A Single Institution's Experience of Definitive Radiotherapy Using Volumetric-modulated Arc Therapy for Hypopharyngeal Cancers

KATSUMARO KUBO¹, YUJI MURAKAMI¹, NOBUKI IMANO¹, YUKI TAKEUCHI¹,
IKUNO NISHIBUCHI¹, TOMOKI KIMURA¹, DAISUKE KAWAHARA¹, KENTARO MIKI¹,
AKITO SAITO¹, TAKEO NAKASHIMA¹, TAKAO HAMAMOTO²,
TSUTOMU UEDA², SACHIO TAKENO² and YASUSHI NAGATA¹

¹Department of Radiation Oncology, Hiroshima University Hospital, Hiroshima, Japan;

²Department of Otorhinolaryngology, Hiroshima University Hospital, Hiroshima, Japan

Abstract. *Background/Aim:* The present study aimed to analyze the treatment outcome after definitive radiotherapy (dRT) using volumetric-modulated arc therapy (VMAT) in patients with hypopharyngeal cancer (HPC), including an examination of late toxicities. *Patients and Methods:* A total of 62 patients with HPC, who underwent dRT using VMAT, were analyzed. Overall survival (OS), progression-free survival (PFS), laryngoesophageal dysfunction-free survival (LEDFS), and locoregional control (LRC) were calculated. *Results:* The median follow-up period was 49 months. The 3- and 5-year OS, PFS, LEDFS, and LRC rates were 77% and 60%, 61% and 56%, 66% and 53%, and both 79%, respectively. Regarding late toxicities, 11 (17.7%) patients developed grade ≥ 2 late toxicity. Grade 3 dysphagia was observed in 4 (6.5%) patients, and grade 2 xerostomia in 6 (9.7%). *Conclusion:* VMAT was an effective treatment for HPC, with a low incidence of late toxicities.

Hypopharyngeal cancer (HPC) is a relatively uncommon malignancy, and the management of this disease varies by Institution (1). Radiotherapy (RT) is a well-established standard treatment for head and neck squamous cell carcinoma, and also one of the treatment options for HPC (2, 3). Definitive RT with or without chemotherapy is considered an organ preservation

approach. However, recently, late toxicities after definitive RT, especially chemoradiotherapy (CRT), have gathered attention. The long-term results of the Radiation Therapy Oncology Group (RTOG) 91-11 trial concluded that new strategies which improve organ preservation and function with less morbidity were needed (4).

We believe that a new radiation technique, such as intensity-modulated radiotherapy (IMRT), is one method of addressing the recommendations of the RTOG 91-11. IMRT, a high-precision radiotherapy, causes fewer adverse events in patients with head and neck cancer while providing similar local control in comparison to three-dimensional conformal radiotherapy (3D-CRT) (5). Volumetric-modulated arc therapy (VMAT) is a further technique that evolved from IMRT. VMAT is able to deliver highly conformal treatment, sparing nearby organs at risk. These advances in radiation techniques might contribute to the reduction of late toxicities after definitive RT and improve organ preservation. However, the clinical findings of IMRT for patients with HPC are more limited than those for nasopharyngeal cancer or oropharyngeal cancer (OPC), and the clinical outcome after definitive RT using current radiation techniques such as IMRT for HPC is unclear (6, 7).

Therefore, in the present study, we analyzed treatment outcomes after definitive RT using VMAT in patients with HPC, including examination of late toxicities such as laryngeal and pharyngeal dysfunction.

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Correspondence to: Katsumaro Kubo, Department of Radiation Oncology, Hiroshima University Hospital 1-2-3 Kasumi Minami-ku Hiroshima-shi, Hiroshima 734-8553, Japan. Tel: +81 822575555, Fax: +81 822571546, e-mail: maro1987@hotmail.co.jp

Key Words: Hypopharyngeal cancer, volumetric-modulated arc therapy, laryngoesophageal dysfunction-free survival.

Patients and Methods

Patients. Data from patients, who were diagnosed with HPC and underwent definitive RT at the Hiroshima University Hospital (Hiroshima, Japan) between July, 2009 and December, 2017, were retrospectively analyzed. Individuals who fulfilled the following criteria were included in the present study: histological diagnosis of squamous cell carcinoma of the hypopharynx; no distant metastasis; and definitive RT treatment using VMAT. A multidisciplinary head

and neck cancer team of the Cancer Board discussed the treatment of each HPC patient.

Before definitive RT, all patients underwent clinical evaluation including assessment of medical history, physical examinations and laboratory investigations, endoscopy, ultrasound examination, and radiographic studies. Laboratory investigations included complete blood cell count, liver function, renal function, and measurement of electrolyte levels. Radiographic studies included contrast-enhanced computed tomography (CT), ^{18}F -fluorodeoxyglucose positron emission tomography-CT (PET/CT), and magnetic resonance imaging (MRI). The clinical tumor node metastasis (TNM) stage was defined according to the Tumor Node Metastasis classification (Union for International Cancer Control, 7th Edition). The study was approved by the Human Ethics Review Committee of Hiroshima University Hospital. The need for informed consent was waived due to the retrospective nature of this study.

Treatment

Radiotherapy. Before treatment, the heads of all patients were non-invasively immobilized using a thermoplastic head-neck-shoulder mask, and subjected to contrast-enhanced CT. CT images were acquired at a slice thickness of 2.5 mm and imported to the Eclipse treatment planning system (Varian Medical Systems, Palo Alto, CA, USA) for VMAT planning (Rapidarc; Varian Medical Systems). Gross tumor volume (GTV) was based on clinical, endoscopic, and radiological findings according to CT, MRI, and PET/CT. Clinical target volume (CTV) 70 was generated by adding a 5-10 mm margin from the GTV, including the primary tumor and affected lymph nodes. CTV63 included the high-risk areas and was created individually based on primary tumor site and lymph node metastases. CTV56 included elective nodal regions. Planning target volume (PTV) 70, PTV63, and PTV56 were generated by adding a 5-10 mm margin from CTV70, CTV63, and CTV56. Usually, 2 or 3 axial coplanar arcs were used for VMAT. All treatment plans were designed based on a TrueBeam linear accelerator equipped with 5 mm leaf-width multi-leaf collimators (Varian Medical Systems). All plans were normalized so that PTV70 D95 (the dose that covers 95% of the PTV70) was equal to 70 Gy using 6-10 MV photon beams. PTV70, PTV63, and PTV56 received a total dose of 70 Gy, 63 Gy, and 56 Gy in 35 fractions, respectively. Cone-beam CT was performed daily for patient set-up and positioning verification.

Chemotherapy. The concurrent chemotherapy regimen was 3 cycles of cisplatin 100 mg/m² at an interval of 3 weeks. Before 2012, the concurrent chemotherapy regimen was 2 cycles of cisplatin plus 5-fluorouracil. If the administration of cisplatin was not appropriate due to the patient's general condition, renal function, age, carboplatin or cetuximab was administered.

Regarding patients with Stage IV disease, induction chemotherapy was indicated. The medication administered was combination chemotherapy consisting of docetaxel (70 mg/m²) on day 1, cisplatin (70 mg/m²) on day 4, and 5-fluorouracil (750 mg/m²) by 24 h continuous infusion for 5 days (*i.e.*, TPF therapy). Two cycles at 3- or 4-week intervals were planned.

Statistical analysis. The Kaplan–Meier method was used to calculate overall survival (OS), progression-free survival (PFS), laryngoesophageal dysfunction-free survival (LEDFS), and locoregional control (LRC). OS was defined as the date of initiation of RT to the date of the final follow-up or death from any cause. PFS

was defined as the date of initiation of RT to the date of any tumor progression or death from any cause. LEDFS was analyzed to evaluate organ preservation in the cohort. For LEDFS, the Larynx Preservation Consensus Panel recommends including death, local recurrence, total or partial laryngectomy, tracheotomy at ≥ 2 years, or use of a feeding tube at ≥ 2 years (8). Swallowing function was evaluated with videofluorography. LRC was estimated as the RT start date until the date of any locoregional progression; patients without locoregional progression at the time of death were censored. Univariate analyses using the Cochran-Mantel-Haenszel test and multivariate analyses using the Cox proportional hazards model were performed to compare and determine statistical differences in OS and LEDFS. BellCurve version 3.20 (Social Survey Research Information Co., Ltd., Tokyo, Japan) for Excel (Microsoft Corporation, Redmond, WA, USA) was used to perform statistical analyses. Differences with p -values < 0.05 were considered statistically significant. Treatment-related toxicities were evaluated according to the Common Terminology Criteria for Adverse Events version 4.0.

Results

Patients. A total of 62 eligible patients, the characteristics of whom are summarized in Table I, were enrolled in the present study. The median age of the patients was 66 years (range=37-85 years) and 91.9% were men. The most common primary tumor site was pyriform sinus (62.9%), followed by posterior pharyngeal wall (29.0%), and postcricoid area (8.1%). T1, T2, T3, T4a, and T4b disease were observed in 5 (8.1%), 19 (30.6%), 8 (12.9%), 18 (29.0%), and 12 (19.4%) patients, respectively. Regarding lymph node metastases, N0, N1, N2, and N3 disease were observed in 22 (35.5%), 3 (4.8%), 35 (56.5%), and 2 (3.2%) patients, respectively. Stage I, Stage II, Stage III, Stage IVA, and Stage IVB disease were observed in 5 (8.1%), 7 (11.3%), 3 (4.8%), 33 (53.2%), and 14 (22.6%) patients, respectively. Induction chemotherapy was conducted in 39 (62.9%) patients. Fifty-six (90.3%) patients received chemotherapy concurrently with RT. Cisplatin was administered to 45 (72.6%) patients, cisplatin plus 5-fluorouracil to 7 (11.3%), carboplatin to 1 (1.6%), carboplatin plus 5-fluorouracil to 1 (1.6%), and cetuximab to 2 (3.2%) with RT. Of 6 patients receiving RT alone, 5 had Stage I disease and 1 had Stage II disease. Median follow-up at the time of evaluation was 49 months (range=26-114 months) in survivors.

Treatment outcome. Locoregional control and recurrence patterns. The 3- and 5-year LRC rates were both 78.7% [95% confidence interval (CI)=68.4-89.0%]. Disease progression was observed in 21 (33.9%) patients. Regarding the pattern of initial recurrence, 11 (17.7%) patients experienced locoregional recurrence, 8 (12.9%) developed distant metastases, and 2 (3.2%) experienced both locoregional and distant failure. Overall, during the observation period, 13 (21.0%) patients experienced locoregional recurrence, and 15 (24.2%) developed distant metastases.

Table I. Patient characteristics.

	N=62	100 (%)
Age, years, median (range)	66 (37-85)	-
Gender		
Male	57	91.9
Female	5	8.1
Location		
Postcricoid area	5	8.1
Pyriform sinus	39	62.9
Posterior pharyngeal wall	18	29.0
T category		
T1	5	8.1
T2	19	30.6
T3	8	12.9
T4a	18	29.0
T4b	12	19.4
N category		
N0	22	35.5
N1	3	4.8
N2a	0	0.0
N2b	28	45.2
N2c	7	11.3
N3	2	3.2
Clinical stage		
I	5	8.1
II	7	11.3
III	3	4.8
IVA	33	53.2
IVB	14	22.6
PET-CT	Yes	56 90.3
Induction chemotherapy	Yes	39 62.9
Concurrent chemotherapy		
Ciplatin	45	72.6
Cisplatin + 5-fluorouracil	7	11.3
Carboplatin	1	1.6
Carboplatin + 5-fluorouracil	1	1.6
Cetuximub	2	3.2
Smoking history	Yes	50 80.6

PET-CT: ¹⁸F-fluorodeoxyglucose positron emission tomography computed tomography.

Regarding salvage treatment, of the 13 patients with locoregional recurrence, 10 patients underwent salvage surgery, including neck dissection in 6 patients, total laryngopharyngoesophagectomy in 2, partial pharyngectomy in 1, and endoscopic submucosal dissection in 1.

Survival. OS, PFS, and LEDFS rates in all patients are presented in Figure 1. At the last follow-up, 39 (62.9%) patients were still alive, 16 (25.8%) died from the disease, and 7 (11.3%) died of other causes. Of the 39 survivors, 36 were alive without disease, and 3 had recurrence of HPC. Of the 7 patients who died of other causes, 3 died from other cancers, 2 died from pneumonia, 1 died from pneumonitis, and 1 died from ischemic heart disease. Of the 2 patients who died of pneumonia, both patients did not have radiation-related severe

dysphagia, and the association between the cause of death and RT was unclear. The 3- and 5-year OS rates were 76.7% (95% CI=65.9-87.4%) and 60.2% (95% CI=46.4-74.0%), respectively. The 3- and 5-year PFS rates were 60.9% (95% CI=48.6-73.1%) and 55.6% (95% CI=42.4-68.8%), respectively.

The 3- and 5-year LEDFS rates were 65.5% (95% CI=53.5-77.5%) and 52.8% (95% CI=38.8-66.8%), respectively. Events associated with laryngoesophageal dysfunction included death in 13 (21.0%) patients (7 died from the disease, and 6 died of other causes), local recurrence in 8 (12.9%), tracheotomy in 2 (3.2%), and feeding tube at ≥ 2 years in 5 (8.1%). Of the 5 patients who depended on a feeding tube, 1 required a feeding tube due to hypoxic-ischemic encephalopathy after food asphyxiation, although the patient did not have severe dysphagia. Another patient could not eat before treatment because of the tumor spread, and needed a feeding tube until the end of the observation period. The other 3 patients required a feeding tube due to RT-related dysphagia.

Toxicity. Acute and late toxicities are listed in Table II. Overall, grade ≥ 3 acute toxicities were observed in 47 (75.8%) patients. During RT, grade 3-4 hematological toxicities included: leukopenia in 23 (37.1%) patients, neutropenia in 19 (30.6%), and anemia in 6 (9.7%). The most common grade 3 non-hematological toxicity was mucositis (46.8%), followed by dysphagia (40.3%), and dermatitis (30.6%). Regarding late toxicities, 11 (17.7%) patients developed grade ≥ 2 late toxicity, and grade 2 xerostomia was observed in 6 (9.7%). Grade 3 dysphagia was observed in 4 (6.5%) patients. There were no grade 4-5 late toxicities in the cohort.

Predictive factors of overall survival and laryngoesophageal dysfunction-free survival. The results of univariate and multivariate analyses of OS and LEDFS are summarized in Table III. In multivariate analysis, N category (N0 vs. N1-3) was a significant predictive factor of OS. Location (pyriform sinus vs. others) and N category (N0 vs. N1-3) were significant predictive factors of LEDFS. The LEDFS rates according to location and N category are presented in Figure 2.

Discussion

Through the advancement of radiation techniques, definitive RT has become a mainstream treatment for HPC. Early-stage disease can be treated equally effectively with surgery or RT, and definitive RT also has a role in the curative management of locally advanced cancers (2, 3). However, while definitive RT with or without chemotherapy is regarded as an organ preservation approach, late toxicities such as laryngeal and pharyngeal dysfunction are problematic. A previous study reported that almost 40% of patients with locally advanced head and neck cancer treated with definitive RT experienced long-term dysphagia (9). In addition, it was reported that 10-20% of

Figure 1. Overall survival (OS), progression-free survival (PFS), and laryngoesophageal dysfunction-free survival (LEDFS) in all patients. (a) The 3- and 5-year OS rates were 76.7% and 60.2%, respectively. (b) The 3- and 5-year PFS rates were 60.9% and 55.6%, respectively. (c) The 3- and 5-year LEDFS rates were 65.6% and 52.8%, respectively.

Figure 2. Laryngoesophageal dysfunction-free survival (LEDFS) according to primary tumor location and N category. (a) The 5-year LEDFS rates of patients with tumors located in the pyriform sinus and those with tumors located elsewhere were 66.0% and 33.6%, respectively. (b) The 5-year LEDFS rates of patients with N0 disease and those with N1-3 disease were 62.8% and 47.5%, respectively.

patients receiving definitive RT depended on a feeding tube at 2 years (10, 11). However, it should be noted that these results are based on non-IMRT techniques, and IMRT might lead to a reduction in late toxicities. Most previous IMRT studies have analyzed OPC, HPC, and laryngeal cancer concurrently, and there are few studies that have specifically focused on HPC (7, 12-15). Therefore, the effect of IMRT on late toxicities is unclear in the case with HPC, especially in the Japanese population. In addition, since OPC treatment results differ depending on human papillomavirus status, and the irradiated

area is also different between OPC and HPC, we believe that OPC and HPC should be evaluated separately. Hence, the present study reported treatment outcomes after definitive RT using VMAT in patients with HPC, including examination of late toxicities such as laryngeal and pharyngeal dysfunction.

Table IV shows the clinical results after definitive RT using IMRT or non-IMRT techniques for patients with HPC. According to previous studies, the 3- and 5-year OS rates after IMRT for patients with HPC were almost 50-80% and 35-44%, respectively (7, 12-15). In contrast, several studies

Table II. *Acute and late toxicities of included patients.*

Toxicity	Common Terminology Criteria for Adverse Events Ver 4.0							
	Grade 0-1		Grade 2		Grade 3		Grade 4	
	N	100 (%)	N	100 (%)	N	100 (%)	N	100 (%)
Acute toxicity								
Non-hematologic toxicity								
Dysphagia	10	16.1	27	43.5	25	40.3	0	0
Mucositis	6	9.7	27	43.5	29	46.8	0	0
Dermatitis	19	30.6	24	38.7	19	30.6	0	0
Dysgeusia	29	46.8	33	53.2	0	0	0	0
Xerostomia	37	59.7	25	40.3	0	0	0	0
Hematologic toxicity								
Leukopenia	20	32.3	19	30.6	22	35.5	1	1.6
Neutropenia	31	50.0	12	19.4	18	29.0	1	1.6
Anemia	27	43.5	29	46.8	6	9.7	0	0
Late toxicity								
Non-hematologic toxicity								
Dysphagia	55	88.7	3	4.8	4	6.5	0	0
Dysgeusia	61	98.4	1	1.6	0	0	0	0
Xerostomia	56	90.3	6	9.7	0	0	0	0
Osteonecrosis of jaw	61	98.4	1	1.6	0	0	0	0

Table III. *Univariate and multivariate analyses of predictive factors.*

Investigated factors	Overall survival					Laryngoesophageal dysfunction-free survival				
	3-year OS	5-year OS	UVA	MVA	Hazard ratio	3-year LEDFS	5-year LEDFS	UVA	MVA	Hazard ratio
	%	%	p-Value	p-Value	(95% CI)	%	%	p-Value	p-Value	(95% CI)
Age										
<65 years	80.6	68.7	0.3133	ns	-	70.2	55.8	0.4429	ns	-
≥65 years	73.2	54.4				61.5	50.2			
Gender										
Male	76.3	60.4	0.6487	0.2077	0.3594 (0.0732-1.7655)	65.9	51.7	0.6767	0.1707	0.3301 (0.0676-1.6115)
Female	80.0	60.0				60.0	60.0			
Location (vs.)										
Pyiform sinus	81.5	67.1	0.3133	0.0817	0.4525 (0.1853-1.1051)	73.8	66.0	0.0813	0.0152	0.3738 (0.1688-0.8274)
Others	68.0	47.6				51.8	33.6			
Stage										
I-II	100	80.0	0.0755	ns	-	100	66.7	0.0808	ns	-
III-IV	70.7	55.2				56.9	50.5			
T category										
T1-2	86.9	62.9	0.3355	ns	-	75.0	50.5	0.5526	ns	-
T3-4	70.2	58.7				59.6	55.9			
N category										
N0	90.7	75.6	0.0481	0.0202	0.2623 (0.0847-0.8118)	86.1	62.8	0.0502	0.0146	0.3073 (0.1192-0.7920)
N1-3	69.0	52.0				54.4	47.5			
Smoking history										
No	100	63.6	0.4619	ns	-	75.0	50.0	0.8921	ns	-
Yes	70.9	60.2				63.1	56.1			

OS, Overall survival; UVA, univariate analysis; MVA, multivariate analysis; CI, confidence interval; LEDFS, laryngoesophageal dysfunction-free survival; ns, non significant.

Table IV. Clinical results of definitive radiotherapy for patients with hypopharyngeal cancer.

	N	Median follow-up (month)	Stage (Stage: %)	Treatment outcome			
				OS (%)	LPS (%)	Late AE (%)	
						Disphagia (≥Grade 3)	Xerostomia (≥Grade 2)
IMRT study							
Liu <i>et al.</i> (2010) (12)	27	53	II: 19 III: 15 IV: 67	3y: 52 5y: 35	3y: 60 5y: 60	4	44
Huang <i>et al.</i> (2010) (13)	33	26	II: 6 III: 15 IV: 79	5y: 44	5y: 40	3	0
Takehana <i>et al.</i> (2016) (7)	56	43	na	3y: 81	3y: 54	na	10
Kılıç <i>et al.</i> (2018) (15)	2098	44	I: 3 II: 11 III: 24 IV: 63	5y: 42	na	na	na
This study (2020)	62	49	I: 8 II: 11 III: 5 IV: 76	3y: 77 5y: 60	3y: 66* 5y: 53*	7	10
Non-IMRT study							
Rabbani <i>et al.</i> (2008) (16)	123	128	I: 5 II: 15 III: 17 IV: 63	5y: 35	na	na	na
Takehana <i>et al.</i> (2016) (7)	148	43	na	3y: 78	3y: 71	na	na
Kılıç <i>et al.</i> (2018) (15)	1830	44	I: 5 II: 11 III: 22 IV: 62	5y: 37	na	na	na
Juloori <i>et al.</i> (2018) (17)**	54	50	III: 22 IV: 78	5y: 62	na	36	77

OS, Overall survival; LPS, functional larynx preservation survival; AE, adverse event; IMRT, intensity-modulated radiotherapy; na, not available.
*Laryngoesophageal dysfunction-free survival. **This study included almost 10% patients treated by IMRT.

mentioned treatment results after 3D-CRT for HPC, and the 3- and 5-year OS rates were almost 50-80% and 35-60%, respectively (7, 10, 11, 15-17). In the present study, the 3- and 5-year OS rates were 77% and 60%, respectively. In addition, the 5-year LRC rates of IMRT and non-IMRT studies were reported as 53-78%, and that in our study was 79%. Overall, previous results, including those of our study, are similar between 3D-CRT and IMRT studies.

Regarding late toxicities, grade ≥2 late toxicities were observed in 18% of patients, grade 2 xerostomia in 10%, and grade 3 dysphagia in 7% in the present study. In addition, the 3- and 5-year LEDFS rates were 66% and 53%, respectively. These results were also similar to other IMRT studies. In contrast, in a 3D-CRT for HPC study reported by Juloori *et al.*, grade 2 xerostomia was observed in almost 77% of patients, and grade 3 dysphagia in 36% (90% of the total cases received 3D-CRT, and others received IMRT) (17). In addition, in RTOG 91-11, grade 2 xerostomia was observed in almost 50% of patients, and grade 3 dysphagia in 15% (4). Therefore, IMRT might reduce adverse events while providing similar disease control in comparison with 3D-CRT, even in patients with HPC.

This study included almost 60% of total patients receiving induction chemotherapy followed by definitive RT. We considered induction chemotherapy for patients with Stage IV disease. Although induction chemotherapy does not demonstrate a survival benefit compared to CRT alone (4), interest in the utility of induction chemotherapy persists for a few reasons including a reduction in the likelihood of distant metastases, and

improvement of local regional control and organ preservation (2). Tumor bulk reduction by induction chemotherapy, as well as radiation dose reduction in VMAT for organs at risk, might have contributed to the low incidence of late toxicities.

The present study also revealed tumor location (pyriform sinus) and N category (N0 disease) as significant predictive factors of good LEDFS. As there are still few reports that mention LEDFS after definitive RT for HPC, the predictive factor of good LEDFS is unclear. Primary tumor location and N category are known to be correlated with survival (18), and might be predictive factors of LEDFS.

Our study had certain limitations, including its retrospective and single-institution design. In addition, because most previous studies of 3D-CRT for HPC lacked functional larynx-preservation survival or LEDFS, it was difficult to compare the functional preservation of the larynx and pharynx after 3D-CRT and IMRT. These factors might have introduced potential biases, such as under- or overestimation of the advantage of IMRT over 3D-CRT in late adverse events. However, our assessment of VMAT for HPC is valuable because of the paucity of currently available data. Furthermore, although we evaluated only 62 patients, this represents a relatively large amount of VMAT treatments for HPC cases alone. Therefore, despite its limitations, this study provides useful information regarding definitive RT using VMAT with a relatively long follow-up duration in a large sample size.

In summary, this study reported treatment outcomes after definitive RT using VMAT in patients with HPC, including examination of late toxicities such as dysfunction of the larynx

and pharynx. We conclude that definitive RT using VMAT is an effective treatment for HPC that might reduce long-term adverse events while providing similar disease control in comparison with 3D-CRT, even in patients with HPC.

Conflicts of Interest

The Authors declare no conflicts of interest regarding this study.

Authors' Contributions

Katsumaro Kubo and Yuji Murakami contributed equally to this work. Investigation, project administration, writing of original draft: Katsumaro Kubo. Methodology, writing, reviewing and editing: Yuji Murakami. Writing, reviewing and editing: Nobuki Imano, Yuki Takeuchi, Ikuno Nishibuchi, Tomoki Kimura, Daisuke Kawahara, Kentaro Miki, Akito Saito, Takeo Nakashima, Takao Hamamoto, Tsutomu Ueda, Sachio Takeno, Yasushi Nagata.

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