

## Original Article



# Comparing efficacy of high-dose rate brachytherapy versus helical tomotherapy in the treatment of cervical cancer

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## ABSTRACT

**Objective:** Boost radiation using brachytherapy (BT) is a standard treatment for local disease control in concomitant chemoradiation therapy (CCRT) for advanced cervical cancer.

However, it is associated with gastrointestinal and genitourinary complications. Hence, this study investigates the feasibility of helical tomotherapy (HT) as an alternative to BT.

**Methods:** Medical records of patients who underwent CCRT between 2000 and 2017 at a single institution were retrospectively reviewed. Patients with stage IIB–IVA cancers were selected based on the 2009 criteria of The International Federation of Gynaecology and Obstetrics. External beam radiation combined with chemotherapy was followed by either BT or HT. The propensity score matching of both groups was calculated using logistic regression analysis. Disease outcomes and treatment-related adverse events were compared between the 2 groups.

**Results:** The matched population included 70 BT patients and 35 HT patients. The 5-year progression-free survival rates for BT and HT were 72.6% and 72.5%, respectively ( $p=0.721$ ). There was no difference in the overall survival rate between the two groups ( $p=0.203$ ). The presence of acute and chronic gastrointestinal complications was also similar between the groups ( $p=0.460$  and  $p=0.563$ , respectively). The chronic genitourinary toxicities were also comparable ( $p=0.105$ ).

**Conclusions:** HT boost treatment showed comparable disease outcomes with those observed with conventional BT in patients with advanced cervical cancer. HT could be a complementary boost protocol as a single modality or hybrid with BT in selected patients. Further studies with longer follow-up periods are warranted to confirm long-term outcomes.

**Keywords:** Brachytherapy; Helical Tomotherapy; Cervical Cancer; Concomitant Chemoradiotherapy

## INTRODUCTION

In 2018, cervical cancer ranked fourth in terms of incidence and mortality among female cancers worldwide [1]. In Korea, cervical cancer constituted 1.7% of the total cancer incidence and was the seventh most common cancer among women [2]. The incidence rate of cervical

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**Conflict of Interest**

No potential conflict of interest relevant to this article was reported.

**Author Contributions**

Conceptualization: P.Y.J., S.J.Y.; Data curation: L.S., H.J.H., L.J.K.; Methodology: S.J.Y.; Resources: L.S., H.J.H., L.J.K., L.N.W.; Supervision: P.Y.J., S.J.Y.; Writing - original draft: K.S.; Writing - review & editing: K.S., P.Y.J., S.J.Y.

cancer shows a gradually decreasing trend in developed countries due to the availability of early diagnosis and early treatment at a precancerous stage [3]. Disease management varies depending on the stage of the disease and the necessity of preserving fertility [4].

Based on the results from multiple randomized trials, concomitant chemoradiation therapy (CCRT) has been the standard treatment for locally advanced cervical cancer since 1999 [5-7]. External beam radiation therapy (EBRT) followed by brachytherapy (BT) is associated with better disease outcomes than EBRT alone [8]. However, side-effects include a considerably high rate of gastrointestinal toxicities and genitourinary complications [9].

Advances in radiation technologies have introduced new treatment methods such as intensity-modulated radiation therapy (IMRT) which is used in many institutions [10-12]. This technique provides accurate target coverage as it employs multiple intensely modulated beams which can spare adjacent tissues and lower complications. Helical tomotherapy (HT) is a form of computed tomography-based image-guided IMRT [13], which delivers highly conformal dose distributions while sparing critical organs from radiation. The application of HT has been mainly tested in the field of gynecologic malignancies [14-16]. There was a case report of successful boost treatment using HT following CCRT in a patient with advanced cervical cancer which involves deep pelvic sidewall [17]. However, the feasibility of HT as an alternative for high-dose BT to boost CCRT has not been comprehensively evaluated.

Therefore, this study aimed to evaluate the outcomes and complications of HT in advanced cervical cancer with relatively larger tumors and deep pelvic invasion in comparison to traditional high-dose BT following EBRT.

## MATERIALS AND METHODS

### 1. Study design and patients

This retrospective cohort study was conducted using the medical records in our institution and involved newly diagnosed cervical cancer patients from 2000 to 2017. The study was approved by ethical committee of Korea University Medical Center Anam Hospital (No. 2018AN0184) and all patients provided written informed consent for biological studies. The population included patients with stage IIB-IVA cervical cancer, according to The International Federation of Gynaecology and Obstetrics 2009 staging criteria, who underwent CCRT as a primary treatment. Patients with distant metastasis, recurrent disease, double primary cancers, history of pelvic radiation treatment, or individuals who had radiation without concomitant chemotherapy were excluded from this study. Several patients who have not completed the scheduled treatment were also excluded. The selection criteria for HT were not absolute because this study was not conducted prospectively. If the patients had relatively larger tumors after EBRT so that the tumor was assumed not able to be covered by BT, or the tumors showed deep pelvic wall, bladder or rectum invasion, HT was introduced as a treatment option. The patients with uterine fibroid or adenomyosis altering cervical position were also considered eligible for HT. We explained to the patients that BT is a standard boost treatment, and informed them of the benefits and risks of both treatments. 6 patient who refused HT boost were treated with conventional BT.

## 2. Chemotherapy and radiotherapy protocols

All patients received whole pelvic radiation using a 3-dimensional conformal radiotherapy (3D-CRT) method, with daily 1.8 Gy, total 45–54 Gy in 25–30 fractions. Combined chemotherapy of cisplatin 40 mg/m<sup>2</sup> intravenously on day 1, every week for 6 weeks was administered according to institutional standards. This was followed by BT performed via intracavitary boost. A dose of 24–30 Gy in 6 fractions was delivered to point A (a reference location 2 cm lateral and 2 cm superior to the cervical os), aiming for a total equieffective dose in 2-Gy fraction (EQD2) dose of 80 Gy. Dose constraints of BT were in line with the recommendations of the American Brachytherapy Society (ABS) [18]. The EQD2 limit to the minimum dose in most irradiated 2 cm<sup>3</sup> tissue volume (D<sub>2cc</sub>) for rectum was 70–75 Gy and D<sub>2cc</sub> for bladder was approximately 90 Gy.

## 3. Tomotherapy boost methods

The patients were placed on a 2–3-mm slice of the planning computed tomography (CT) while filling the bladder and keeping the rectum strictly empty. All patients underwent follow-up magnetic resonance imaging (MRI) after 20–25 fractions of EBRT to identify residual tumors (primary and lymph node). Follow-up MRI and planning CT were fused and used as reference for target delineation. Tomotherapy treatment planning system (Accuray Inc., Sunnyvale, CA, USA) was used to delineate the target volume and healthy organs identified as organ at risk (OAR). The OARs were intestines (small and large intestines), rectum, bladder, femoral head, and urethra. Delineation and constraints were based on the Radiation Therapy Oncology Group (RTOG) protocol. The residual gross tumor on planning CT and follow-up MRI was defined as gross tumor volume (GTV). Clinical target volume (CTV) for the primary tumor was defined as 0.5–1 cm extension by considering the involvement of the surrounding tissues at the initial stage (Fig. 1). CTV for the lymph nodes was defined as GTV without margin. The internal target volume (ITV) margin was determined with reference to the cone-beam CT images taken at every 3D-CRT, and the planning target volume (PTV) was set at a CTV extension of 0.5–1 cm. The tomotherapy plan used a field width of 1.05, a pitch of 0.287, a modulation factor of 2.5–3, and a 6 MV energy level. The doses for the primary tumor were 3 Gy to 95% of PTV and 4 Gy to 95% of ITV while 1.6–1.8 Gy was prescribed to 95% of lymph node PTV. Dose constraints of HT were according to the recommendation of ABS. A total of 10 fractions were irradiated at HT using the simultaneous integrated boost (SIB) method. The doses of PTV and ITV were adjusted with consideration to the proximity of surrounding normal tissue (especially the small intestines). All patients underwent mega-voltage computed tomography (MVCT) after each HT treatment to confirm

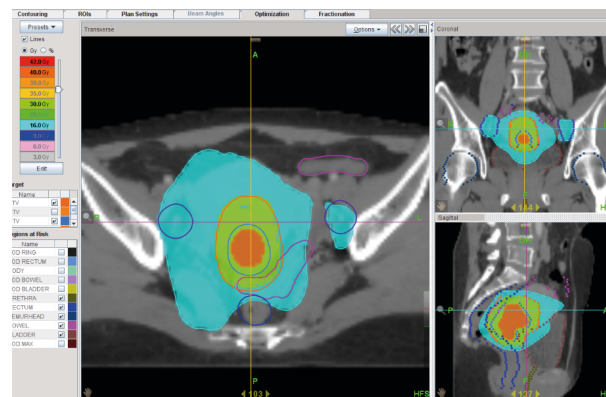


Fig. 1. Target contouring and dose distribution of helical tomotherapy boost for cervical cancer in our institution.

the consistency with ITV. The target for HT was modulated by checking MVCT at every treatment. If the target appears to be out of the lesion for 2 consecutive sessions then the HT radiotherapy planning was reconfigured.

To improve the tumor-target accuracy, patients were kept on strict bladder filling and rectal emptying. Generally, patients emptied their bladder 2 hours before treatment and held voiding without any oral intake until the radiotherapy. The filled bladder was checked via MVCT prior to every treatment, and the treatment only commenced after adequate bladder filling.

#### 4. Follow-up after treatment

The initial response to the treatment was evaluated via CT scan or MRI 3 months after the last visit for CCRT. Patients were followed up every 3 months for the first 2 years, and then every 6 months for the next 3 years. During the follow-up period, disease assessments included physical examination by a gynecologic oncologist, CT scan, or MRI. Because tomotherapy was only initiated 6 years ago at our institution, the follow up data was limited to 70 months in both groups to reduce the time gap between them. Adverse events were assessed using the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) version 4.3.

#### 5. Statistics

Propensity score analysis was performed between BT and HT groups to minimize selection biases associated with retrospective studies. For each patient, a propensity score for the boost method group was calculated using logistic regression analysis of variables including stage, histology and age. Progression-free survival (PFS) and overall survival (OS) were estimated using the Kaplan-Meier method, and the two groups were compared using the log-rank test. PFS was defined as the duration from the day of completion of CCRT, the day of first evidence of disease recurrence or progression, or the last follow-up if there is no evidence of recurrence. OS was defined as the time between the end of treatment and death from any cause or the last follow-up of living patients. The Kolmogorov-Smirnov test was used to verify standard, normal distributional assumptions. The Student's t-test and Mann-Whitney U-test were used for parametric and non-parametric variables, respectively. Differences between proportions were compared using the Fisher's test or  $\chi^2$  test. A p-value <0.05 was considered statistically significant. Statistical analysis was performed using Statistical Package for the Social Sciences 22.0 (IBM Analytics, Armonk, NY, USA) and R (v 3.1.2 R; R Foundation for Statistical Computing, Vienna, Austria).

## RESULTS

### 1. Patients and tumor characteristics

A total of 151 patients were enrolled in the initial analysis: 101 and 50 in BT and HT group, respectively. Patient characteristics are shown in **Table 1**. Due to a clear difference in the clinical stages between the two groups, propensity score matching was conducted between them with a 2:1 ratio. The matched population were composed of 70 and 35 patients for each group. After matching, there was no significant difference in the clinical parameters and tumor characteristics between the two groups. The median follow-up period was 57 and 31 months in BT and HT, respectively. The mean tumor size was relatively larger in the HT group although the difference was not significant. There was no difference in the nodal status assumed on CT or MRI images between the 2 groups.

## Helical tomotherapy in cervical cancer

**Table 1.** Characteristics of original patients and propensity score of matched population

Characteristics	Original population			Propensity score matched population		
	BT (n=101)	HT (n=50)	p-value	BT (n=70)	HT (n=35)	p-value
Age (yr)	56.2±12.1	57.9±13.8	0.682	53.7±10.8	57.3±12.9	0.132
BMI (kg/m <sup>2</sup> )	24.7±4.0	24.5±4.2	0.810	24.9±3.8	24.4±3.8	0.507
SCC antigen (ng/mL)	8.9±14.0	11.7±15.6	0.256	9.20±15.5	8.93±12.3	0.929
CEA (ng/mL)	9.1±36.1	23.8±110.1	0.259	11.0±42.8	24.6±127.2	0.451
FIGO stage			0.006			0.237
IIB, III	89	35		58	32	
IVA	12	15		12	3	
Histology			0.412			0.746
SCC	88	41		59	28	
Adenocarcinoma	11	6		9	5	
Others	2	3		2	2	
Tumor size (cm)*	4.19±1.65	4.79±1.48	0.030	4.19±1.65	4.69±1.43	0.125
Lymph node enlargement†	75 (74.3)	33 (66.0)	0.290	37 (52.9)	21 (60.0)	0.488

Values are expressed as mean±standard deviation or number (%). In the original population, there were more patients with advanced disease in the tomotherapy group, but no difference was observed in the matched population.

BMI, body mass index; BT, brachytherapy; CEA, carcinoembryonic antigen; FIGO, International Federation of Gynecology and Obstetrics; HT, helical tomotherapy; SCC, squamous cell carcinoma.

\*A longest diameter of the primary cervical lesion measured on images; †Number of lymph nodes which is larger than 1 cm on computed tomography or magnetic resonance imaging.

## 2. Disease outcomes

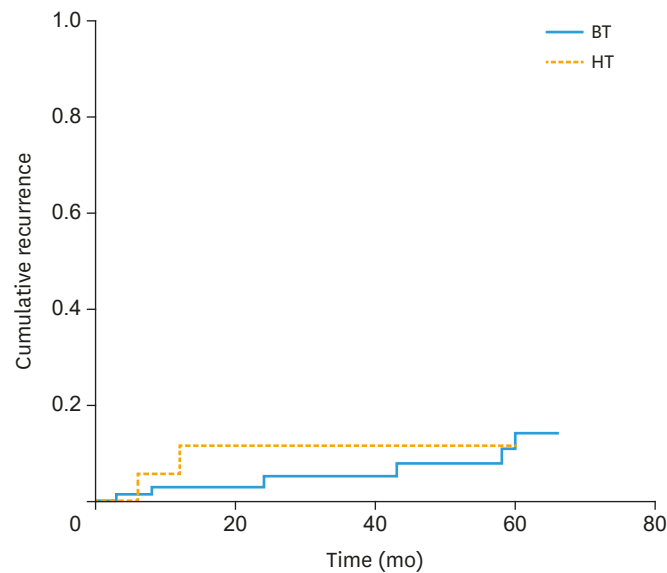
Detailed information on patients with recurrence is available in **Table 2**. Among the 70 patients in the BT group, 17 showed disease progression during their follow up period. Histological analysis indicated that the recurrence was mostly squamous cell carcinoma. Half of the patients treated with BT showed complete response to the initial treatment and cases of recurrence were

**Table 2.** Detailed information of patients with disease progression

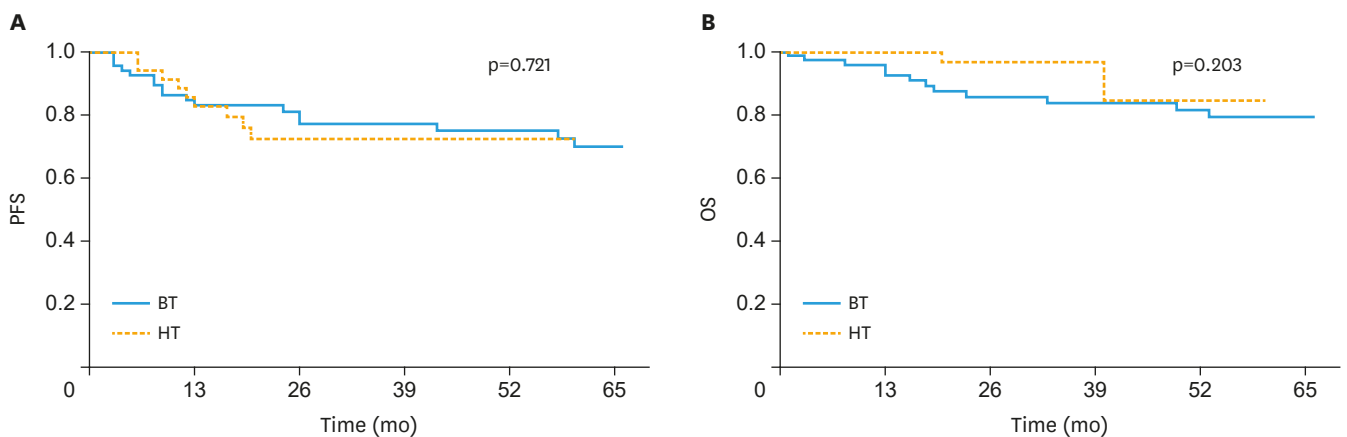
Therapy	Number	Stage	Histology	Progression interval (m)	Treatment response	Recurrence/progression location	Recurrence treatment
BT	1	IIB	Mucinous adenocarcinoma	5	PR	Central/PLN/PALN/lung	CTX
	2	IIB	SCC	26	PR	Central/supraclavicular LN	CTX
	3	IVA	SCC	3	PR	Lateral pelvic (ureter)	CTX
	4	IIB	SCC	9	CR	PALN	CTX
	5	IIB	SCC	8	PR	Supraclavicular LN	CTX
	6	IIB	SCC	58	CR	Central pelvic	CTX
	7	IIB	SCC	8	CR	Central pelvic	CTX
	8	IIB	SCC	9	PR	PALN	CTX
	9	IIIA	SCC	3	PR	Central pelvic	CTX
	10	IIB	SCC	13	CR	PLN	CTX
	11	IIB	Mucinous adenocarcinoma	4	PR	Central/PALN	CTX
	12	IIB	SCC	12	CR	Supraclavicular LN	CTX
	13	IIIB	Adenocarcinoma	3	PR	Central/PALN/supraclavicular LN	CTX
	14	IIB	SCC	24	CR	Central pelvic	CTX
	15	IIB	SCC	43	CR	Central pelvic	Surgery + CTX
	16	IIB	SCC	60	CR	Central pelvic	CTX
	17	IIB	SCC	26	CR	Lung	CTX
HT	1	IIIB	SCC	19	CR	Lung	CTX
	2	IIB	SCC	17	PR	PALN	CTX
	3	IIB	Adenocarcinoma	9	PR	Lateral pelvic (ovary)/omentum	Surgery + CTX
	4	IIB	SCC	12	CR	Central pelvic (bladder wall)	Surgery + CTX
	5	IIB	SCC	6	PR	Central pelvic	CTX
	6	IIB	SCC	12	CR	Central pelvic	CTX
	7	IIIA	Adenocarcinoma	6	PR	Central pelvic	CTX
	8	IVA	SCC	13	CR	PALN	CTX
	9	IVA	SCC	20	CR	Supraclavicular LN	CTX

BT, brachytherapy; CCRT, concomitant chemo-radiation therapy; CR, complete remission; CTX, chemotherapy; HT, helical tomotherapy; LN, lymph node; PALN, para-aortic lymph node; PLN, pelvic lymph node; PR, partial remission; SCC, squamous cell carcinoma.

mostly treated with chemotherapy. Meanwhile, 9 patients showed recurrence in the HT group and the clinical data was not different from those of BT group. The central failure rates were 35.3% (6/17) in BT group and 44.4% (4/9) in HT group. In comparison of actuarial locoregional recurrence, there was no significant difference between 2 groups (**Fig. 2**). Survival analyses of the original population indicated that the PFS was significantly lower in the HT group than in the BT group (5-year progression-free rate: 47.2% vs. 77.2%,  $p=0.001$ ). However, when the population was matched, there was no significant difference in PFS between the 2 groups. ( $p=0.721$ ) (**Fig. 3**). The 5-year PFS for BT and HT were 72.6% and 72.5%, respectively. There was no statistical difference in OS between the two groups of original population (5-year survival rate: 78.0% vs. 76.5%,  $p=0.614$ ). In matched population, a preferable trend in the overall



**Fig. 2.** Actuarial locoregional recurrence of matched groups. There was no difference between 2 groups ( $p=0.319$ ). BT, brachytherapy; HT, helical tomotherapy.



No. at risk							No. at risk						
1	70	51	41	37	33	3	1	70	59	46	42	37	3
2	35	30	16	7	4	0	2	35	35	20	8	4	0

**Fig. 3.** Disease outcome analysis of matched groups using Kaplan-Meier method. The PFS (A) and OS (B) were not significantly different between the 2 groups ( $p=0.721$  and  $p=0.203$  on log-rank test, respectively). BT, brachytherapy; HT, helical tomotherapy; OS, overall survival; PFS, progression-free survival.

**Table 3.** Adverse events related to treatment

Complications	Events	BT	HT	p-value
Acute complications	Gastrointestinal	7 (10.0)	2 (5.71)	0.460
	Grade 3	6	2	
	Grade 4	1	0	
	Thrombocytopenia, grade 3	3 (4.29)	1 (2.86)	
	Leukopenia, grade 3	1 (1.43)	1 (2.86)	
	Dermatitis, grade 3	1 (1.43)	1 (2.86)	0.614
Chronic complications	Gastrointestinal	26 (37.1)	11 (31.4)	0.563
	Grade 1	22	8	
	Grade 2	4	3	
	Genitourinary	20 (28.6)	5 (14.3)	
	Grade 1	19	5	
	Grade 2	1	0	

HT was associated with a low incidence of chronic genitourinary complications.

BT, brachytherapy; HT, helical tomotherapy.

survival of the HT group was observed, but it was not statistically significant ( $p=0.203$ ). The 5-year OS for BT and HT were 79.2% and 84.5%, respectively.

### 3. Toxicities related to treatment

Acute and chronic adverse events are shown in **Table 3**. Gastrointestinal complications were the most common acute toxicity, followed by thrombocytopenia. There was no significant difference in acute complications between the groups. Late adverse events were also mostly related to gastrointestinal symptoms, and genitourinary complications were the second most common events, and they were not statistically different between 2 groups. Patients with these complications were successfully managed with conservative treatment.

## DISCUSSION

IMRT is becoming more widely utilized in the field of malignancies [19]. Several studies identified the feasibility of IMRT for whole pelvic radiation [20,21]. In these studies, IMRT significantly reduced acute and late toxicities to the organs at risk with comparable disease outcomes to traditional methods. In comparison to conventional IMRT, HT delivers highly conformal dose distribution with an increased number of beam directions and delivery of the dose to broad lesions [16,22]. Simone et al. reported the possibility of chemoradiation using HT with simultaneous integrated boost after surgery in patients with cervical cancer [14]. The treatment was associated with a lower rate of acute gastrointestinal and genitourinary adverse events.

In this study, HT showed a comparable disease outcome and complication profiles with BT. In one study, stereotactic body radiotherapy (SBRT) with CyberKnife was used as a boost radiation in patients with cervical cancer without grade 3 or 4 rectal or bladder toxicity [23]. In another study, SBRT showed better target coverage with better dose distribution to adjacent organs except in the bone marrow compared to BT in patients with locally advanced cervical cancer [24]. These findings show that these novel techniques provide a less toxic alternative to the focal high-dose radiation in BT.

One study reported that HT boost was effectively used in a single patient with advanced cervical cancer [17]. In that report, SBRT via HT was administered to a patient with stage IIIB cervical cancer, following whole pelvis radiation. HT was considered in this case due to the presence of multiple uterine fibroids with abnormal uterine bleeding. IMRT with HT has been reported

to be beneficial especially in patients with anatomical disturbances, making the appropriate use of BT difficult due to decreased flexibility and feasibility of extracorporeal approach to the pathologic lesion from any direction. The authors later reported preliminary results of the same treatment used on 9 patients that show favorable short-term outcomes [25].

Otherwise, radiation related toxicities of HT were comparable to those of BT group. The complications could be results of an unintended 'hot point' around the bladder or rectum during BT. But the exact 3-dimensional dose to the bladder could not be determined in this study, because BT was conducted via conventional method in our institution. However, all reported urinary complication were grade 1 or 2 in both groups, and urinary complications could occur a long time after the treatment. Further observation and additional analysis are required to determine long-term outcomes.

There was a population report from the National Cancer Data Base (NCDB) on radiation therapy consolidation modality for cervical cancer [26]. This study indicated a decline in the utilization of BT while new radiation technologies including IMRT showed poorer disease control. There are several factors that distinguish the result from present study previous studies. Firstly, the population in the NCDB report received radiation treatment from 2004 to 2011, while IMRT has been utilized since 2013 in our institution. In that time, the detailed technology and protocols have been changed and advanced from earlier techniques making IMRT/SBRT more accurate and elaborate [27]. This could improve the local disease control and survival outcome.

Another recent study by O'Donnell et al. [28] showed that those who received IMRT boost had worse OS than those who had BT. In that study, the propensity score matching was conducted with 1:1 ratio which is different from current study. Additionally, they included not only tomotherapy but also other tools which was used for IMRT. These variations could have contributed to the differences observed in comparison with the present study.

The main limitation is the retrospective nature of this study. As mentioned above, the indication of applying HT is not clear. However, the study population was established using the propensity score to minimize selection bias, and the matched groups showed statistically similar characteristics, even though there could still be hidden factors which were not considered in the matching process. Secondly, although disease outcomes of matched populations were not different between two groups, the poorer PFS after HT in original population should not be overlooked. That could be due to absence of perfect countermeasures for movement of target in every time of HT treatment, so image-guided radiation was utilized as much as possible to perform adaptive radiotherapy. Thirdly, the exact 3-dimensional dose for rectum or bladder was not able to be calculated due to the use of conventional BT in our institution. To compare exact radiation dose profile of BT to that of HT, the further evaluation using 3-dimensional BT should be performed. Lastly, the follow-up periods in the HT group were relatively short compared to those in the BT group. However, our data about PFS is considered sufficient to evaluate short-term outcomes, and the efficacy of HT boost is regarded as a feasible option. The long-term outcomes need to be investigated further.

In conclusion, HT led to disease outcomes comparable to those observed with conventional BT, without severe complications, as a boost radiation in patients with advanced cervical cancer. With constant improvement of protocols, HT could be a complementary boost protocol as



a single modality or hybrid with BT in advanced or anatomically unusual cases. Additional prospective studies with longer follow up periods are warranted to validate these results.

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