irradiation at the MD Anderson Cancer Center. The median dose prescribed was 61.5Gy for adjuvant treatments and 66Gy for definitive treatments. The 2-year loco regional control and overall survival rates were 72.8% and 69%, respectively [34]. Eighteen (30%) patients had acute Grade 3 toxicity and 12 (20%) developed late Grade 3 toxicity, with a 2-year actuarial rate of late Grade 3 toxicity of 26% [34]. Patient's reirradiation to the pharyngeal mucosa tended to have higher toxicity. Two patients had treatment-related deaths: one had hemoptysis secondary to hyoid bone necrosis, and the other developed osteonecrosis of the clivus. Further analyses revealed that high dose re-treatment volume (clinical target volume 1, CTV1) of ≥ 50 cm^3 was correlated with increased risk of both acute and late Grade 3 toxicity [34].

The optimal dose/ fractionation of proton therapy is to be determined. Unlike photon beam which has no mass or charge, the proton is a heavy positively charged particle. When compared to photon, the proton beam has a higher linear energy transfer – energy deposited to the material traversed per unit distance. Therefore, in theory, proton has a higher relative biological effectiveness than photon therapy. This may account for the higher rates of late toxicities seen in proton series compared to the SBRT series as the proton deposited higher doses in its entry beam path to the tumor compared to SBRT. However, proton therapy has the advantage of being able to treat larger volumes compared to SBRT.

Conclusion

Both proton therapy and SBRT have the advantage of steep dose gradient, potentially reducing side effects and future treatment-related complications in patients with recurrent head and neck cancer. However, in this group of patients with limited life expectancy, the gain in local control and survival should be balanced with morbidity of treatment. Severe acute and late toxicity should be limited as much as possible. Further studies in proton therapy and SBRT are warranted to improve patient selection for appropriate and optimal radiation modality, particularly in the re-irradiation setting.

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Austin Head Neck Oncol - Volume 1 Issue 1 - 2017
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Citation: Ng S P and Phan J. Stereotactic Radiotherapy and Proton Therapy for Locally Recurrent Head and Neck Cancer. Austin Head Neck Oncol. 2017; 1(1): 1002.