

SBRT for recurrent head and neck cancer

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Abstract. The management of patients with recurrent head and neck cancers is complex. Concerns over toxicity with re-irradiation have limited its use in the clinical setting. Stereotactic Body Radiation Therapy (SBRT) has emerged as a highly conformal and precise type of radiotherapy and has the advantage of sparing normal tissue. Although SBRT is an attractive treatment modality, its use in the clinic is limited, given the technically challenging nature of the procedure. In this review, we attempt to provide a comprehensive overview of the role of re-irradiation in patients with recurrent head and neck cancers, with particular attention to the advent of SBRT and its use with systemic therapies such as cetuximab.

1. Introduction

SBRT is not only more convenient as it reduces the overall duration of treatment, but it also exploits alternate mechanisms of cell kill and tumor control over traditional fractionated radiotherapy, which might be highly relevant for recurrent disease. Results of SBRT have been highly encouraging in several malignancies including lung, spine, and liver tumors [1-6]. However, use of SBRT in head and neck cancers has been guarded because of several reasons: Head and neck has a complex anatomy with several radiosensitive structures. Tolerance to high doses per fraction of SBRT is still not known for these structures. Conventional fractionated radiation therapy as a primary modality in head neck cancers is quite successful in providing disease control and increasing the dose per fraction might result in higher late toxicities. Furthermore, several head neck cancers metastasize to neck lymph nodes, which have been traditionally treated electively. Including elective nodal radiation in an SBRT field can potentially increase the likelihood for toxicity.

2. Studies reporting SBRT for recurrent HN Cancers

The Role of SBRT in head and neck cancers is evolving with investigators studying to find the appropriate patients and dose fractionation schedule. There have been reports of doses ranging from 6 Gy to 9 Gy per fraction over 5-6 treatments (Table 1). These studies are not only aimed at providing palliation, but also long term LC. A report from Henry Ford (2009) used 30-38 Gy over 5-6 fractions and reported a RR of 77% and complete response (CR) rate of 31% [7]. Cegniz et al., demonstrated a RR of 58% with 27% of patients with stable disease (SD) that did not progress with SBRT [8].

2.1 Tumor Volume

Kodani et al. reported a 2-year OS of 50% and a relative response of 61% for 21 patients who were re-irradiated with head and neck tumors. The study also demonstrated that overall survival was better in patients with a smaller target volume. In this study, the median tumor volume irradiated was 11.6 cc



[9]. In another study, Vargo et al., analyzed 34 patients with pathologically proven recurrent, non-squamous cell cancers of the head and neck (NSCHNs) who underwent re-irradiation with SBRT to a median dose of 40 Gy in 5 fractions and found that local control was significantly improved for tumors <25 ml [10].

2.2 Toxicities

Siddiqui et al., treated 65 patients with SBRT for recurrent head and neck cancer and demonstrated that 4 patients developed grade 4 toxicities, all of whom were previously irradiated. These toxicities included 3 patients with fistulas and one with ulceration [7]. Vargo et al., reported acute and late grade 3 toxicities in 6% of patients respectively and there were no grade \geq 4 toxicities [10]. Kodani et al., reported that 6/21 patients who were previously irradiated developed grade IV late complications, with two dying from carotid blow out syndrome. In both of these patients, the site of disease recurrence was the cervical lymph nodes and the maximum dose to the carotid artery was 30.7 Gy and 31.7 Gy, respectively [9]. In another study by Cegniz et al., 46 patients were treated with a SBRT technique (median dose of 30 Gy) for recurrent unresectable and previously irradiated head and neck cancer. They reported a CBOS rate of 17% [8]. The authors also noted that carotid blow out occurred in patients whose tumor surrounded half or more of the carotid artery wall and when the arteries received a 100% of the prescribed re-irradiation dose.

3. Systemic therapy combined with SBRT for locally recurrent tumors

Heron et al., performed a single institution matched case control study of patients treated with SBRT alone (n=35) or SBRT with weekly cetuximab infusion during SBRT (n=35) (8). A complete response was obtained in 34.3% of patients who underwent SBRT alone compared to 45.7% in patients who underwent combined treatment with cetuximab. The 1 and 2 year LC rates were 53.8% and 33.6% for matched SBRT alone patients and 78.6% and 49.2% respectively for patients undergoing combined treatment (p=0.009). Of even more important significance, the 1- and 2 year OS rates were 52.7% and 21.1% for SBRT only and 66% and 53.5% in the combined arm (p=0.031). There were no grade 4 or 5 higher toxicities observed and no significant difference in grade 1-3 events between groups [11]. In a follow up study, 50 patients were enrolled and received concurrent cetuximab (400 mg/m² on day-7 and then 240 mg/m² on days 0 and +8) with SBRT to a dose of 40-44 Gy in 5 fractions on alternating days. The 1 year local PFS was 60%, loco-regional PDF was 37%, and distant PFS was 71%. The 1 year OS was 40% with a median OS of 10 months. The treatment was well tolerated with acute and late grade 3 toxicity observed in only 6% of patients [10]. Comet et al., performed a Phase I feasibility study for combined SBRT and cetuximab for locally recurrent HNC [12]. Overall, 40 patients were prospectively treated and 15 patients received concomitant cetuximab. Of the patient who received concomitant cetuximab, the overall response rate was 75% ,2 patients experienced a skin rash with cetuximab and 3 experienced grade 3 toxicities such as mucositis, dysphagia, induration and fibrosis. Lartigau and colleagues performed a Phase II trial of 56 patients with inoperable recurrent or new primary tumor in a previously irradiated area to a dose of 36 Gy in 6 fractions and concomitant cetuximab beginning with a test dose of 400 mg/m² the week before SBRT [13]. During the two weeks of SBRT and in the following 2 weeks, patents received a weekly injection of 250 mg/m². The one-year OS rate was 47.5%. The overall objective best response rate was 69.4%. A complete response was noted in 49% of patients, partial response in 20.4%, and stable disease in 22.5% of patients. Only 8.2% of patients had progressive disease. 18 patients had grade 3 toxicity and there was one toxic death from hemorrhage.

4. Planning/Physics Considerations

Proper patient selection is paramount for achieving good tumor control and minimizing toxicity in these patients. Factors that influence patient selection include tumor size or volume, location of the tumor, re-irradiation schedule/dose, and other co-morbid conditions such as diabetes mellitus, which may impair proper wound healing. Tumor delineation using co-registration with PET-CT or/and MRI

is mandatory. Several studies have found that PET/CT imaging changes treatment volumes in a significant portion of patients. Treatment volumes were smaller in patients after PET/CT was employed in several series [14, 15]. In tumors of base of skull, sinuses and nasopharynx, MRI based contours have a high likelihood of reducing target volumes. SBRT studies have found a correlation between tumor volume and local control with 25-30 cc appearing as a cut-off point. However, Rwigema et al, 2011 showed that dose escalation to 50 Gy/5 fractions for patients with GTV>25 cc resulted in comparable SBRT response rates and toxicities to those with GTV<25 cc [16]. Location of the tumor is also another critical component of patient selection. Tumor invading into rosenmueller's fossa or/and foramen lacerum, tumor involving more than half the circumference of the carotid and diffuse mucosal involvement/ulceration are all unfavorable characteristics which could cause higher rate of late toxicity. Another important consideration to minimize late toxicity such as carotid blow out syndrome (CBOS) is the radiation schedule. Yazici et al., demonstrated that every other day SBRT protocol compared to daily SBRT resulted in improved CBOS free median OS [17]. Furthermore, CBOS did not occur in any patients with a maximum carotid artery radiation dose <34 Gy. The planning process including treatment field design is also very important. Non-opposing non-coplanar beams are preferable and typically >10 beams of radiation should be used with roughly equal weighting. Because of uncertainties in beam commissioning resulting from electron disequilibrium within small beam apertures, a minimum field size of 3.6 cm is recommended except when the entire PTV is not covered in the beam. It is also important to remember to prescribe to the 80% isodose line, as the dose fall off from the prescription isodose to half the prescription dose typically occurs over the shortest distance if the dose is prescribed to the 80% isodose shell. RTOG SBRT protocol dose conformity guidelines for other sites can be adapted as general rules for target coverage and dose fall-off in H&N SBRT as well, while respecting organs-at-risk doses

5. Conclusions

In summary, SBRT represents an attractive treatment modality for recurrent, previously irradiated unresectable head and neck tumors. The studies reported so far have shown low toxicity rates, good overall response rates, with potential for improved local control. Larger multi-institutional studies are needed to further identify the ideal patient population and to explore appropriate dose-fractionation schedule.

6. References

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Table 1. Summary of Re-irradiation studies using SBRT

Study	N	Follow up (Months)	Median TV	Fractions	Total Dose (Range)	Response	Toxicity
Roh 2009	36	17.3	22.6 cc	3-5	18-40 (median 30)	RR:80% 2 yr OS 30.9%	Acute G3-50% ST necrosis: 8%
Siddiqui 2009	36	NA	15.5 cc	5-6	30-38 Gy (18-40)	CR:31% 1 yr OS: 60% MS: 6.7 M	Late Grade 4: 8%
Heron 2010	85	19.4	25 cc	1-5	35 Gy (15-44)	RR 68% 2 yr OS 16.1% 2 yr LC 30.7%	Late Grade 3: 4%
Cengiz 2011 (Turkey)	55	NA	NA	1-5	30 Gy (18-35)	RR 58% 1 yr OS 46% MS 10.5 Mo	Late G2 or greater: 13.3% CBO: 17.8%
Unger 2010	65	26	75 cc	5	30 Gy	2 yr OS 33% MST 11.5 M	Late Grade 4: 9%
Voynov 2007	22	19	19.1 cc	NA	24 (10-36)	2 yr OS: 22% 2 yr LC: 26% MST: 12 M	No grade 4 or 5 toxicity
Himei 2003 (Japan)	31	16.3	41.2 cc	1-6	30 Gy (15-40.3)	RR: 74%	Acute mucositis: 15%
Ogita 2009	58	NA	31.8 cc	3-8	31 Gy	2 yr OS: 29.2% MS 15.5 M	Ulcer: 414%
Kodani 2011 (Japan)	34	51 M	10 cc	3-8	30 Gy(19.5-42)	RR 61% 2 yr OS: 50%	Severe late: 28%