Hypofractionated Stereotactic Radiotherapy Using CyberKnife as a Boost Treatment for Head and Neck Cancer, a Multi-institutional Survey: Impact of Planning Target Volume

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Abstract. *Aim: To evaluate the role of hypofractionated stereotactic radiotherapy (hSRT) as a boost treatment for head and neck cancer. Patients and Methods: We conducted a multi-institutional retrospective review for the outcome of boost irradiation using CyberKnife for head and neck cancer patients from the charts of four Institutes. Twenty-five patients were treated with hSRT boost for primary site with a median follow-up of 28 months. Treatment sites were 11 nasopharynx, 7 oropharynx, one hypopharynx, 3 nasal cavity or paranasal sinus and three oral cancers. All patients underwent preceding conventional radiotherapy of 35 to 72 Gy (median, 50 Gy) in 1.2- to 2Gy-fractions. The dose and fractionation scheme of the Cyberknife SRT boost was individualized and the prescribed dose ranged from 12 Gy to 35 Gy in 1 to 5 fractions (median, 15 Gy in 3 fractions). Results: There were 18 complete responses, 6 partial responses and one progressive disease, resulting in 96% (24/25) response rate. Local control (LC) rates at 2- and 5-years were 89% and 71%, respectively. Progression-free survival (PFS) and overall survival (OS) at 2- and 5-years were 70%/ 83% and 70%/ 70%, respectively. Planning target volume (PTV) at boost treatment planning and initial response were predisposing factors for PFS and OS. Patients with PTV ≤20 cm^3 showed better PFS (92%) and OS (100%) than those with a PTV > 20 cm^3 (PFS, 61% and OS, 47%). Good initial response predicts better outcome in LC, PFS and OS. Conclusion: The results of the present study showed potential benefits of the CyberKnife hSRT boost. Smaller PTV and good initial response predict good outcome.*

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External-beam radiotherapy with or without concurrent chemotherapy is generally considered a standard treatment method for head and neck cancer (1). However, close proximity of several critical organs, such as optic pathways, brain stem and spinal cord, sometimes limit high-dose delivery from conventional radiotherapy techniques. Recently, development of the image-guided stereotactic radiotherapy devices make it possible to deliver highly conformal radiotherapy for head and neck cancers, as is the case in central nervous system tumors (2, 3). The CyberKnife system was specifically developed to perform frameless stereotactic radiosurgery for intracranial lesions and the technique can now be applied to deliver conformal doses of radiation to tumors throughout the entire body including the head and neck region (2, 3). Although the effects of normal tissue sparing can theoretically allow the use of hypofractionation, necessity of therapeutic and prophylactic nodal irradiation make it difficult to use large dose per fractionation for relatively large target volume in the head and neck region. Thus, at first, hypofractionated stereotactic radiotherapy (hSRT) is mainly used for salvage treatment of locally-recurrent tumors (4). It has been

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generally accepted that a dose–response relationship exists between local tumor control and radiation dose in head and neck cancer, especially for nasopharyngeal cancer (5, 6). Therefore hSRT is a suitable option for boost treatment but few studies have investigated feasibility and clinical outcome (7-10) including CyberKnife (5, 8). Since we have employed the CyberKnife system for a boost treatment for tumors in the head and neck area, we thus reviewed those outcomes as a multi-institutional survey because of the scarce number of patient in each institution.

Patients and Methods

Patients and radiotherapy techniques. Records of patients who treated with CyberKnife hSRT (Accuray, Sunnyvale, CA, USA) at four hospitals (Soseikai General Hospital, Osaka University Hospital, Fujimoto Hayasuzu Hospital, Okayama Kyokuto Hospital) during 2000 and 2010 were reviewed for inclusion into the study. Patients who received hSRT as a planned boost for primary lesion after external radiotherapy were included. They received boost therapy with Cyberknife mainly due to unfavorable condition such as tumors in close proximity to serial organs and/or their comorbidities. Initial radiotherapy was delivered by a conventional technique using a linear accelerator (Linac) and boost hSRT was performed using the CyberKnife systems. Patient included 16 males and 9 females, with age ranged from 18 to 83 years (median, 65 years). Treatment sites were 11 nasopharynx, 7 oropharynx, one hypopharynx, 3 nasal cavity or paranasal sinus (one nasal, one ethmoid sinus and one maxillary sinus) and three oral cancers. All, but three, tumors were histologically confirmed as squamous cell carcinoma. One adenoid cystic carcinoma in nasal cavity, one primitive neuroectodermal tumor in ethmoid and one lymphoepithelioma in nasopharynx were also included. Table I shows the patients' characteristics. The T, N category was identified using the Union for International Cancer Control (UICC) tumor node metastasis (TNM) system, sixth edition (11). All patients underwent preceding conventional radiotherapy of 35 to 72 Gy (median, 50 Gy) in 1.2-Gy (twice a day) to 2-Gy fractions. The dose and fractionation scheme of the Cyberknife SRT boost was individualized and the prescribed dose ranged from 12 Gy to 35 Gy in 1 to 5 fractions (median, 15 Gy in 3 fractions). Involved node was also irradiated until 60 Gy or more by conventional fractionation. The total prescribed dose was summed using the Equivalent dose in 2 Gy fraction formula $EQD2Gy=n\times d\times(\alpha/\beta+d)/(\alpha/\beta+2)$. Basically, chemotherapy were administered in T3< or N2< cases during initial conventional radiotherapy. Cisplatin (*i.e.*, 70-80 mg/m^2/3 weeks) or 5-fluorouracil (5-FU) therapy (*i.e.*, 5-FU at 250 mg/m^2 and cisplatin at 5 mg/m^2 for the initial 3 three weeks) were used. However, some cases did not receive chemotherapy because of their comorbidity or patients will.

Statistical analysis. All statistical analyses were performed using the Stat-view 5.0 statistical software (SAS Institute, Inc., Cary, NC, USA). The percentage values were analyzed using the χ^2 test and means were compared using the Student's *t*-test for normally distributed data and the Mann-Whitney *U*-test for skewed data. Survival data were estimated by the Kaplan–Meier method and examined for significance using the log rank test. Cut-off value was set at average or median value of each variable if otherwise stated. All analyses used the conventional $p<0.05$ level of significance.

Table I. *Patients' characteristics*.

Variable		N
Age (years)	Median (range)	63 (18-83)
Gender	Male	16
	Female	7
Primary site	Nasopharyngeal cancer	11
	Oropharyngeal cancer	7
	Hypopharyngeal cancer	1
	Oral cancer	3
	Nasal and paranasal sinus	3
T category	1	2
	2	8
	3	5
	4	8
	Not available	1
N category	0	15
	1	2
	2	6
	3b	1
	Not available	1
PTV	cm^3	12.8 (1-81)
Initial effect	Complete response	18
	Partial response	6
	Progressive disease	1

PTV, Planning target volume.

Results

Median follow-up time for surviving patients was 28 months (range=7-128 months) after hSRT. There are 18 complete responses, 6 partial responses and one progressive disease, resulted in 96% (24/25) response rate. A 63-year-old male with oropharyngeal cancer showed progressive disease even after 40 Gy in 20 fractions of external-beam radiotherapy combined with a boost of 22 Gy in 3 fractions by CyberKnife. He choked and died 9 months after radiotherapy, although tumor was stable up to that time point. Local control (LC) at 2- and 5-years were 89% and 71%, respectively (Figure 1). Progression-free (PFS) and overall survival (OS) at 2- and 5-years were 70% (83%) and 70% (70%), respectively (Figure 1). No patients showed lymph node recurrence without local failure. Univariate analysis revealed that initial response and planning target volume (PTV) were significant prognostic factors for progression free survival and overall survival (Table II). Patients with a PTV ≤20 cm^3 showed better PFS (92%) and OS (100%) than patients with a PTV >20 cm^3 (61% and 47%, respectively) (Figure 2). Good initial response correlated to better outcome in LC, PFS and OS (Table II).

For toxicity, fistula was seen in two patients. One patient (T4N1 upper gum cancer) showed fistula between nasal cavity and oral cavity with simultaneous recurrent tumor and another patient (T3N0 nasal adenoid cystic cancer) showed

Table II. *Analysis of prognostic factors after CyberKnife boost therapy.*

			At 2 years					
Variable	Strata	N	LC	*p*-Value	PFS	*p*-Value	OS	*p*-Value
Age, years	65 or more	12	83%	0.779	68%	0.75	92%	0.41
	<65	13	92%		75%		74%	
Gender	Male	16	87%	0.87	75%	0.88	73%	0.098
	Female	9	80%		64%		100%	
T Category	-T3	18	87%	0.28	77%	0.24	89%	0.41
	T4	7	83%		48%		64%	
N category	0	19	87%		73%	0.73	72%	NA
	1-	6	100%		44%		100%	
Location	Nasopharynx	11	89%	0.38	80%	NA	89%	0.38
	Oropharynx	7	57%		71%		71%	
	Hypopharynx	1	100%		100%		67%	
	Oral	3	100%		33%		67%	
	Nasal and paranasal cavity	3	50%		50%		100%	
PTV volume	≤20 cm^3	13	100%	0.1	92%	0.027	100%	0.015
	20 cm^3<	11	81%		47%		61%	
Total prescribed dose	≤80Gy	13	100%	0.23	84%	0.22	92%	0.63
(EQD2Gy:α/β=10)	80Gy<	12	71%		58%		75%	
Tumor response	Complete response	18	100%	<0.0001	83%	<0.0001	100%	0.0037
	Partial resonse	6	40%		33%		44%	
	Progressive disease	1	0%		0%		0%	

LC, Local control; PFS, progression free survival; OS, overall survival, EQD2Gy, Equivalent dose in 2 Gy fractions.

fistula into the oral cavity with necrosis after re-treatment for recurrent tumor. These toxicities occurred with and were considered owned to concurrent recurrent tumors. No toxicity more than grade 3. Grade 2 reactions included 3 mild ulcerations, one bleeding and one hearing loss.

Discussion

Because of the vicinity of the tumor to neighboring critical structures (*e.g.*, brainstem and optic apparatus), dose-escalation with conventional external-beam radiation therapy (EBRT) and/or brachytherapy is limited by the radiation tolerance of the adjacent normal tissues. Recently, the use of intensity-modulated radiotherapy (IMRT), which allows for higher tumor dose delivery, while sparing the surrounding normal tissues, resulted in excellent LC and acceptable toxicity rates at selected institutions, suggesting that dose escalation is feasible with accurate tumor targeting (5). Stereotactic radiosurgery has been used for many years as an effective treatment for intracranial tumors. The dose distribution provided by radiosurgery for large or advanced tumors is more homogeneous and thereby can spare more normal tissues than brachytherapy or EBRT (5). Lee *et al*. reported an excellent LC, 100% at 3 years, with acceptable late toxicities in 45 patients with nasopharyngeal cancer who received boost radiotherapy; out of those, 12 patients were treated using the

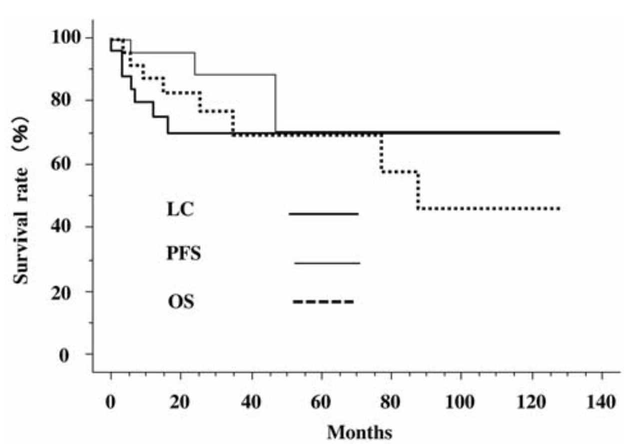

Figure 1. *Local control (LC), progression-free survival (PFS) and overall survival (OS) rates for all patients. The thick line depicts LC rate, thin line depicts PFSrate and dotted line depicts OS rate.*

CyberKnife with a median dose of 12 Gy delivered in a single fraction after a median total dose of 66 Gy by conventional radiotherapy, with an interval of 4-8 weeks.

Al-Mamgani *et al*. reported boost treatment outcome for oropharyngeal cancers (12) by means of CuberKnife hSRT (3-times 5.5 Gy, prescribed to the 80% isodose line), after 46 Gy of IMRT to the primary tumor and neck (when

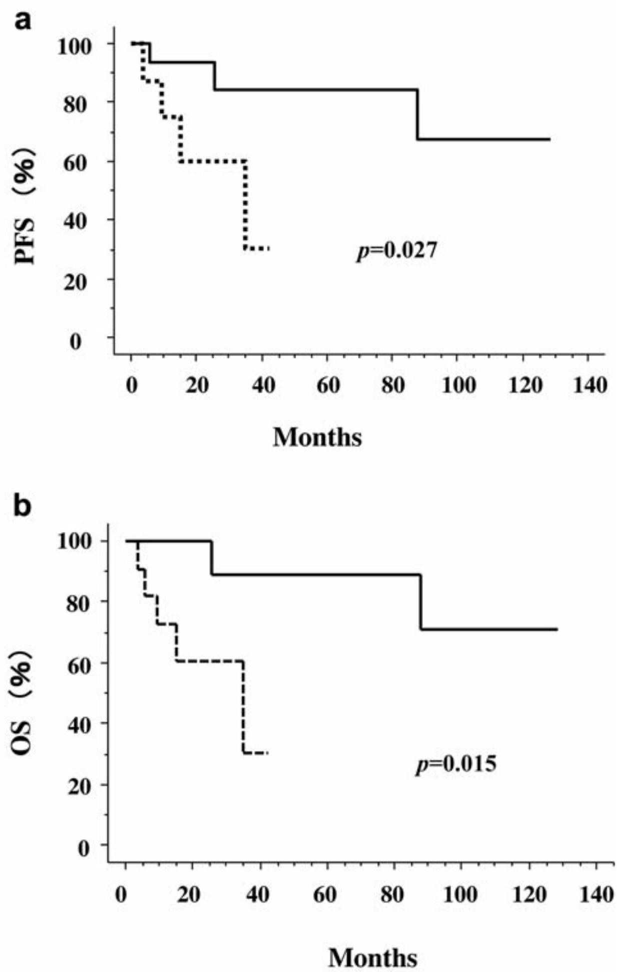

Figure 2. *Progression-free survival (PFS) and overall survival (OS) rates according to planning target volume (PTV). Patients with PTV ≤20 cm³ (thick line) showed better PFS rate (92%) and OS rate (100%) than patients with PTV >20 cm³ (dotted line) (61%, p=0.027 and 47% p=0.015, respectively).*

indicated). Between 2005 and 2010, 51 patients with Stage I-IV oropharyngeal cancer received boosts. After a median follow-up of 18 months (range, 6-65 months), the 2-year actuarial rates of LC, PFS and OS were 86%, 80% and 82%, respectively, and the 3-year rates were 70%, 66% and 54%, respectively. Furthermore, the authors of this work accumulated experience in 102 T1-2 oropharyngeal carcinoma patients. The 3-year actuarial incidence of LC was 97%. The figures for PFS and OS were 92% and 81%, respectively (13). The incidence of tube feeding were 17% and 20%, respectively. The figures for grade >2 late dysphasia were 11% and 8% and for xerostomia were 16% and 12%, respectively. These were fairly good outcomes and concurred to our data.

It is interesting and plausible that PTV could be identified as a prognostic factor for PFS and OS. Initial tumor volume is a well-known determinant of prognosis after radiotherapy (14). Tumor volume during radiotherapy reflected tumor response to initial radiotherapy and was also a good indicator for treatment outcome (15). It is also natural that initial response correlated to outcome. Patients with better tumor initial response could enjoy longer survival. Complete response (CR) cases seemed to show smaller PTV (20.3±25 cm^3) than partial response (PR) cases (30.7±14.6 cm^3cc) or progressive disease (PD) cases (33.4 cm^3, not significant).

This study had several limitations. First, we analyzed a small patient group from heterogenic disease sites with a short follow-up period. Therefore, it is difficult to determine appropriate schedules for CyberKnife boost treatment. Second, timing, species and dosage of chemotherapy were heterogeneous and thus difficult to analyze. Finally, lymph node status is an important predisposing factor, however, it is difficult to address this issue because we only focused on local boost therapy.

In conclusion, our results showed potential benefits of the CyberKnife SRT boost. Smaller PTV and good initial response predict good outcome after CyberKnife boost treatment.

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