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The Impact of Tumor Volume and Radiotherapy Dose on Outcome in Previously Irradiated Recurrent Squamous Cell Carcinoma of the Head and Neck Treated With Stereotactic Body Radiation Therapy

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Abstract

Purpose—To assess the effect of stereotactic body radiotherapy (SBRT) dose and tumor volume on outcomes in patients with recurrent, previously irradiated squamous cell carcinoma of the head and neck.

Materials and Methods—A total of 96 patients with recurrent, previously irradiated squamous cell carcinoma of the head and neck were treated with SBRT using Cyberknife and Trilogy-intensity-modulated radiosurgery. Kaplan-Meier survival analyses were used to estimate locoregional control (LRC) and overall survival rates. Response was evaluated using positron emission tomography/computed tomography or computed tomography and detailed physical examination.

Results—The median follow-up for all patients was 14 months (2–39 months). The median dose of prior radiation was 68.4 Gy (32–170 Gy). Patients were divided into 4 SBRT dose groups: I (15–28 Gy/n = 29), II (30–36 Gy/n = 22), III (40 Gy/n = 18), and IV (44–50 Gy/n = 27). The median gross tumor volume (GTV) was 24.3 cm³ (2.5–162 cm³). For GTV ≤25 cm³ (n = 50), complete response rates were 27.8%/30%/45.5%/45.5%, and for GTV >25 cm³ (n = 46), complete response rates were 20%/25%/42.8%/50% for SBRT groups I–IV, respectively. The 1-/2-/3-year LRC rates for doses 40 to 50 Gy were 69.4%/57.8%/41.1%, respectively, whereas for 15 to 36 Gy, they were 51.9%/31.7%/15.9%, respectively (*P* = 0.02). The overall 1- and 2-year overall survival rates were 58.9% and 28.4%, respectively. Treatment was well tolerated with no grade 4/5 toxicities.

Conclusions—Dose escalation up to 50 Gy in 5 fractions is feasible with SBRT for recurrent head and neck squamous cell carcinoma. Higher SBRT doses were associated with significantly

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higher LRC rates. Large tumor volume required higher SBRT doses to achieve optimal response rates compared with smaller tumor volume.

Keywords

head and neck cancer; outcome; radiation dose; reirradiation; stereotactic body radiotherapy; tumor volume

Despite improvements in disease control and survival outcomes with modern advances in treatment of head and neck cancers,^{1,2} tumor recurrence remains a significant problem with approximately 15% to 50% locoregional recurrence rates.^{3–6} Surgical salvage remains the mainstay approach in the management of recurrent disease. Nonoperative approaches such as radiation therapy are alternatives to surgery when disease invades or surrounds major vessels in the head and neck or whenever the morbidity of surgical resection outweighs its benefits. When reirradiation is contemplated in this setting, treatment planning is frequently difficult because of the propensity for regional nodal spread and anatomic proximity to critical structures in the head and neck region, and requires integration of several factors such as extent of disease and overall patient performance status.

Few studies have reported data on the use of stereotactic radiosurgery in head and neck cancers due to limited clinical experience. Recent studies by Siddiqui et al,⁷ Roh et al,⁸ and Unger et al⁹ recently reported data in 21, 36, and 65 patients, respectively, with recurrent head and neck cancers of mixed histologies. The current study is unique in that it includes a larger number of patients all with recurrent squamous cell carcinoma of the head and neck (SCCHN). Reirradiation in the setting of prior high-dose radiation with 3-dimensional or intensity-modulated radiation therapy remains a challenge because of the proximity of nearby critical structures and makes stereotactic radiotherapy the ideal treatment of choice due to its highly precise delivery of large doses to the disease site while minimizing toxicities to normal tissues.

We have previously reported studies on the experience of our institution using this technique, first in 22 patients with recurrent nonmetastatic previously irradiated head and neck cancer treated with 10 to 25 Gy.¹⁰ Results of that study demonstrated the feasibility and safety of stereotactic body radiotherapy (SBRT) in these patients. The results of our prospective phase I dose escalation trial also supported these findings.¹¹ Encouraged by these results, we previously performed a larger retrospective review of our 5-year experience with recurrent previously irradiated SCCHN demonstrating the evolution of this salvage program using SBRT.¹² Results of this latter study showed improved locoregional control (LRC) with higher prescription dose while severe toxicities remained rare.¹²

In the current study, we sought to perform a thorough assessment of the relationship between radiation dose, volume, and treatment outcome. We performed a volumetric analysis for patients with recurrent previously irradiated SCCHN, who were treated with SBRT in a dose escalation program over several years. LRC has been shown to be dependent on tumor volume and prescription dose.^{13–15} However, dose response and volume response in SBRT for head and neck cancer have not been previously established. Therefore, we sought to establish such parameters for future clinical trials. Based on our previous results, we hypothesized that tumor volume was inversely correlated with LRC and increasing SBRT dose was directly correlated with locoregional tumor control probability, with larger tumor volume requiring higher prescription dose for LRC compared with smaller tumor volume.

METHODS AND MATERIALS

Study Design and Patient Selection

The study is a retrospective cohort in which patients included had recurrent, unresectable, previously irradiated SCCHN, who were treated using SBRT. All patients were treated at the University of Pittsburgh Cancer Institute and had signed a written informed consent for treatment. This study was approved by the institutional review board (IRB 0406113).

Retrospectively acquired data were de-identified according to the Health Insurance Portability and Accountability Act guidelines. All patients in this study were ≥ 18 years, had a Karnofsky performance of 50 or more, and were previously treated with standard therapies including surgery, chemotherapy, and external beam radiation or a combination thereof.

Radiosurgical techniques used in this program included Cyberknife System (Accuray Inc, Sunnyvale, CA) and Dynamic Tracking System (version 3.0) software, and Varian Trilogy Intensity-modulated radiosurgery (IMRS, Varian Medical Systems Inc, Palo Alto, CA). The Cyberknife-SRS has been described in our previous report¹⁰ and elsewhere.^{16–20} Trilogy-IMRS is implemented using a Varian stereotactic treatment planning system and Varian high resolution Millennium multileaf collimator. Varian on-board imaging and cone beam computed tomography (CT) are used to guide patients' setup for Trilogy-IMRS.

Patients excluded from this analysis included those treated with Cyberknife-SRS as a planned boost after definitive radiation therapy, patients who had not received prior irradiation, patients who did not complete prescribed treatment, and patients with nonsquamous cell histologies. Of 85 patients from our previous report,¹² 73 were included in this study, whereas the remaining 12 patients were excluded here as they had extended treatment courses secondary to treatment breaks because of various reasons. Biopsy of the recurrent lesion was not mandated if a sufficiently high clinical suspicion of recurrent tumor was established using other means such as positron emission tomography (PET)-CT, magnetic resonance imaging, or physical examination. Original pathology reports of all primary lesions were available for review. Human papilloma virus testing was not routinely performed in these patients. All patients had no chemotherapy or radiation therapy for at least 1 month before entry into the study, and underwent a head and neck physical examination within 4 weeks of entry into the study. Imaging studies used to assess the baseline extent of disease (ie, PET/CT scan) were performed within 4 weeks before receiving SBRT.

Treatment Planning and Delivery

The SBRT treatment involved 2 components: the development of the radiosurgical treatment plan and the delivery of the prescribed radiation dose. The CT scan of the region was acquired with 1.25-mm thick slices. The CT images were then reviewed by the treatment team (the head and neck surgeon, radiologist, and the radiation oncologist). Each patient also required a pretreatment [¹⁸F]-fluorodeoxyglucose PET scan to assess the metabolic activity of the recurrent disease. The use of [¹⁸F]-fluorodeoxyglucose PET/CT for radiation therapy planning has been described by our institution.²¹ Physicians used PET/CT to delineate the gross tumor volume (GTV), spinal cord, and other critical structures. A radiosurgical treatment plan was then developed based on tumor geometry, proximity to critical structures, and location. An illustrative case of SBRT treatment planning is shown in Figure 1. Quality assurance verification of the treatment plan was performed using phantom dose measurements by the radiation physicist. Lesions were located and tracked relative to skull osseous landmarks or optical array (Trilogy) with a 1-mm spatial accuracy.²²

The second phase of the treatment is the actual delivery of radiation. For treatment, the patients were set up on treatment table with an immobilization device. All patients were

fitted with an individualized thermoplastic facemask secured to a radiographically transparent headrest. During the treatment, near real-time digital x-ray images or cone-beam CT images were obtained for each patient to confirm and ensure the accuracy of the treatment positioning and target location. The patient was observed by closed circuit television during treatment.

The optimum dose and fractionation schedule of SBRT for recurrent SCCHN is currently under investigation. Consequently, we previously carried out a dose-escalation study to determine biologic activity, dose limiting toxicities, and maximally tolerated dose of SBRT. To evaluate the effect of radiation dose on LRC over a range of tumor volumes, patients were stratified into SBRT dose groups based on our previous protocol of dose escalation.¹¹ The dose limits used for the spinal cord were 8 Gy (1 fraction); 9 Gy for the brainstem; 20 Gy for the brain; 10 Gy for the retina, optic nerves, and chiasm; 6 Gy for the lens of the eye; 20 Gy for the carotid artery; and <20 Gy for the esophagus and larynx. These were selected based on the clinical experience of the radiation oncologist involved, as well as on appreciation of prior radiation doses and the likely contribution from SBRT on normal tissues. These organs were carefully outlined during the planning session if they were in sufficient proximity to the tumor. As most of these normal tissues are not considered to be arranged “in series” from a radiobiological standpoint, small portions were allowed to reach the maximum tolerance dose, and dose volume histograms were used to evaluate the acceptability of each plan; for tissues considered to be arranged in series (eg, spinal cord) the restrictions were applied rigidly. Each plan was evaluated to ensure that 95% of the target volumes were covered by the prescription isodose. After the plan was reviewed and approved jointly by the SBRT team, treatment was initiated on an outpatient basis. Treatment duration was between 30 and 120 minutes per fraction depending on the dose delivered per fraction and the number of treated nodes. In all patients, treatment fractions were administered every other day, usually 2 to 3 times per week.

Statistical Analysis

The following primary endpoints were assessed post-SBRT: treatment response rates, LRC, and overall survival (OS) rates, and toxicities. Kaplan-Meier survival analyses were used to estimate the LRC, and OS rates which were determined from the initiation of SBRT. A log-rank test was used to compare the difference in LRC, and OS rates between volume and dose groups, with a significance level at $P < 0.05$ (2-tailed). Multivariate Cox regression method was used to model predictors of outcome including patient, tumor, and treatment characteristics.

Patients were assessed for treatment response according to standard RECIST (Response Evaluation Criteria for Solid Tumors) criteria,²³ wherein tumor response was documented as complete response (CR), partial response (PR), stable disease, or progressive disease by the physician during follow-up visits after SBRT. All patients were initially seen for a 1-month follow-up visit after SBRT, and then for routine follow-up visits every 3 months, thereafter. Toxicities were graded using the National Cancer Institute Common Toxicity Criteria Events Scale, Version 3.0 (CTCAE v.3), and defined as acute if occurring within 90 days of treatment, or as late if documented at 90 or more days after treatment. To further assess the effects of tumor volume and dose parameters on LRC probability, MATLAB computing language (The MathWorks Inc, Natick, MA) was used to generate a 3-Dimensional model for LRC in response to changes in tumor volume and dose at a defined time interval. Pearson correlation coefficients were used to estimate the relationship between tumor volume and time to local progression (TTLP). SPSS software package version 17.0 was used for statistical computation (SPSS Inc, Chicago, IL).

RESULTS

Patient, Tumor, and Treatment Characteristics

Between January 2003 and October 2008, 96 patients (70 males, 26 females, mean age, 66.0 $\pm$ 12.2 years) with recurrent, previously-irradiated SCCHN, who were treated with Cyberknife (n = 85) and Trilogy-IMRS (n = 11) were included in the study. The median follow-up of all patients was 14 months (2–39 months), and was 23 months (6–39 months) for patients still alive at last follow-up (n = 42). In patients who remained alive with no documented disease progression at last follow up (n = 25), the median follow-up was 29 months (15–39 months). Patient, tumor, and treatment characteristics are summarized in Table 1. All patients were previously treated with full dose irradiation to the primary tumor, and in some cases, had received further irradiation with low- and high-dose rate brachytherapy, or intensity-modulated radiation therapy for their recurrent tumors. Many patients had received prior surgery (69%) and chemotherapy (58%).

A total of 92 patients received fractionated SBRT in 2 to 5 fractions, and 4 patients received single-dose SBRT. Among patients treated with fractionated SBRT, 87 patients were treated under our current salvage SBRT program with 20 to 50 Gy delivered in 5 fractions, and the remaining 5 patients were treated with 15 to 24 Gy in 2 to 4 fractions based on clinical, social, and dosimetric considerations. Among patients who received single dose SBRT, doses were 16 Gy (n = 3) and 18 Gy (n = 1). Patients were analyzed based on the following 4 SBRT dose groups: There were 29 patients (30.2%) in group I (15–28 Gy), 22 patients (22.9%) in group II (30–36 Gy), 18 patients (18.8%) in group III (40 Gy), and 27 patients (28.1%) in group IV (44–50 Gy). A total of 89 patients (92.7%) had PET/CT or CT performed at 1- to 3-month intervals after treatment, the remaining 7 (7.3%) were evaluated by detailed physical examination for treatment response. The overall median interval to failure from completion of prior radiation therapy was 16 months (4.6–423.1 months), and was not statistically different between the 4 dose groups ($P > 0.05$, data not shown).

The use of concurrent cetuximab with SBRT for recurrent SCCHN has been increasingly adopted over time at our institution based on improved outcomes in our clinical experience. A total of 39 (40.6%) patients received concurrent cetuximab with SBRT, and there was no significant difference in cetuximab use among the different SBRT dose groups: 12 (41.4%) patients in group I, 8 (36.4%) patients in group II, 8 (44.4%) patients in group III, and 11 (40.7%) patients in group IV ($P > 0.05$). All patients completed the treatment course without toxicity-related breaks.

Impact of SBRT Dose on LRC

On multivariate analysis, SBRT dose was significant predictor of LRC, wherein high dose predicted for improved LRC ($P = 0.02$, HR (Hazard Ratio) 0.7 [0.3–0.9]). The 1-, 2-, and 3-year LRC rates for high-dose group (40–50 Gy) were 69.4%, 57.8%, and 41.1%, respectively, whereas for the lower dose group (15–36 Gy), the 1-, 2-, and 3-year LRC rates were 51.9%, 31.7%, and 15.9%, respectively ($P = 0.02$, Fig. 2A).

The relationships between LRC and dose at all reference durations (ie, 1-,2-,3-year LRC rates) demonstrate a sigmoid pattern (Fig. 2B), where the LRC curve gradually rises from a near plateau (dose group I and II) followed by a significant steep rise to higher dose groups (III and IV). Overall comparison of dose groups I and II, as well as dose groups III and IV shows that they are statistically similar ($P = 0.064$ and $P = 0.096$, respectively). In contrast, the inflection point from group II to III is statistically significant ($P = 0.022$).

Impact of Tumor Volume on LRC

In addition to SBRT dose, tumor volume also predicted for improved LRC on multivariate analysis. Of 50 patients with GTV ≤ 25 cm³, 17 (34%) had locoregional progression during follow-up compared with 31 of 46 (67%) with GTV > 25 cm³ ($P = 0.001$, HR = 0.5 [0.2–0.8]). The 1- and 2-year LRC rates for tumor volume ≤ 25 cm³ were 72.6% and 67.4%, respectively, and superior to the 1- and 2-year LRC rates for larger tumors (> 25 cm³) at 48.2% and 18.6%, respectively ($P = 0.007$, Fig. 3A). There was no significant difference prescribed dose between both tumor volume groups ($P > 0.05$). Among those patients with initial response followed by disease local progression at last follow-up ($n = 39$), the median TTLP was 6.97 months. There was a significant inverse correlation between TTLP and tumor volume ($P < 0.001$, $R = -0.56$) (Fig. 3B).

Response Assessment

The prescribed doses were plotted against tumor volumes in this study to assess whether there was a selection bias in dose distribution. As shown in Figure 4A, the overall pattern shows a nearly even distribution of doses between GTV > 25 cm³ and GTV ≤ 25 cm³, which suggests that both dose and volume are independent predictors of LRC in this cohort, where patients were stratified into groups of GTV > 25 cm³ and GTV ≤ 25 cm³.

Among those patients with GTV ≤ 25 cm³ ($n = 50$), CR rates were 27.8%/30%/45.5%/45.5% for I to IV dose levels, respectively. For GTV > 25 cm³ ($n = 46$), CR rates were 20%/25%/42.8%/50% for I to IV dose levels, respectively. Figure 4B shows the relationship of CR rates with tumor volume and dose, where mean doses of I to IV dose levels are plotted against response rates. To isolate the effect of tumor volume on CR, dose and number of patients were controlled between the 2 volume groups (Table 2). Also, there was no significant difference in degree of tumor differentiation between the different volume and dose groups ($P > 0.05$, data not shown). A summary of overall treatment responses by dose category is shown in Table 3. The rates of CRs and PRs (CR + PR) were 83.3%/85.1% in the high dose groups, III and IV, respectively, and superior to those in the lower dose groups of 59.1%/62% in I and II, respectively ($P = 0.015$).

Survival Assessment

The median OS was 15 months. The overall 1- and 2-year OS rates were 58.9% and 28.4%, respectively (Fig. 5). Among those with no distant metastasis before SBRT ($n = 81$), high SBRT dose (40–50 Gy) showed a borderline significant trend toward improved OS compared with low dose (15–36 Gy) ($P = 0.059$, HR 0.74 [0.37–0.11]). Small tumor volume (GTV ≤ 25 cm³) did not significantly predict for improved OS ($P = 0.08$; HR: 0.8 [0.20–0.12]).

Post-SBRT Salvage Treatment and Patterns of Failure

During follow-up, 58 patients had chemotherapy for disease progression, of which 10 patients died of distant metastatic failure alone. The remaining patients had local ($n = 9$), regional ($n = 19$), locoregional ($n = 7$), local-distant ($n = 4$), and regional-distant ($n = 9$) disease progression. There was no significant difference in chemotherapy use and patterns of failure between both tumor volume and dose groups ($P > 0.05$). In GTV > 25 cm³, 31 (53.4%) patients received chemotherapy for disease progression that included carboplatin/paclitaxel ($n = 13$), docetaxel ($n = 6$), methotrexate ($n = 7$), pemetrexed/bevacizumab ($n = 3$), and cisplatin ($n = 2$). In GTV ≤ 25 cm³, 27 (46.6%) patients received chemotherapy that included carboplatin/etoposide ($n = 2$), carboplatin/paclitaxel ($n = 8$), cisplatin/5-fluorouracil/gefitinib ($n = 4$), docetaxel ($n = 3$), methotrexate ($n = 9$), and pemetrexed/bevacizumab ($n = 1$). We examined chemotherapy use by patients in the different SBRT dose groups after

SBRT failure. Results revealed that patients who were treated with post-SBRT chemotherapy were 22 (75.9%) patients in group I, 15 (68.2%) patients in group II, 10 (55.5%) patients in group III, and 11 (40.7%) patients in group IV ($P > 0.05$).

Complications

Treatment was well-tolerated with no grade 4 or 5 treatment-related toxicities. Most toxicities were mild (grade 1 and 2), such as mucositis, dysgeusia, dysphagia, pain, xerostomia, hoarseness, and edema that resolved with conservative management. The overall incidence of acute toxicities was 37.5% grade 1, 17.7% grade 2, and 5.2% grade 3. Acute grade 3 toxicities were dysgeusia ($n = 1$), dysphagia ($n = 2$), and xerostomia ($n = 2$). For long-term complications, there were 16.7% grade 1, 9.3% grade 2, and 3.1% grade 3. Late grade 3 complications were dysphagia (2 patients at 19 months and 27 months) and fibrosis (1 patient at 32 months). There was no relationship between rates of toxicities and prescribed SBRT doses.

DISCUSSION

Reirradiation of patients with recurrent head and neck carcinoma remains clinically challenging, due to the increased risk of toxicities and mortality, tumor radio-resistance, and less-defined anatomic location. Equally as troublesome is the poor survival in these patients with a median survival of 6.5 to 14 months using conventional radiation salvage techniques.^{24–27} Improvements in LRC can potentially curb tumor recurrence and thereby lead to enhancement in patient survival, as more than 50% of patients who die of the disease have locoregional disease as the only site of failure.^{28–32} Clear understanding of the relationship between LRC, dose and tumor volume has been lacking, but remains crucial as it offers valuable insight in planning effective nonsurgical salvage strategies in these patients.

In the current study and our previously reported experience in previously irradiated recurrent SCCHN, we chose hypofractionated SBRT for the following reasons: (1) to minimize the reirradiated volume through tumor locoregionalization with stereotaxy, (2) to decrease the tumor margins by utilizing PET/CT and stereotaxy, (3) to utilize high dose fraction per treatment session, in order to increase the biologically effective dose necessary in patients who failed previous treatment with high-dose radiotherapy, (4) to minimize toxicity by minimizing the treatment volume through precise delivery of radiation to disease site while sparing normal tissues, and (5) to increase patient compliance by decreasing overall treatment time.

Results of the current study indicate that both tumor volume and prescription dose are both significant predictors of treatment outcomes in previously irradiated, recurrent SCCHN treated with SBRT. To our knowledge, this is the largest study to report a volumetric and dose analysis of LRC and treatment response in recurrent, previously irradiated SCCHN using SBRT. A previous study by Doweck et al³³ showed that tumor volume predicted outcomes for advanced head and neck cancer treated with targeted primary chemoradiotherapy. Many prior studies have shown that radiation dose is a prognostic factor in reirradiation of head and neck tumors using conventional techniques,^{24,34,35} however, associated with prolonged treatment courses and significant grade 3 or 4 toxicities.^{36–38}

Unlike recent SBRT studies by Roh et al⁸ and Unger et al,⁹ both of whom reported grade 4 late complications at 8.6% and 9%, respectively, our study shows that treatment was well-tolerated with no severe treatment-related long-term toxicities. The lack of severe late toxicities in our experience may be explained by the differences in our protocol wherein we administer SBRT fractions every other day allowing healing time between treatment

fractions, in addition to utilization of PET/CT for target volume definition that allowed us to minimize treatment volumes whereas in these studies, patients were treated on consecutive days. Another study by Siddiqui et al that used a similar protocol as ours reported a 7% late grade 4 toxicities in patients who developed fistulas, but these were confirmed to be secondary to tumor regression or recurrence rather than radionecrosis.⁷

Our data demonstrated that a tumor volume of 25 cm³ was a critical breakpoint for separating favorable and unfavorable tumor LRC. The number of patients requiring chemotherapy for disease progression following SBRT between the 2 tumor volume groups is not statistically different; however, patients with GTV ≤25 cm³ had a significantly longer median duration of locoregional tumor control compared with GTV >25 cm³ (32 vs. 12 months; Fig. 3A). The interaction between dose and tumor volume is illustrated in Figure 6, which shows estimated LRC probabilities, computed using polynomial functions identified as best fit models for sigmoid response patterns observed between LRC and both tumor volume and dose. For instance, one can observe that LRC probabilities for tumor volume less than 25 cm³ at doses greater than 35 Gy are more than 70% at 1-year.

We have previously shown that SBRT dose up to 44 Gy was associated with minimal toxicities in a phase I dose escalation trial.¹¹ LRC rates in this study are similar to other reported series.^{39–41} In this study, we showed that dose escalation up to 50 Gy in 5 fractions is associated with higher LRC rates. Patients receiving 40 Gy or higher had significantly higher LRC compared with those receiving 36 Gy or lower. It appears that the actuarial LRC curves continue to separate further demonstrating that the higher dose groups achieve more sustainable LRC over time compared with the lower dose groups (Fig. 2A). There were more patients in lower dose groups requiring chemotherapy after SBRT failure, because lower dose groups were associated with a higher incidence of disease progression, but the difference was not statistically significant.

In the present study, OS rates were similar to previously published studies in SBRT.^{7,8,39} High SBRT dose was associated with a trend toward improved OS. Recent data from our institution suggests that improvements in LRC with SBRT through dose escalation may be further boosted by concurrent cetuximab with SBRT in these patients leading to significant improvements in patient survival.⁴²

Tumor volume was an important indicator of optimum dose required to achieve optimal response rates (Fig. 4B). For tumor volume greater than 25 cm³, no optimum dose was identified as evidenced by a continued dose response relationship where CR rates in the 44–50 Gy group exceeded those observed in the 40 Gy group. Conversely for tumor size ≤25 cm³, radiation doses of 44–50 Gy did not increase the rate of CRs observed in the 40 Gy dose category as shown by plateau phase. The overall clinical benefit (CR + PR + Stable Disease) was similar among different dose groups: 89.6%, 81.8%, 94.4%, and 92.5% from the lowest dose to the highest dose, respectively (Table 3).

CONCLUSIONS

Based on our results, higher SBRT doses were associated with significantly higher LRC rates. Larger tumor volume required higher SBRT doses to achieve maximum CR rates compared with lower tumor volume. Tumor volume had significant inverse relationship with TTLP. We developed a 3-dimensional model that may guide clinicians in predicting the likelihood of locoregional disease control at a prescribed SBRT dose for a given tumor volume, and may serve as a nomogram for selecting prescription dose in recurrent SCCHN. Dose escalation up to 50 Gy in 5 fractions is feasible with SBRT for recurrent SCCHN.

Finally, results of this study may form the basis for stratifying patient in future clinical trials in SBRT for recurrent SCCHN.

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FIGURE 1.

A representative stereotactic body radiotherapy (SBRT) plan of a patient with recurrent oral squamous cell carcinoma.

FIGURE 2.

Impact of SBRT dose on locoregional control. A, Actuarial curves of freedom from locoregional progression in different dose groups. B, Impact of radiation dose on 1-, 2-, 3-year locoregional tumor control. Mean doses of groups I to IV are plotted against locoregional control rates.

FIGURE 3.

Impact of tumor volume on locoregional control. A, Actuarial curves of freedom from locoregional progression with tumor size. B, Relationship between tumor size and time to locoregional progression in patients with initial treatment response followed by disease progression.

FIGURE 4.

Response assessment. A, The distribution of prescription dose with gross tumor volume. The dotted line shows the median tumor volume (24.3 cm³) of the study cohort. B, The relationship of complete response rates with tumor volume and dose.

FIGURE 5.
Overall survival of all patients (n = 96) after completion of SBRT.

FIGURE 6. Probability of locoregional control at 1 year versus tumor volume and SBRT dose. The graded color bar indicates increments in locoregional control from lowest (blue) values to highest (red values).

TABLE 1**Patient, Tumor, and Treatment Characteristics**

Characteristic	No. (%)
Age (yr)	
Median	67
Range	39–88
Gender	
Male	70 (73)
Female	26 (27)
Sites treated with SBRT	
Larynx	13 (13.5)
Hypopharynx and neck	23 (24)
Oral cavity	26 (27.1)
Nasopharynx	7 (7.3)
Oropharynx	8 (8.3)
Base of skull	5 (5.2)
Parotid	4 (4.2)
Sinuses	5 (5.2)
Outer ear	2 (2.1)
Orbit	2 (2.1)
Other	1 (1)
Tumor volume (cm ³)	
Median	24.3
Range	2.5–162
Total radiation dose prior to CK-SRS site (Gy)	
Median	68.4
Range	32–170.7
SBRT dose (Gy)	
Median	35
Range	15–50
Fractionated SBRT	92 (95.8)
Fraction size, median (range), Gy	8 (4–10)
Single dose SBRT	4 (4.2)
Treatment duration (elapsed days)	
Median	10
Range	1–16

SBRT indicates stereotactic body radiotherapy; CK-SRS, Cyberknife-SRS.

TABLE 2

SBRT Dose and Complete Response (CR) Rates With Tumor Volume

$\leq 25 \text{ cm}^3$			$> 25 \text{ cm}^3$		
Dose (Gy)*	N†	CR	Dose (Gy)*	N†	CR
22.2 ± 4.61	18 (62.1%)	5 (27.8%)	22.6 ± 3.94	11 (37.9%)	2 (18.2%)
33.3 ± 2.06	10 (45.5%)	3 (30%)	34.1 ± 1.61	12 (54.5%)	3 (25%)
40.0 ± 0	11 (61.1%)	5 (45.5%)	40.0 ± 0	7 (38.9%)	3 (42.8%)
44.0 ± 0	11 (40.7%)	5 (45.5%)	44.7 ± 1.99	16 (59.3%)	8 (50%)

There is no significant difference in dose (mean ± SD) ($P > 0.05$)* and number of patients ($P > 0.05$)†, between both tumor volume groups.

SBRT† indicates stereotactic body radiotherapy.

TABLE 3

Summary of Overall Treatment Responses in Different Dose Groups

Dose Group (Gy)	Mean Dose (Gy)	N	Treatment Response—No (%)		
			Complete	Partial	Stable
I: 15–28	22.4	29	7 (24.1)	11 (37.9)	8 (27.6)
II: 30–36	33.7	22	6 (27.3)	7 (31.8)	5 (22.7)
III: 40	40	18	8 (44.4)	7 (38.9)	2 (11.1)
IV: 44–50	44.4	27	13 (48.1)	10 (37.0)	2 (7.4)
Total		96	34 (35.4)	35 (36.4)	17 (17.7)