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Comparison of Re-irradiation Outcomes for Charged Particle Radiotherapy and Robotic Stereotactic Radiotherapy Using CyberKnife for Recurrent Head and Neck Cancers: A Multi-institutional Matched-cohort Analysis

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Abstract. *Aim: To compare survival outcomes for charged particle radiotherapy (CP) and stereotactic body radiotherapy using CyberKnife (CK) in patients who had undergone re-irradiation for head and neck cancers. Patients and Methods: We conducted a retrospective multi-institutional matched-cohort analysis on 25 patients treated with CP and 25 matched patients treated with CK according to three prognostic factors (nasopharyngeal cancer or not, interval between initial radiotherapy and re-irradiation, and planning target volume). Results: CP was used more often to treat non-squamous cell cancer ((non-SCC): 52% vs. 0%) with a higher prescribed dose (median=57.6 Gy(RBE)/16 fractions) than CK (32 Gy/5 fractions). The local control rate (LC) for patients treated with CP was 71.2% at 1 year and that for patients treated with CK was 63.8% (p=0.24). The 1-year overall survival (OS) rates were 67.1% for CP and 36.3% for CK (p=0.0002), respectively. Non-SCC patients showed better OS rates at 1 year than SCC patients. In the SCC sub-group analysis, the 1-year LC, OS rates were 65%, 58.3% in the CP group and 64%, 36.3% in the CK group (p=0.81, p=0.02), respectively. A total of 16 patients (32%) experienced grade 3 or worse toxicities (24% in CK and 40% in CP, p=0.36), including six grade 5 toxicities. Conclusion: CP produced higher survival rates than CK, treated more non-SCC patients and used a higher prescribed dose. On the other hand, severe toxicities occurred in both groups, which, however, require further investigation.*

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Recent progress in the treatment of head and neck cancers, particularly advances in treatment modalities and chemotherapy, has enabled patients to survive for more than 5 years (1). However, in-field recurrence is one of the major obstacles to a cure (1-3). As only 20-30% of patients are candidates for salvage surgery (3, 4), chemotherapy is still the mainstay treatment for patients after locoregional failure with a median survival time of 6-10 months. Re-irradiation has emerged as a potentially curative therapy with the advent of modern radiotherapy techniques, such as intensity-modulated radiotherapy and stereotactic body radiotherapy (SBRT) (5). CyberKnife (CK) is a nearly real-time image-guided SBRT system suitable for precise dose delivery over short treatment periods. Several groups have investigated treatment with CK, including ours, and have demonstrated reduced acute toxicity due to short treatment periods and limited irradiation fields (6-9).

Charged particle radiotherapy (CP) treatments, such as proton and carbon ion radiotherapy, have a greater energy deposition than photon beams, delivering maximum dose at

precise depth, generating the Bragg peak. Compared with conformal radiotherapy, CP, thus, creates an inherently three-dimensional conformal dose distribution without exposing the surrounding normal tissue to extra doses (10). Although CP has been available in the clinical setting for decades, it is difficult to compare the outcomes of photon and CP because of heterogeneity of institutions and the lack of prospective comparison studies. Therefore, the aim of this study was to compare the survival outcomes for patients treated with CP and CK using a matched-pair method. Previously, we have found three important prognostic factors; the primary site (nasopharynx or not), planning target volume (PTV) and treatment interval are all important prognostic factors for survival after re-irradiation for recurrent head and neck cancers (11) and, therefore, we conducted a 1:1 case matched-cohort study using those three factors with data from multi-institutional charts to compare CP and CK outcomes and assess the influence of the factors listed above.

Patients and Methods

We included patients with recurrent head and neck tumors treated at the Soseikai General, Fujimoto Hayasuzu, Okayama Kyokuto, Osaka University Hospitals and Hyogo Ion Beam Medical Center (HIBMC) between 2000 and 2010. All recurrences occurred in an area previously irradiated with ≥40 Gy. The charged particle beam dose is reported in Gy (relative biological effectiveness (RBE)), which is the physical dose multiplied by RBE of the protons or carbon ions. We excluded patients who underwent re-irradiation as a planned boost after conventional external radiotherapy and those with other disease sites outside the re-irradiation area. The first course of radiotherapy was delivered by either X-ray therapy or charged particle therapy with either a curative intent or delivery of postoperative radiotherapy. A total of 25 patients were treated with CP and we chose 25 case-matched CK patient pairs according to primary site (nasopharynx or not), interval between initial radiotherapy and re-irradiation (≤30 months or >30 months) and PTV (≤40 cm^3 or >40 cm^3) from 107 patients treated with CK (11). The median age of patients was 59 years (range=19-88), including 36 males and 14 females. The most common primary site was the nasal or paranasal sinus. Cut-off values of each variable were applied from a previous study (11). The patients had a follow-up of at least 5 months (for survivor) and the median follow-up period was 8 (range=0.4-54.5) months.

CK re-irradiation was performed using the CK system. Patients were treated with a median dose of 32 Gy (range=25-39) in a median of five fractions (range=3-8) prescribed as D90, D95 or a marginal dose. D90 and D95 doses were defined by a minimum dose covering 90% and 95%, respectively, of PTV. The marginal dose was defined as the percentage (100%=maximum dose) of an isodose curve covering PTV. The gross tumor volume (GTV) was defined as the visible tumor in the imaging studies. No additional margin was added for clinical target volume (CTV=GTV). Determination of PTV was made by physicians in each institution (PTV=CTV + 0-3 mm). The most frequently used doses were 30 Gy in five fractions (n=5), 35 Gy in five fractions (n=4), 37 Gy in 8 fractions (n=3), 30 Gy in 8 fractions (n=2) and 32 Gy in five fractions Gy (n=2). No patient underwent concurrent chemotherapy during treatment.

Details of the CP protocol at HIBMC have been described elsewhere (10, 12-14). In brief, after a custom-made thermoplastic cast was used to immobilize each patient in the supine position with an adequate head angle, 1 mm computed tomography (CT) slices and 1-3 mm magnetic resonance imaging (MRI) slices were obtained. Re-irradiation treatments were planned on a CT-based three-dimensional treatment planning system (FOCUS-M CMS, St. Louis, MO, USA and Mitsubishi Electric, Tokyo, Japan) until April 2008 and Xio-M (FOCUS-M CMS and Mitsubishi Electric) from May 2008. The target volumes and organs at risk were delineated on the CT–MRI fusion images. CTV was generally defined as GTV plus a 5 mm basic margin. PTV was defined as CTV plus a setup margin of 3 mm. CP was delivered daily (five doses per week) to the isodose encompassing PTV.

Toxicity was evaluated using the National Cancer Institute Common Toxicity Criteria scale version 3.0. The biologically equivalent dose was calculated as the equivalent of 2 Gy fractions (EQD2) using a linear-quadratic model, where $\alpha/\beta=10$ for tumors and $\alpha/\beta=3$ for organs at risk. EQD2 was calculated by (prescribed dose × (α/β + dose per fraction))/(α/β + 2).

Biological effects of CP at HIBMC were evaluated *in vitro* and *in vivo* where the RBE values for proton and carbon ion irradiation were determined to be 1.1 and 2-3.7 (depending on the depth in the spread-out Bragg peaks), respectively (15). In this article, however, all doses are reported in Gy to avoid confusion.

Statistical analysis. All statistical analyses were performed using Stat-view 5.0 statistical software (SAS Institute, Inc., Cary, NC, USA). Percentages were analyzed using the χ^2 test and values were compared using the Mann-Whitney *U*-text. The durations of survival were calculated from the first day of reirradiation. Actuarial survival curves were generated using the Kaplan-Meier method and comparisons were made using the log-rank test. Cox's proportional hazard model was used for the multivariate analysis (variables $p<0.1$ in univariate analysis were inserted). All analyses used the $p<0.05$ level of significance unless otherwise indicated.

Results

Patients' and disease characteristics of patients treated with CP and CK are listed in Table I. CP was used to treat more non-squamous cell cancer (non-SCC) patients (52%) than CK (0%) with higher prescribed doses of 57.6 Gy(RBE) (range=43.2-70.2) in 16 fractions (range=12-30) (EQD2=65.2 (range=48.9-74.2) Gy(RBE)) than 32 Gy (range=25–39) in five fractions (3-8 fractions) (EQD2=41.9 (range=30.0-74.7) Gy), respectively. The local control rates for patients treated with CP and CK at 1 year were 71.2% (95% confidence interval (CI)=51.4%-91.0%) and 57.7% (CI=37.4-78.0%), respectively (p=024) (Figure 1a). The 1-year overall survival (OS) rates were 67.1% (CI=48.3%-85.9%) (MST=24.4 months) in the CP group and 36.3% (CI=16.4%-56.3%) (MST=6.6 months) in the CK group (p=0.0002) (Figure 1b). Univariate analysis revealed that the modality (CP better than CK), histology (non-SCC better

Table I. *Characteristics and treatment factors of patients.*

Variables	Strata	Charged particle (CP) n=25	(%)	CyberKnife (CK) n=25	(%)	*p*-Value
		No. or Median (range)		No. or Median (range)		
Age		55 (19-82)		61 (42-88)		0,0424
Gender	Female	10	(40%)	4	(16%)	NS
	Male	15	(60%)	21	(84%)	
Primary site	Nasopharynx	3	(12%)	3	(12%)	#NS
	Other	22	(88%)	22	(88%)	
	Oral	2	(9%)	4	(9%)	
	Oro-hypopharynx	0	(0%)	9	(20%)	
	Salivary gland	3	(13%)	0	(0%)	
	Nasal and paranasal sinus	15	(65%)	9	(20%)	
	External ear, lacrimal gland	2	(9%)	0	(0%)	
Interval from initial radiotherapy	≤30 months	19	(76%)	19	(76%)	#NS
	30 months <	6	(24%)	6	(24%)	
Histology	Squamous cell carcinoma	12	(48%)	25	(100%)	**<0.001**
	Other	13	(52%)	0	(0%)	
	Melanoma	3	(20%)	0	(0%)	
	Adenoid cystic ca.	7	(47%)	0	(0%)	
	Undif ca., Alveolar rhabdomyosarcoma, Adeno ca.	3	(20%)	0	(0%)	
Planning target volume	≤40 cm^3	4	(16%)	4	(16%)	#NS
	< 40 cm^3	21	(84%)	21	(84%)	
Surgical history	(–)	16	(64%)	12	(48%)	NS
	(+)	9	(36%)	13	(52%)	
Prescribed dose (Gy(RBE) and Gy)		57.6 (43.2-70.2)		32 (25-39)		**<0.0001**
Number of fractions		16 (12-30)		5 (3-8)		
EQD2 (Gy or Gy(RBE) (α/β=10))		65.2 (48.9-74.2)		41.9 (30.0-74.7)		**<0.0001**
Prescribed previous dose (Gy(RBE) or Gy)		64 (30-74.3)		60 (40-116)		NS
Previous number of fractions		30 (5-26)		30 (20-57)		
*Cumulative EQD 2 Gy (Gy(RBE) or Gy) (α/β=10))		131 (90-142)		100 (66-151)		**<0.0001**

EQD2, biological effective dose in 2 Gy fraction; *summation of previous radiotherapy and re-irradiation; #adjusted variables. Bold values indicate statistical significance.

than SCC) and higher prescribed doses (better than lower prescribed dose) were the significant predisposing factors for OS (Table II). Non-SCC patients showed an OS outcome of 75.2% (CI=50.6-99.8%, MST=36.8 months) at 1 year, which was better than the 42.6% (CI=25.7-59.4%, MST=7.4 months) of the SCC patients (p=0.003) (Figure 2). No factor remained in the multivariate analysis as a statistically significant predictor for OS.

SCC patients. A subgroup analysis was undertaken for SCC patients. There were no statistically significant differences in gender, primary site, PTV and treatment interval between CP (n=12) and CK groups (n=25). The CP group received higher prescribed doses (median=57.6 Gy (range=43.2-70.2)) than the CK group (median=32 Gy (range=25-39)). The local control rate for patients treated with CK and CP at 1 year was 63.8% (CI=43.1-84.4%) and 71.2% (CI=51.4%-91.0%), respectively, (not significant (NS), p=0.81) (Figure 3a). The 1-year OS rates were 58.3% (CI=48.3%-85.9%) in the CP group and 36.3% (16.4%-56.3%) in the CK group (p=0.02) (Figure 3b).

Toxicity. A total of 16 patients (32%) presented with grade 3 or worse toxicities (24% of patients treated with CK and 40% of patients treated with CP; NS), including six grade 5 toxicities. There were five incidences of bleeding, resulting in four deaths (grade 5) (Table III). Two fistulas, four skin or soft tissue and/or bone necrosis (with or without infection), two ulcerations (with or without pain), two nerve palsies, as well as two visual disturbances were observed. In patients with previous surgical history, 41% (9/22)

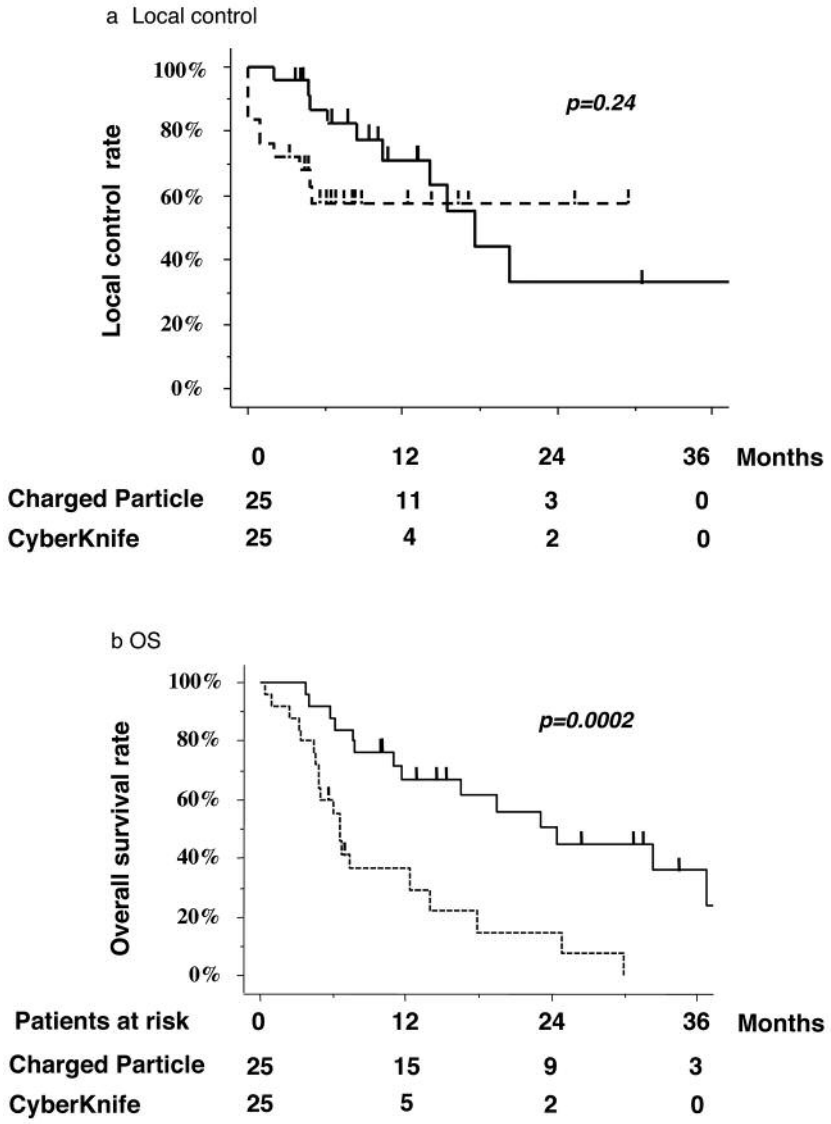

Figure 1. *Local control rate and overall survival rate for charged particle radiotherapy (CP) and CyberKnife (CK). a) Local control rate. b) Overall survival rate. The thick line depicts CP and the thin line depicts CK. SBRT, Stereotactic body radiotherapy.*

Table II. *Results of uniivariate analysis according to overall survival after re-irradiation.*

		Overall survival		
Variable	Strata	Hazard ratio	95% confidence interval	*p*-Value
Modality	CK *vs*. CP	3.783	1.798-7.960	**0.0005**
Gender	Male *vs*. Female	0.753	0.347-1.635	0.473
Age		1.003	0.978-1.029	0.8227
Histology	SCC *vs*. non-SCC	0.255	0.096-0.679	**0.0062**
Prescribed dose (EQD2) (Gy)		0.952	0.927-0.977	**0.0002**
Previous surgical intervention	yes *vs*. no	0.9	0.446-1.816	0.768

EQD2, Biologically equivalent dose calculated into equivalent 2-Gy fractions $\alpha/\beta=10$. Bold values indicate statistical significance.

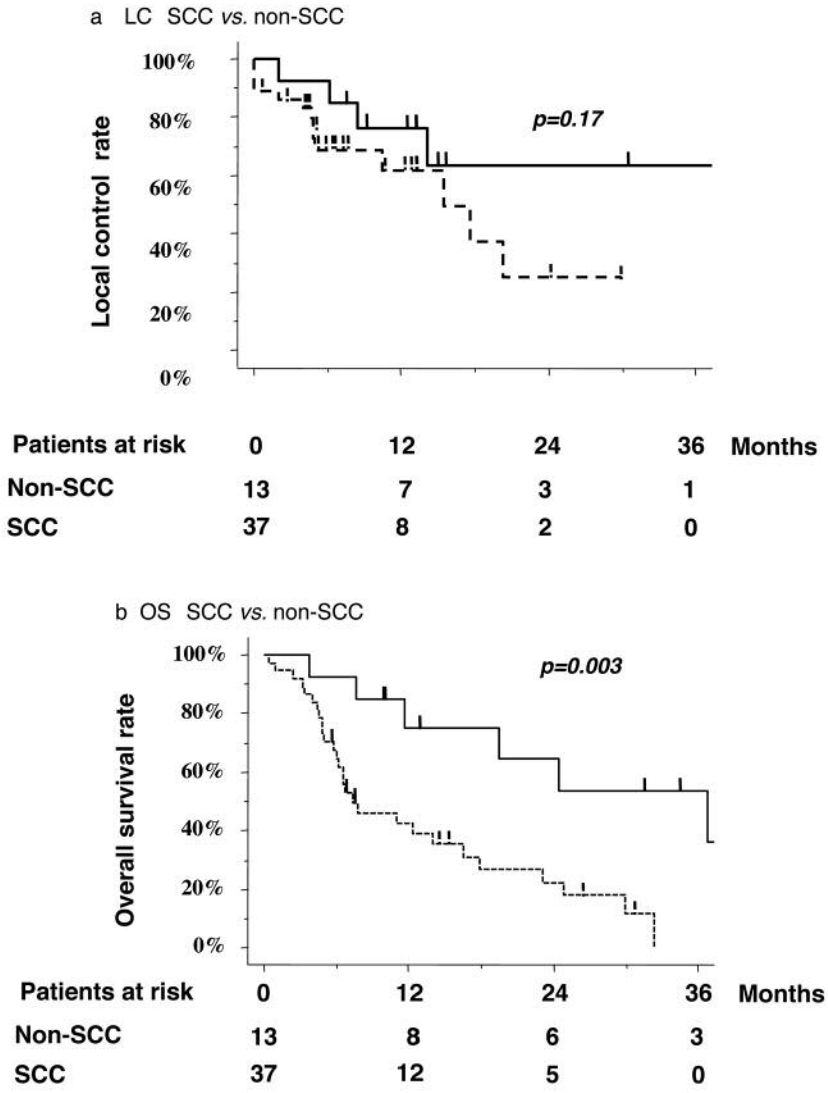

Figure 2. *Local control rate and overall survival rate for squamous cell carcinoma (SCC) and others (non-SCC). a) Local control rate. b) Overall survival rate. The thick line depicts non-SCC patients and the thin line depicts SCC patients.*

Table III. *Toxicity of re-irradiation.*

Grade	CyberKnife (CK)			Charged particle (CP)			*p*-Value
0-2	19	(76%)		15	(60%)		NS (0.36)
3	4	(16%)	Ulceration and bleeding (1) Soft tissue necrosis (1) Fistula (2)	3	(12%)	Nerve palsy (2) Ulceration and pain (1)	
4	0	(0%)		3	(12%)	Visual disturbance (2) Soft tissue necrosis (1)	
5	2	(8%)	Bleeding (2)	4	(16%)	Bleeding (2) Skin/bone necrosis and infection (1) Soft tissue necrosis and infection (1)	

NS, Not significant.

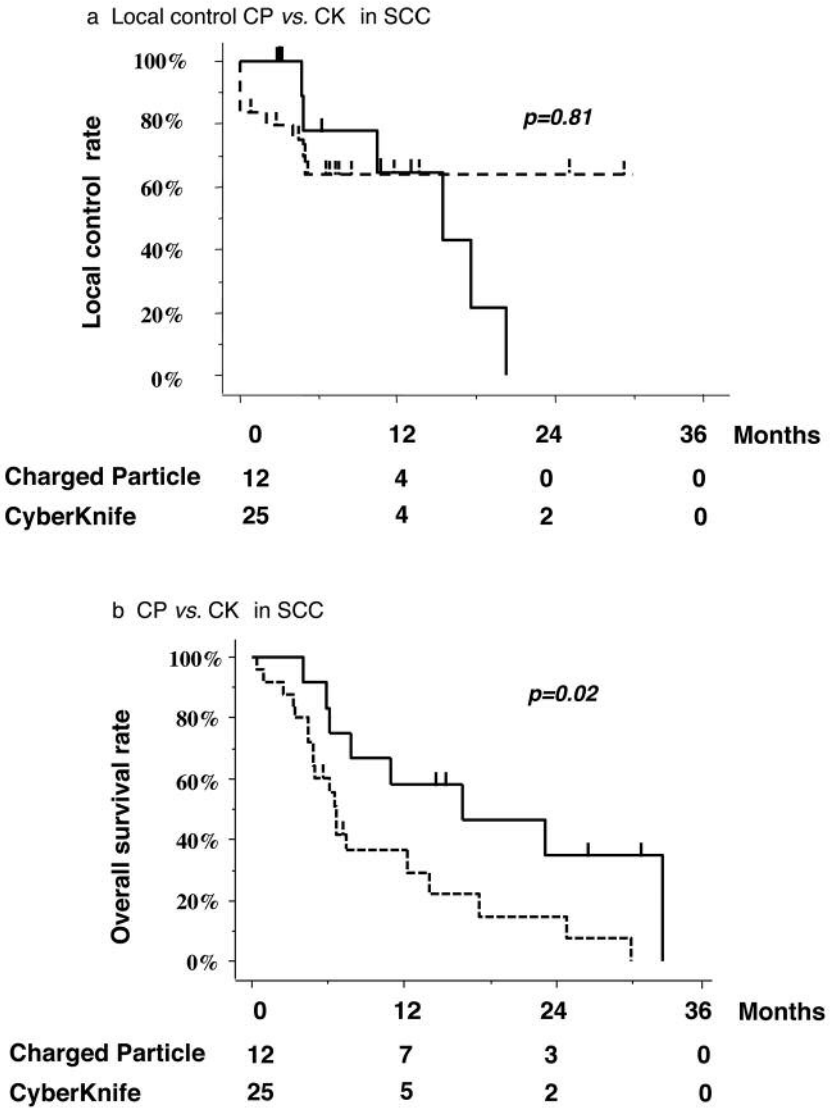

Figure 3. *Local control rate and overall survival rate for charged particle radiotherapy (CP) and CyberKnife (CK) in SCC subpopulation. a) Local control rate. b) Overall survival rate. The thick line depicts CP and the thin line depicts CK. SCC, squamous cell carcinoma.*

experienced toxicities of grade 3 or worse, whereas only 25% (7/28) of patients without previous surgical histories were grade 3 or worse (p=0.36).

Discussion

This is the first study comparing outcomes for CP and photon SBRT. Previously reported prognostic factors after re-irradiation include nasopharyngeal primary site *versus* other sites (16, 17), radiotherapy interval (6, 18), irradiated dose (17, 19), tumor volume (8, 20), tumor burden (21), resectability (17, 19, 22) and mucosal ulceration (11). As we found three prognostic factors (nasopharyngeal cancer or not, interval between initial radiotherapy and re-irradiation, as well as planning target volume), we adjusted those factors in CP and CK patients accordingly (11). We showed that CP resulted in a superior OS rate compared to that with CK, not only in the total population but also in the SCC subgroup analysis. Furthermore, the local control rate showed better tendency in patients treated with CP than in patients treated with CK. In a previous analysis, we found that small volume nasopharyngeal cancer after long disease-free period could enjoy better outcome. Actually, two long survivors (more than two years) with primary tumor control in CK group

were all nasopharyngeal cancer patients, which elevated outcome of CK group. The question arose as to whether this superiority of CP was dependent on the prescribed dose or other factors. If increased prescribed doses could improve outcomes, we should make an effort to increase prescribed doses for patients treated with CK.

There were cases of higher than grade 3 toxicities in both groups, suggesting that future investigation is required. A total of 16 patients (32%) presented with grade 3 or worse toxicities (24% in CK *vs*. 40% in CP; NS), including six grade 5 toxicities. We performed a toxicity analysis after a previous study that focused on carotid blow-out syndrome in patients treated with CK (24) and showed that more than 10% patients suffered lethal bleeding after reirradiation. We found that greater than 50% of carotid invasion, mucosal ulceration and lymph node area irradiation could be risk factors related to bleeding. Similar tactics could also be applied to reduce toxicity in patients treated with CP. A phase I/II dose escalation study using SBRT for patients without the risk factors listed above is required. Furthermore, additional chemotherapeutic agents (S-1 or cetuximab, *etc*.) could also be explored to enhance efficacy.

There were several limitations in this study. First, this is a retrospective study dealing with a small number of patients and limited follow-up periods. Next, there may be a huge selection bias to compare the results in disease histology. CP is generally indicated for the less common histological subtypes, such as adenocarcinomas, adenoid cystic carcinomas and malignant melanomas, as these histological subtypes are considered to be relatively resistant to conventional photon radiotherapy (23). As a results, CP treated 13 non-SCC patients and CK none. Although survival benefit in SCC subgroup analysis between CP and CK was also found, the current study represents a preliminary analysis that needs to be further investigated. Finally, we were unable to examine the details of previous chemotherapy and/or surgery because of the large heterogeneity in reporting practices between institutions. Despite potential economical barriers, a prospective trial with a larger number of patients and longer follow-up period should be performed to confirm our findings.

In conclusion, CP produced higher survival rates than CK, treated more non-SCC patients and used a higher prescribed dose. On the other hand, severe toxicities occurred in both groups, which require further investigation.

Conflicts of Interest

None.

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