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Stereotactic Body Radiotherapy Treatment for Recurrent, Previously Irradiated Head and Neck Cancer

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Abstract

Purpose: Locally recurrent, previously irradiated primary head and neck tumors have historically been associated with poor outcomes. Stereotactic body radiation therapy has emerged as a feasible and promising treatment option for tumor recurrence, particularly in nonsurgical candidates. This study aimed to assess the associated outcomes of stereotactic body radiation therapy used in this setting. **Methods:** Retrospective analysis of a prospectively collected database of 25 patients treated with CyberKnife for unresectable, recurrent head and neck cancer in a previously irradiated field. The primary end points evaluated were rates of survival, tumor control, and treatment-related toxicities. **Results:** Median survival of the study population was 7.5 months (range, 1.5-47.0 months). Median survival of the 20 (80%) patients who were treated with curative purpose was 8.3 months. One-year overall survival rate for the entire population was 32%. The respective 1-year and 2-year survival rates for the curative subcohort were 40% and 20%, respectively. Local and locoregional failure occurred in 8 (32%) and 7 (28%) patients, respectively. Low severe acute (4%) and late (6%) treatment-related toxicity rates were observed. No grade 4 or 5 toxicities were observed. **Conclusion:** Stereotactic body radiation therapy is a viable treatment option for patients with unresectable, recurrent head and neck cancer. Significant tumor control rates are achievable with minimal severe toxicity. Although perhaps associated with patient selection and a heterogeneous sample, overall survival of stereotactic body radiation therapy outcomes appears unfavorable.

Keywords

head and neck cancer, recurrence, stereotactic body radiation therapy, CyberKnife

Abbreviations

CT, computed tomography; CTCAE, Common Terminology Criteria for Adverse Events; GTV, gross tumor volume; HNC, head and neck cancer; KPS, Karnofsky Performance Scale; MRI, magnetic resonance imaging; OS, overall survival; PET, positron emission tomography; PET-CT, positron emission tomography–computed tomography; PTV, planned tumor volume; QOL, quality of life; rHNC, recurrent head and neck cancer; SBRT, stereotactic body radiation therapy.

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Introduction

Locally recurrent head and neck cancer (rHNC) in a previously irradiated field remains a treatment dilemma associated with poor outcomes. Although salvage surgery continues to be the treatment modality of choice, various patient and tumor factors such as disease progression, proximity to vital structures, and comorbidities may render surgery infeasible.[1,2] In the setting of unresectable rHNC, radiation therapy is a treatment option. However, there can be considerable apprehension to treat recurrent tumors with traditional radiation techniques, since

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adverse effects may outweigh the benefits of tumor response. Langer *et al*[3] reported that nearly 85% of patients treated with irradiation on a RTOG trial experienced grade 3 or worse toxicities within the first 2 years of treatment, with 8% treatment-related deaths.

The need to improve outcomes with previously irradiated, unresectable rHNC has generated interest in the use of stereotactic body radiation therapy (SBRT). In contrast to conventional radiation, SBRT allows for more precise control of radiation dose distribution and shorter treatment durations (typically 5 fractions). Additionally, SBRT uses accelerated fractionation capable of delivering high doses of radiation per fraction. Despite the lower overall dose delivered over the course of a treatment, a beneficial biological equivalent dose delivered to the target tissue is achievable. Several series have reported low toxicity for SBRT in the treatment of rHNC.[4-10] Stereotactic body radiation therapy could potentially be an ideal treatment for rHNC since it is logistically easier for patients to go through this course of treatment, with lesser increase in toxicity compared to traditional radiation techniques.

Methods and Materials

This report is a retrospective analysis of a prospectively maintained SBRT database. This report constitutes the subset of patients treated for recurrent, previously radiated head and neck cancer (HNC). Written informed consent was obtained and subsequent analyses were performed according to Cooper University Hospital institutional review board–approved protocol 10-094EX. Twenty-five patients met eligibility criteria for this analysis.

The study population included 19 (76%) males and 6 (24%) females with a median age of 64 years (range, 43-85 years). All patients had received previous radiation therapy for the treatment of primary HNC in combination with, or without, surgical resection or chemotherapy. The median dose of previous radiotherapy treatment was 70 Gy (range, 30-110 Gy). Note, only 1 patient in this study had previous radiation of less than 60 Gy. Fourteen (56%) patients had previously undergone surgery, and 20 (80%) had completed prior chemotherapy regimens. Three (12%) of the patients had undergone previous reirradiation for a prior recurrence.

The sites of primary cancer were largely heterogeneous, with the most common being the base of tongue (36%), followed by the nasopharynx (12%) and parotid glands (12%). Local in-field recurrence was determined using a multiple modality diagnostic approach that included radiology imaging (computed tomography [CT] or magnetic resonance imaging [MRI] scan), metabolic imaging with positron emission tomography (PET) scan, and in nearly all cases, histopathologic confirmation with biopsy was performed. The most common site of recurrence was the primary tumor bed (88%), predominantly including tumors of the oropharynx (36%), oral cavity (12%), and nasopharynx (8%). The median gross tumor volume (GTV) was 31.75 cm^3 (range, 5.5-121.8 cm^3). Five of the patients had known metastatic disease prior to reirradiation SBRT (Table 1).

Table 1. Summary of Patient, Tumor, and Treatment Characteristics.

Characteristic	N = 25, Value (%)
Sex	
Male	19 (76)
Female	6 (24)
Age (years), median (range)	64 (43-85)
Primary radiotherapy	
Dose (Gy), median (range)	70 (30-110)
25th, 75th percentiles (Gy)	66, 70
Interval (months), median (range)	14 (3-72)
25th, 75th percentiles (months)	10, 50
Prior surgery	14 (56)
Prior chemotherapy	20 (80)
Previous reirradiation	3 (12)
Primary site	
Tongue	9 (36)
Nasopharynx	3 (12)
Parotid	3 (12)
Hypopharynx	2 (8)
Oropharynx	2 (8)
Tonsil	2 (8)
Epiglottis	1 (4)
Lacrimal gland	1 (4)
Larynx	1 (4)
Maxillary sinus	1 (4)
Primary tumor and lymph node stages	
T1-T2	6 (24)
T3-T4	14 (56)
Unknown	5 (20)
N0	8 (32)
N1-N2	11 (44)
N3	1 (4)
Unknown	5 (20)
Known metastatic disease	5 (20)
SBRT target site	
Primary	22 (88)
+ Regional lymph nodes	6 (24)
Concurrent chemotherapy	11 (44)
GTV (cm^3), median (range)	31.75 (5.5-121.8)
25th, 75th percentiles (cm^3)	16.9, 51.6
SBRT dose (Gy), median (range)	40 (24-44)
25th, 75th percentiles (Gy)	40, 40.5
Isodose line (%), median (range)	78 (57-92)
25th, 75th percentiles (%)	68, 83
Fraction size (Gy), median (range)	8 (5-8.8)
Duration (days), median (range)	12 (5-24)

Abbreviations: GTV, gross tumor volume; SBRT, stereotactic body radiotherapy.

Goals for SBRT reirradiation treatment included curative intent (20 patients, 80%) or palliative purposes (5 patients, 20%). Seven (28%) of the patients were dependent on pretreatment PEG tube usage. All cases were reviewed by an institutional multidisciplinary tumor board prior to reirradiation along with determination of nonresectability based on evaluation by a head and neck oncologic surgeon. Patients treated with SBRT as a planned boost for primary tumor radiotherapy were excluded from the study population.

All SBRT reirradiation treatments were completed using the CyberKnife system (Accuray, Sunnyvale, California) at MD

Anderson at Cooper from 2011 to 2016. A 2-phase treatment approach was employed, which included imaging, planning, and simulation and subsequent delivery of the radiation. During the simulation phase, patients were fitted and immobilized using personalized thermoplastic masks. Computed tomography, MRI, or positron emission tomography–computed tomography (PET-CT) imaging was obtained in 1.25-mm-thick slices. Gross tumor volume and nearby vital structures were contoured. At the discretion of the treating physician, a planned tumor volume (PTV) was added to the GTV depending on proximity to surrounding structures, tumor geometry, and prior treatment outcomes. In 13 (52%) cases, a PTV was calculated using 1 to 3 mm expansions from the measured GTV. Critical organs including brain and spinal cord were restricted to a maximum dose of 8 Gy. Additional planning and treatment characteristics including calculation of biologically effective doses, conformational index, and quality control were performed as reported previously.[5]

The median prescribed SBRT dose was 40 Gy (range, 24-44 Gy) delivered in a median of 5 fractions (range, 3-5) to a median isodose line of 78% (range, 57%-92%). All but one of the treatments were scheduled as 5 fractions on alternating days over a period of 10 to 14 days. The single exception to this regimen was a lower SBRT dose (24 Gy), delivered as 3 fractions on alternating days over 5 days. The median duration of treatment was 12 days (range, 5-24 days). Due to an unforeseen limitation in access to care, 1 patient received 5 fractions elapsed over 24 days. All other patients completed the treatment course without interruption.

Eleven (44%) of the patients received concurrent cetuximab chemotherapy treatments during the course of reirradiation. This consisted of 3 doses of cetuximab given 1 week before SBRT and then the next 2 weeks concurrent with SBRT. Concurrent chemotherapy was included in treatment depending on multiple tumor characteristics, patient factors, and at the discretion of the medical oncologist.

Follow-up patient interviews and physical examinations were conducted 1 month after completion of treatment. Positron emission tomography–computed tomography, CT, or MRI scans were conducted 1 to 3 months after treatment, then every subsequent 3 months if initial imaging results were unremarkable. If an area of concern was identified on posttreatment imaging, or a significant decline in patient health was indicated during physical examination, additional scans were ordered on an as-needed basis.

SPSS software was used to perform all statistical analysis (IBM SPSS Statistics Software version 23.0). Overall survival (OS) was defined as the interval from the start of SBRT reirradiation to the date of death from any cause or the last follow-up examination. Local failures were classified as recurrences within the targeted treatment field. Locoregional failures were defined as recurrences outside of the previously treated field within the head and neck region, while new metastasis outside of the head and neck were considered distant failures. All survival functions were estimated using the Kaplan-Meier method, with comparisons between groups made using log-rank tests. $P < .05$ using 95% confidence intervals was considered statistically significant. Patients lost to follow-up were censored accordingly during statistical analysis.

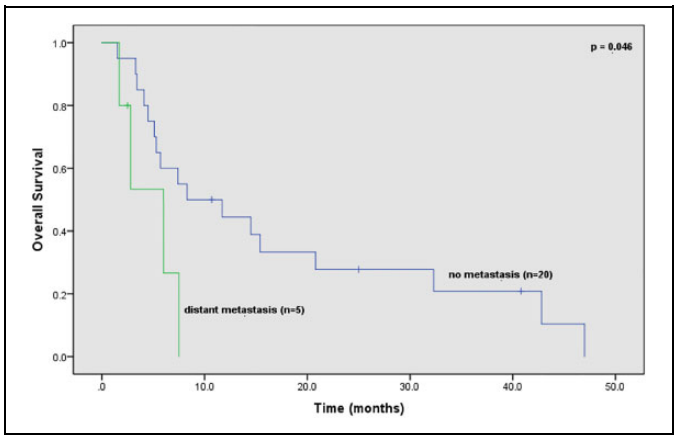

Figure 1. Overall survival correlated with the presence of distant metastatic disease prior to stereotactic body radiation therapy (SBRT).

Acute toxicities were defined as adverse effects resulting from SBRT reirradiation arising within 90 days from the start of treatment. Likewise, late toxicities were defined as sequelae arising after 90 days from the start of treatment. Toxicity grades were prospectively recorded and retrospectively reviewed by the authors of this study based upon physician follow-up notes and medical records. Toxicity grades were based upon various versions of the Common Terminology Criteria for Adverse Events (CTCAE).

Results and Analysis

Survival Analysis

The 1-year and 2-year OS for patients treated for curative purpose (n = 20) was 40% and 20%, respectively. The 1-year and 2-year OS for all patients was 32% and 16%, respectively. The median survival for the entire population was 7.5 months (range, 1.5-47.0 months). The median survival for patients with and without metastatic disease was 8.3 and 2.0 months, respectively ($P = .042$; Figure 1). Zero patients treated for palliative purpose (n = 5) survived longer than 6 months.

Multiple factors (interval time to disease recurrence from initial treatment, Karnofsky Performance Scale [KPS], presence of metastatic disease, volume of disease, use of PTV, use of concurrent chemotherapy with SBRT, SBRT dose, isodose line) were examined to determine any relation with OS rate. The only factor that appeared to correlate with the OS was the presence of distant metastatic disease at the time of reirradiation SBRT. The OS was significantly greater for patients without distant disease (Mdn = 8.3 months, 39% 1-year OS) than for those with known metastatic disease (Mdn = 2.0 months, 1-year OS 0%; Mann-Whitney $U = 20$, $P = .042$).

Zero patients experienced distant metastatic progression outside of the head and neck region during the posttreatment follow-up period. Local failure occurred in 8 (32%) patients,

Table 2. Summary of Acute and Late Treatment-Related Toxicities.

Toxicity Grade	Acute	Late[a]
Grade I	6 (24%)	–
Grade II	4 (16%)	–
Grade III	1 (4%)	1 (6%)
Total	11 (44%)	1 (6%)

[a]Late toxicity cohort (n = 18) excluded patients dead or lost to follow-up <3 months after treatment.

and median time to local failure was 5.8 months (range, 0.9-27.1 months). Locoregional failure occurred in 7 (28%) patients, and median time to failure was 8.5 months (range, 0.6-35.3 months). The same factors as the OS analysis (KPS, volume of disease, concurrent chemotherapy, etc) were examined to identify any relationship with rates of local and locoregional failures. No factors predicted for worse local or locoregional control.

Toxicity and Quality of Life Assessment

Eleven (44%) of the 25 patients experienced acute treatment-related toxicities; 10 (40%) of which were either grade 1 or grade 2 according to CTCAE. The most common acute grade 1 and grade 2 toxicities included mucositis and dysphagia (32%), as well as dermatitis (12%). Six (55%, n = 11) of the acute toxicity patients received SBRT treatments targeted to the base of the tongue or oropharynx, with resultant local mucositis and dysphagia. Three (12%, n = 25) patients developed a grade 1 skin rash that was thought to be attributed to the concurrent cetuximab treatments. Limited sample size restricted significance of univariate analysis assessing factors (SBRT target, concurrent chemo, etc) related to toxicity specifics. Only 1 (4%) patient, who received palliative SBRT targeting the supraglottis, developed an acute grade 3 toxicity: mucositis, transient dysphagia, and dysphasia which required hospitalization for treatment and speech therapy. In the subset of populations that experienced acute toxicities, the median interval between primary radiation exposure and reirradiation was 13 months. Comparatively, the median interval for the patients who did not develop any treatment-related sequelae was 17 months. This subanalysis did not reach statistical significance ($P = .34$).

Seven (28%) patients died or were lost to follow-up less than 3 months upon completion of treatment. Thus, these patients were excluded from the statistical analysis of late toxicities. Of the remaining 18 patients, only 1 (6%) developed a late toxicity: grade 3 radiation necrosis with associated pain and malodor that required surgical debridement for relief. After surgical debridement and several months of conservative management, this toxicity is resolved and the patient is currently disease- and toxicity-free. None of the patients in this study experienced grade 4 or grade 5 toxicities (Table 2).

The KPS scores were recorded pretreatment and posttreatment for available patients. The KPS was available on 22 (88%) patients. The median KPS for both pre- and posttreatment was 80. The KPS score remained the same for 15 patients, decreased in 3 patients, and improved in 2 patients.

Discussion

We found SBRT to be a safe and viable treatment option for unresectable, previously irradiated rHNC. There were no treatment-related deaths, and outcomes revealed low severe toxicity profiles. The rate of grade 3 toxicities in our study (8%) was similar to that of previously reported studies, with median SBRT reirradiation doses >35 Gy.[9-11] No patients experienced carotid blowout syndrome, an infrequent but well-documented late complication of reirradiation for HNCs.[12]

The rates of grade 1 and grade 2 toxicities are often underreported in published SBRT series, due to an increased focus on severe toxicities. Although the rate of grade 1 and grade 2 acute toxicity was significant within our study population (40%), this rate is comparable to that in the radiation oncology literature.[4,5,10,11] We found a trend toward less acute toxicity based on interval from initial radiation: patients with acute toxicity completed the initial radiation a median of 13 months from SBRT, while patients without acute toxicity completed a median of 17 months. Although the small sample size prevented statistically significant univariate and multivariate analysis results, our team hypothesizes that the interval between radiation exposures may have an influence on reirradiation-related toxicity. Although it has been proposed that the time interval between previous radiation and reirradiation is a significant predictor of tumor control rates and survival,[11,13,14] no previous study has identified the reirradiation interval with the incidence of treatment-related toxicities. Although this concept makes sense—more time between radiation exposures allows for fuller recovery from the initial treatment—the importance of further analysis is vastly significant. Such quantitative data may influence both patients' and physicians' decisions regarding options of care.

Our survival outcomes (OS: 8.3 months for patients treated with curative intent) were similar to other reports. University of Pittsburgh phase I[7] (dose escalation study) found a median OS of 6 months and a phase II[9] (single arm, SBRT plus cetuximab) study reported a median OS of 10 months. Siddiqui *et al*[15] report SBRT outcomes for patients with recurrent disease showing a median OS of 6.7 months, with 14% 2-year OS rate. Additional studies with similar patient populations have reported median OS of 11.8, 13.6, and 16.2 months.[10,16-19] Our overall 1-year survival rate (32%) is only marginally inferior to the reported rates in these studies; however, our 1-year and 2-year OS rate for the subpopulation treated for curative intent is comparable to the aforementioned reports (39% and 21%, respectively). Reports from Georgetown University Hospital[20,21] have demonstrated median OS of 12 to 17.3 months with associated 2-year survival rates 24% and 40%. However, the patients in this series were not excluded on the basis of surgical

candidacy, with 30% undergoing surgical treatment prior to reirradiation.

Local, locoregional, and distant tumor control rates in our study were similar to the other SBRT series. In a previous study, Wang *et al*[22] demonstrated that 61% of failures following salvage SBRT in this setting occurred within overlap/marginal regions of the GTV (overlap: 20%-75% of recurrence within GTV; marginal: 20% or less of recurrence within GTV and within 1 cm of GTV). In their study, margins were not utilized (GTV = PTV). Thus, the authors concluded that addition of 5 mm margins around the GTV may effectively reduce failures, albeit at the risk of increasing toxicities. Their study also showed that PET-CT treatment planning was associated with better tumor control rates following salvage reirradiation. Of interest, 52% of the treatment plans in our study utilized PTVs. Our analysis did not reveal any influence on local and locoregional tumor failures with the use of PTVs. However, inconsistent use of PET-CT planning and a small sample size may have prevented such associations from presenting as statistically significant. If a correlation exists between the area subjected to reirradiation and the incidence of local failures, significance is placed on the role of PET-CT planning prior to SBRT reirradiation.

After establishing SBRT as a viable treatment option, research focus must shift to compare safety and efficacy with other modern conventional radiation techniques. Although older reirradiation reports found significant toxicity along with marginal effectiveness,[3] modern studies have been conducted using IMRT. Multiple institutions have reported strong outcomes using IMRT for rHNC. MD Anderson reported on 78 recurrent, previously irradiated patients with HNC (27% of whom had salvage surgery) treated with IMRT and demonstrated a median OS of 27.6 months.[23] In a similar study design, Zwicker *et al*[24] reported a median OS of 17 months. Lee *et al*[25] reported a 2-year OS rate of 42%. In a multi-institution analysis, Ward *et al*[14] demonstrated that concurrent surgery, pretreatment feeding tube use, or tracheostomy usage has significant influence on resultant OS. Kong *et al*[26] reported a median OS and progression-free survival of 37 and 20.5 months, respectively, following salvage IMRT for recurrent nasopharyngeal cancer treated with definite IMRT as the sole primary treatment. However, 65% of these patients experienced grade 3 to 5 late toxicities, including a 35% cohort mortality from treatment-induced adverse effects. Although these IMRT studies have demonstrated improved 1- and 2-year OS rates, this technique has limitations within the context of rHNC. The reported severe toxicities in the IMRT reirradiation series,[2,23,24,27] ranging from 20% to 65%, are higher than that seen in SBRT studies. Furthermore, reirradiation with IMRT usually entails smaller fraction sizes (1-2 Gy/d) delivered over an extended course (6-8 weeks). Such logistics of treatment may not be feasible for all patients.

In the largest comparison to date, Vargo *et al*[28] demonstrated superior OS with IMRT versus SBRT reirradiation among a particular subset of patients: those with unresected tumors who received initial treatment >2 years prior or those who received initial treatment <2 years prior without the current use of a tracheostomy or feeding tube (2-year OS rate 39.1% for IMRT vs 18.6% for SBRT). However, smaller tumors (<25 cm^3) or pretreatment dependence of a feeding tube or tracheostomy nullified this superiority. Moreover, SBRT was associated with lesser rates of severe toxicities compared to IMRT. Interestingly, 80% of our study cohort would not meet the criteria for the IMRT superiority group, due to small tumor size, pretreatment PEG tube use, or interval time from initial surgery. These data, in conjunction with our report, further signify the importance of pretreatment patient selection. In agreeance with the authors of the study, CyberKnife may confer potential logistical and radiobiological advantages for patients of poorer prognosis and performance status.

Stereotactic body radiation therapy should also be compared to chemotherapy treatment alone. The EXTREME[29] study enrolled patients with recurrent and metastatic HNC and found a median OS of 10.1 months for the combination of cetuximab, platinum, and 5-fluorouracil. Around 80% of the study population experienced severe treatment-related adverse toxicities. Additionally, patients enrolled in this study were not limited to just those who had previous radiation exposure.

Future comparison of SBRT with emerging immunotherapy should be made, given the recent interest of pembrolizumab (anti-programmed death receptor 1 antibody) for the treatment of rHNC. The KEYNOTE-012 trial, and its expanded cohort,[30-32] yielded encouraging results with promising tumor control rates. These initial studies have demonstrated comparable toxicity profiles with the published SBRT series. As this body of literature continues to grow, the use of SBRT reirradiation in conjunction with pembrolizumab should be investigated.

Stereotactic body radiation therapy likely has a role in palliation of recurrent HNC. Our study found that KPS remained stable or improved in the majority of patients following SBRT. It must be acknowledged that KPS is not a robust measure of quality of life (QOL). However, other reports using patient-competed QOL surveys have shown that SBRT can maintain or improve QOL.[9,33] Another recent publication has reported the palliative benefit of 25 Gy in 5 fractions in HNC.[34] The authors note that this fractionation scheme was so well tolerated that higher doses may be used. Stereotactic body radiation therapy would certainly allow for safe dose escalation in the palliative setting.

Conclusion

It remains unclear how effective SBRT is as a definite, curative treatment option in the recurrent setting. Available data do not demonstrate improved survival rates compared to other treatment options (chemotherapy alone, IMRT). There are many inherent difficulties in comparing tumor response and survival, among nonsurgical salvage treatments for rHNC. For example, conventional reirradiation is very toxic and it is possible that patients offered such treatments are very robust; many of the patients reported in SBRT series may not have been offered reirradiation IMRT. In contrast, patients selected for SBRT

treatment may have favorable biases such as small tumor sizes. The only way to provide level 1 evidence regarding treatment options for previously irradiated, rHNC would be a randomized study (SBRT vs IMRT, or a 3-arm study using a chemotherapy-only arm).

This study certainly has biases similar to many of the other studies investigating recurrent HNC. This was a single-arm study, and there are selection biases involved as to which patients receive treatment compared to those who are not offered SBRT (and thus not available for analysis). We feel that this single-institution report is important in providing additional data regarding SBRT as a treatment option for recurrent HNC.

Declaration of Conflicting Interests

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