Clinical Impact of Escalating Relative High-dose-rate Intracavitary Brachytherapy Dose in Stage IIB Cervical Cancer

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Abstract. *Background/Aim:* To investigate whether high-dose-rate (HDR) intracavitary brachytherapy (IBT) dose ratios can predict treatment outcomes in patients with stage IIB cervical cancer. *Patients and Methods:* Ninety-three patients treated with weekly cisplatin-based concurrent chemoradiotherapy and HDR IBT were analyzed. Potential prognostic factors and treatment outcomes were compared between low-HDR-IBT-ratio (≤ 0.43) and high-HDR-IBT-ratio (> 0.43) groups, and univariate and multivariate analyses were performed. *Results:* Five-year disease-specific survival (DSS) and progression-free survival (PFS) rates were significantly shorter in the low-compared to the high-HDR-IBT-ratio group. A high HDR IBT ratio was confirmed as an independent prognostic factor for DSS and PFS. *Conclusion:* A high HDR IBT dose ratio improves DSS and PFS in patients with stage IIB cervical cancer. Therefore, active administration of HDR IBT beyond previously accepted levels may be necessary for the treatment of locally advanced cervical cancer.

The current treatment for patients with locally advanced cervical cancer is weekly cisplatin-based concurrent chemoradiotherapy (CCRT) followed by intracavitary brachytherapy (IBT) (1). In particular, IBT in combination with central pelvic external-beam radiotherapy (EBRT) has played a key role in increasing survival in patients with locally advanced cervical cancer.

A previous study demonstrated that the use of active IBT with a central pelvic EBRT dose (CPD) of 40.0-45.0 Gy resulted in favourable treatment outcomes with low complication rates in patients with International Federation

of Gynaecology and Obstetrics (FIGO) stage IIB cervical cancer (2). In an American population-based study, treatment of patients with FIGO stage IB-IVA disease with IBT and central pelvic EBRT was associated with a better survival rate than treatment with central pelvic EBRT alone (3). This was no different in patients who had received high-dose-rate (HDR) IBT to replace low-dose-rate IBT. A 2012 report of international brachytherapy patterns for cervical cancer revealed that a Japanese group used a total dose of 65.7 Gy [equivalent dose in 2.0 Gy fractions (EQD2) using an alpha/beta ratio of 10.0 Gy at point A] (4), which is significantly lower than the 80.9 Gy (EQD2) reported in other countries. Conversely, the mean HDR IBT ratio, defined as the ratio of the HDR IBT dose (EQD2) to the sum of the CPD and HDR IBT dose (EQD2), was reported to be 0.51 in Japan, which was significantly higher than the average of all other countries (0.45) (4). Japanese trials that have been conducted using both a low total EQD2 at point A (52.0 Gy for FIGO stage I-II, and 62.0 Gy for FIGO stage III-IVA) and a high HDR IBT ratio (0.61 for FIGO stage I-II, and 0.51 for FIGO stage III-IVA) achieved treatment outcomes that are comparable to those using conventional treatment methods (5, 6). Therefore, it may be beneficial to increase the HDR IBT ratio for the treatment of primary tumours.

Despite indirect evidence of the clinical significance of the HDR IBT ratio, there have been no immediate studies addressing it. Therefore, we aimed to investigate whether the HDR IBT ratio is associated with treatment outcomes in patients with FIGO stage IIB cervical cancer.

Patients and Methods

Study population. This study was approved by the Institutional Review Board (AJIRB-MED-OBS-16-031) of Ajou University Hospital (Suwon, Republic of Korea). All study participants provided written informed consent. Research was conducted in accordance with the 1964 Declaration of Helsinki and the Title 45, U.S. Code of Federal Regulations, Part 46, Protection of Human Subjects (effective 13th December 2001).

In total, 93 patients who were clinically diagnosed with FIGO stage IIB cervical cancer and treated with weekly cisplatin-based

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pelvic CCRT and HDR IBT between August 2001 and November 2013 were selected. All patients had undergone a physical examination and tumour histology was confirmed by a uterine cervical biopsy. Squamous cell carcinoma (SCC) antigen level, complete blood counts, and imaging data, including chest radiography, pelvic magnetic resonance imaging (MRI), with/without positron-emission tomography-computed tomography, were acquired at diagnosis. Cystoscopy and sigmoidoscopy were performed in patients with suspected rectal or bladder invasion. These patients were followed-up every 3 months for the first 3 years and every 6 months thereafter. The median follow-up of the whole patient group was 59 (range=15-136) months. Disease progression was evaluated by physical examination, Pap smear, MRI, or positron-emission tomography-computed tomography. Patients with disease progression were treated with chemotherapy, radiotherapy, or conservative care. The endpoints of this study were disease-specific survival (DSS) and progression-free survival (PFS). Radiation-related toxicities that occurred 8 months after the end of treatment were regarded as late complications.

Radiotherapy and chemotherapy. EBRT was delivered with a 10.0-15.0 MV photon beam to the whole pelvis until a total dose of 45.0 Gy (25 fractions of 1.8 Gy per day for 5 weeks) was achieved. Thirty-one patients underwent dose modification, including 18.0 Gy delivered in 12 fractions or 15.0 Gy delivered in 10 fractions twice daily in the third week, in order to shorten the overall treatment duration (defined as the time interval between the commencement and completion of radiotherapy) (7). These patients were treated to a total dose of 45.0 or 45.6 Gy, delivered in 27 fractions. The parametrium and lymph nodes were boosted with 3-5 fractions of 5.4-10.0 Gy after whole-pelvic EBRT. Midline blocks (4.0 cm in width) were applied after 36.0-51.5 Gy in 87 patients; inferior and superior borders were below the radiation field and above the tandem insertion site, respectively. Midline blocks were not applied in the remaining six patients. Two-dimensional HDR IBT with iridium-192 (MicroSelectron; Nucletron Technologies GmbH, Munich, Germany) was implemented biweekly after midline block insertion. The prescribed dose was 10.0-30.0 Gy (2-7 fractions of 4.0-5.0 Gy per fraction) at point A. Its location, as defined by the International Commission on Radiation Units and Measurements (Report 38), was modified to 1.0 or 1.5 cm in patients with a small uterus. The EQD2 using an alpha/beta ratio of 3.0 Gy for the bladder and rectal points was planned to be delivered to <80.0 Gy or <70.0 Gy in two-dimensional simulations, respectively. The total dose (EQD2) was defined as the sum of the CPD and the HDR IBT dose (EQD2) at point A. The HDR IBT ratio was defined as the ratio of the HDR IBT dose (EQD2) to the total dose (EQD2). Between 40.0 and 70.0 mg/m² of cisplatin was administered concurrently with central pelvic EBRT for 4-6 consecutive weeks. Chemotherapy was delayed for patients with absolute neutrophil counts of <500 cells/ μ l or platelet counts of <50,000 cells/ μ l. Granulocyte colony-stimulating factor and intravenous antibiotics were administered to patients with neutropenic fever.

Measurements of volumetric parameters. Of the 93 patients who underwent pre-treatment pelvic MRI, imaging data was available for 89 patients. Tumour areas were defined using the Eclipse^{TM} Treatment Planning System, version 10.0 (Varian Medical Systems, Palo Alto, CA, USA). From the initial MRI, we were able to

determine whether the cervical tumour had deviated in the anterior (bladder) or posterior (rectum) direction or not. Forty-two patients underwent pelvic MRI at 36.0-45.0 Gy. The tumour volumes of these patients were delineated in the same manner. The residual tumour volume was defined as the pre-treatment tumour volume (V1) divided by the tumour volume at 36.0-45.0 Gy (V2).

Statistical analyses. Initially, we analysed volumetric factors and fluctuations in the baseline CPD that might be relevant to the determination of CPD followed by the HDR IBT dose (EQD2). Next, we compared potential prognostic factors [age, pathological subtype, tumour size, pelvic lymph node involvement, SCC antigen/haemoglobin levels, overall treatment duration, and total dose (EQD2)] and treatment outcomes between patients with a low HDR IBT ratio and patients with a high HDR IBT ratio. Fisher's exact tests or chi-square tests were performed for categorical variables and *t*-tests or Mann-Whitney *U*-tests were performed for continuous variables. SCC antigen levels were categorised according to their median value. All potential prognostic factors, including the HDR IBT ratio, were analysed using the Kaplan-Meier method or a Cox proportional hazards model. The Cox proportional hazards model was used for multivariate analysis, including factors with a *p*<0.10 from the univariate analysis. All statistical analyses were performed using R software version 3.2.3 (The R Foundation for Statistical Computing, Vienna, Austria). A value of *p*<0.05 was considered statistically significant.

Results

Patient characteristics. A summary of the patients' demographic and clinicopathological characteristics, and volumetric parameters are provided in Table I.

Treatment outcomes. Seventeen out of 93 patients experienced disease progression. Two patients experienced relapse at the cervix without distant metastases (DMs). The residual cervical tumour progressed after treatment in four patients with DMs and in the remaining 11 patients, DMs occurred without local progression. Metastatic sites included the para-aortic lymph nodes (n=4 patients), lungs (n=3 patients), bone (n=3 patients), peritoneum (n=2 patients), liver (n=2 patients), back muscles (n=1 patient), supraclavicular lymph nodes (n=1 patient), and adrenal gland (n=1 patient). Of the 17 patients with disease progression, nine received >3 cycles of second-line chemotherapy (cisplatin plus paclitaxel). The remaining eight patients received conservative treatment because they were either intolerant to or had refused chemotherapy. Fourteen patients died of cervical cancer. The 5-year DSS and PFS rates for all patients combined were 85.9% and 81.6%, respectively.

Central pelvic EBRT doses. Figure 1 indicates that the baseline CPD increased from 35.4 to 44.3 Gy (EQD2) with increasing numbers of patients undergoing pelvic MRI during CCRT from 2007. The CPD (mean $\pm$ standard deviation) was significantly higher in patients who had undergone pelvic

Table I. Patient demographic and clinicopathological characteristics.

Characteristic	Value
Age at diagnosis	
Median (range), years	56 (30-82)
≤65 Years, n (%)	59 (63.4)
>65 Years, n (%)	34 (36.6)
Histology, n (%)	
ADSC/ADC	5 (5.4)
SCC	88 (94.6)
Pelvic lymph node involvement, n (%)	
Present	62 (66.7)
Absent	31 (33.3)
SCC antigen level	
Median (range), ng/ml	4.4 (0.5-59.4)
Haemoglobin level	
Median (range), g/dl	11.7 (4.9-13.0)
≤11 g/dl, n (%)	25 (26.9)
>11 g/dl, n (%)	68 (73.1)
Overall treatment duration	
Median (range), days	51 (41-78)
≤56 Days, n (%)	71 (76.3)
>56 Days, n (%)	22 (23.7)
CPD (EQD2), Gy	
Median (range)	40.1 (35.4-59.4)
HDR IBT dose (EQD2)	
Median (range), Gy	31.3 (12.5-37.5)
Total dose (EQD2) ^a	
Median (range), Gy	68.1 (59.0-87.1)
≤70 Gy	52 (55.9)
>70 Gy	41 (44.1)
HDR IBT ratio ^b	
Median (range)	0.43 (0.18-0.48)
Tumour volume on MRI ^c	
Pre-treatment tumour volume (V1)	
Median (range), cc	37 (3.1-164.2)
≤50 cc, n (%)	59 (66.3)
>50 cc, n (%)	30 (33.7)
Tumour volume at 36-45 Gy (V2)	
Median (range), cc	4.5 (0.0-38.2)
≤10 cc, n (%)	35 (83.3)
>10 cc, n (%)	7 (16.7)
V1 + V2	
Median (range), cc	37.2 (3.1-140.5)
V1 only	
Median (range), cc	36.5 (4.4-164.2)
Residual tumour volume (V1/V2)	
Median (range), %	14.2 (0.0-52.4)
≤20%, n (%)	32 (76.2)
>20%, n (%)	10 (23.8)
Tumour asymmetry ^c , n (%)	
Anterior (bladder)	12 (13.5)
Posterior (rectum)	20 (22.5)
None	57 (64.0)

ADC, Adenocarcinoma; ADSC, adenosquamous carcinoma; CPD, central pelvic external-beam radiotherapy dose; EQD2, equivalent dose in 2-Gy fractions using an alpha/beta ratio of 10 Gy at point A; HDR, high-dose rate; IBT, intracavitary brachytherapy; MRI: magnetic resonance imaging; SCC, squamous cell carcinoma. ^aDefined as the sum of the central pelvic EBRT dose (EQD2) and the HDR IBT dose (EQD2); ^bdefined as the ratio of the HDR IBT dose to the total dose (EQD2); ^cimaging data were not available for four out of 93 patients who underwent pre-treatment magnetic resonance imaging.

MRI during CCRT compared to patients who had not undergone pelvic MRI during CCRT [38.3±3.9 vs. 45.9±5.6 Gy (EQD2); $p<0.001$]. Table II suggests that the determination of CPDs for patients who had not undergone pelvic MRI during CCRT was related to tumor symmetry and a large V1, whereas the determination of CPDs for patients who had undergone MRI during CCRT was related to a large V2. However, the HDR IBT ratio was lower in the group with the asymmetric tumor and V1 >50.0 cc than the other three groups with symmetric tumor and V1 ≤50.0 cc, asymmetric and V1 ≤50.0 cc, or symmetric tumor and V1 >50.0cc. Conversely, HDR IBT ratios were not significantly different between the V2 ≤10.0 cc and V2 >10.0 cc groups.

Clinical findings according to HDR IBT ratio. Table III indicates that 13 patients in the low-HDR-IBT-ratio group (≤0.43) developed disease progression, including two with local recurrence, seven with DMs, and four with both local recurrence and DMs. Eleven out of these 13 patients experienced disease-related death. Conversely, three out of four patients with DMs in the group with high HDR IBT ratio (>0.43) experienced disease-related death ($p=0.020$ and $p=0.026$, respectively). The 5-year DSS and PFS rates were significantly lower in the group with low HDR IBT ratio compared to the group with the high HDR IBT ratio (5-year DSS: 78.3% vs. 93.1%; $p=0.003$ and 5-year PFS: 72.7% vs. 90.7%; $p=0.007$, respectively). Kaplan–Meier curves comparing treatment outcomes between the two groups (stratified according to the median HDR IBT ratio) highlight these differences (Figure 2A-B). Two out of four patients with confirmed rectal bleeding from sigmoidoscopy [total dose, 77.2 and 49.2 Gy (EQD2) and CPD, 75.5 and 44.3 Gy (EQD2), respectively] were treated with coagulation. For the remaining two patients, this complication was self-limited [total dose, 68.1 and 35.4 Gy (EQD2) and CPD, 71.6 and 38.9 Gy (EQD2), respectively]. One patient developed a radiation-induced vesicovaginal fistula, confirmed by an urologist and treated with an iliac conduit [total dose, 80.1 Gy (EQD2) and CPD, 56.7 Gy (EQD2)]. The group with low HDR IBT ratio included three patients who required intervention for late complications, whereas that with high HDR IBT ratio included two patients who did not require any intervention.

Multivariate analyses. Table IV summarises the univariate and multivariate analyses of all potential prognostic factors. Adjusted hazard ratios (HRs) for patients in the group with high HDR IBT ratio were independently low for both DSS (HR=0.26, 95% confidence interval=0.06-1.02; $p=0.053$) and PFS (HR=0.25, 95% confidence interval=0.06-0.96; $p=0.043$). The group aged >65 years had an independently high adjusted HR for DSS (HR=3.09, 95% confidence interval=0.99-9.62; $p=0.052$).

Figure 1. Relationships of baseline central pelvic external beam radiotherapy (EBRT) dose (EQD2, equivalent dose in 2-Gy fractions using an alpha/beta ratio of 10 Gy at point A with treatment years.

Table II. Associations between pre-treatment tumour volumes, tumour symmetry and residual tumour volumes and determination of central pelvic external-beam radiotherapy dose.

Tumour volume on MRI, cc	V1 (≤ 50 cc)+SYM	V1 (≤ 50 cc)+ASYM	V1 (> 50 cc)+SYM	V1 (> 50 cc)+ASYM	p-Value
V1 only (n=47)	(n=20)	(n=11)	(n=11)	(n=5)	-
CPD (EQD2), Gy	37.7 $\pm$ 3.8	37.3 $\pm$ 2.8	37.8 $\pm$ 3.1	43.1 $\pm$ 6.0	0.048*
HDR IBT dose (EQD2), Gy	31.1 $\pm$ 2.6	32.2 $\pm$ 1.4	32.2 $\pm$ 1.4	27.1 $\pm$ 6.1	0.023*
HDR IBT ratio	0.45 $\pm$ 0.04	0.46 $\pm$ 0.02	0.46 $\pm$ 0.03	0.39 $\pm$ 0.09	0.072
V1+V2 (n=42)	(n=16)	(n=12)	(n=10)	(n=4)	-
CPD (EQD2), Gy	44.6 $\pm$ 6.0	46.9 $\pm$ 4.8	46.4 $\pm$ 5.7	47.1 $\pm$ 6.9	0.261
HDR IBT dose (EQD2), Gy	25.6 $\pm$ 7.1	28.0 $\pm$ 5.9	25.8 $\pm$ 8.0	25.7 $\pm$ 9.8	0.779
HDR IBT ratio	0.36 $\pm$ 0.09	0.37 $\pm$ 0.06	0.35 $\pm$ 0.09	0.35 $\pm$ 0.11	0.819
	V2 (≤ 10 cc)		V2 (> 10 cc)		
V1+V2 (n=42)	(n=35)		(n=7)		-
CPD (EQD2), Gy	45.2 $\pm$ 5.8		49.2 $\pm$ 3.3		0.089
HDR IBT dose (EQD2), Gy	26.2 $\pm$ 6.8		26.5 $\pm$ 9.3		0.923
HDR IBT ratio	0.37 $\pm$ 0.08		0.34 $\pm$ 0.09		0.524
	Residual tumour volume (V1/V2) ($\leq 20\%$)		Residual tumour volume (V1/V2) ($> 20\%$)		
V1+V2 (n=42)	(n=32)		(n=10)		-
CPD (EQD2), Gy	45.1 $\pm$ 5.4		48.5 $\pm$ 5.9		0.100
HDR IBT dose (EQD2), Gy	25.9 $\pm$ 6.2		27.4 $\pm$ 10.0		0.649
HDR IBT ratio	0.37 $\pm$ 0.08		0.34 $\pm$ 0.09		0.798

ASYM, Tumour asymmetry; CPD, central pelvic external beam radiotherapy dose; EQD2, equivalent dose in 2-Gy fractions using an alpha/beta ratio of 10 Gy at point A; HDR, high-dose rate; IBT, intracavitary brachytherapy; MRI, magnetic resonance imaging; SYM, tumour symmetry; V1, pre-treatment tumour volume; V2, tumour volume at 36-45 Gy. Data are means $\pm$ standard deviation. *Significantly different at $p < 0.05$.

Table III. Two-group comparisons according to the median high-dose-rate (HDR) intracavitary brachytherapy (IBT) ratio.

Factor	HDR IBT ratio		<i>p</i> -Value
	≤0.43 (n=47)	>0.43 (n=46)	
Age at diagnosis (>65 years), n (%)	23 (48.9)	11 (23.9)	0.022*
Histology (ADSC/ADC), n (%)	1 (2.1)	4 (8.7)	0.345
Pelvic lymph node involvement, n (%)	30 (63.8)	32 (69.6)	0.714
Haemoglobin level (>11 g/dl), n (%)	33 (70.2)	35 (76.1)	0.686
SCC antigen level (>4.4 ng/ml), n (%)	27 (57.4)	19 (41.3)	0.177
Overall treatment duration (>56 days), n (%)	14 (29.8)	8 (17.4)	0.245
Use of MRI at 36-45 Gy, n (%)	33 (73.3)	9 (20.5)	<0.001*
Total dose (EQD2)			
>70 Gy, n (%)	25 (53.2)	16 (34.8)	0.114
Mean±SD	70.6±5.1	70.8±4.8	0.865
CPD (EQD2) ^a , Gy	45.8±5.4	37.6±3.2	<0.001*
HDR IBT dose (EQD2) ^a , Gy	24.8±5.4	33.2±1.8	<0.001*
Disease progression, n (%)	13 (27.7)	4 (8.7)	0.036*
Local progression	2 (4.3)	0 (0.0)	0.484
Local progression + DM	4 (8.5)	0 (0.0)	0.131
DM	7 (14.9)	4 (8.7)	0.546
Disease-specific death, n (%)	11 (23.4)	3 (6.5)	0.047*
5-year PFS rate, %	72.7	90.7	0.007*
5-year DSS rate, %	78.3	93.1	0.003*
Late complications, n (%)			
Rectal bleeding - self-limited	0 (0.0)	2 (4.3)	
Rectal bleeding - coagulation	2 (4.3%)	0 (0.0)	
Vesicovaginal fistula	1 (2.1)	0 (0.0)	0.083
Tumour volumes on MRI ^b , n (%)			
Pre-treatment tumour volume (V1 >50 cc)	17 (37.8)	13 (29.5)	0.555
Tumour asymmetry (anterior/posterior)	17 (37.8)	15 (34.1)	0.887

ADSC, Adenosquamous carcinoma; ADC, adenocarcinoma; CPD, central pelvic external-beam radiotherapy dose; DM, distant metastasis; DSS, disease-specific survival; EQD2, equivalent dose in 2-Gy fractions using an alpha/beta ratio of 10 Gy at point A; MRI, magnetic resonance imaging; PFS, progression-free survival; SCC, squamous cell carcinoma. ^aMean±standard deviation; ^bimaging data were not available for four out of 93 patients who underwent pre-treatment MRI. *Significantly different at *p*<0.05.

Discussion

HDR IBT ratios predicted treatment outcomes in patients with FIGO stage IIB cervical cancer treated with CCRT followed by HDR IBT. Patients in the group with low HDR IBT ratio had significantly shorter DSS and PFS rates compared to those of the group with high HDR IBT ratio, with no significant differences observed for conventional prognostic factors. Elevated HDR IBT ratios were associated with longer DSS and PFS rates.

There may have been more patients in the group with low HDR IBT ratio than in that with a high HDR IBT ratio who did not respond rapidly to central pelvic EBRT since the CPD may be determined by tumour response during central pelvic EBRT. Moreover, a large tumour volume and poor response to central pelvic EBRT (EQD2) might result in a low HDR IBT ratio. Therefore, it must be established whether the CPD was determined by tumour response or not before explaining the clinical significance of HDR IBT

ratios. Our data suggest that patients who had undergone MRI at 36.0-45.0 Gy had a significantly higher baseline CPD compared to patients who had not. In particular, the CPD for patients who did not have MRI data available for tumour responses was higher in the group with both tumour asymmetry and a V1 of >50.0 cc compared to the other groups. This resulted in a low HDR IBT ratio. The increase in the CPD may be explained by concerns of insufficient dose coverage in the asymmetric region, regardless of tumour response. Conversely, patients who had undergone MRI during CCRT tended to have a higher CPD in the V2 >10.0 cc group compared to the V2 ≤10.0 cc group. This did not result in a reduction in HDR IBT ratio due to maintaining the HDR IBT dose (EQD2). Finally, we were unable to find any evidence in support of an association between tumour response and HDR IBT ratios from our data.

The group with low HDR IBT ratio included a greater proportion of patients who had undergone MRI at 36.0-45.0 Gy and with an age of >65 years compared to the group with

Figure 2. Kaplan–Meier plots of disease-specific (A) and progression-free (B) survival rates of patients with stage IIB cervical cancer stratified according to a median high-dose-rate (HDR) intracavitary brachytherapy (IBT) ratio of 0.43. Patients with a low (≤ 0.43) or a high (> 0.43) HDR IBT ratio are represented by solid and dashed lines, respectively. The HDR IBT ratio was defined as the ratio of the HDR IBT dose (EQD2, equivalent dose in 2-Gy fractions using an alpha/beta ratio of 10 Gy at point A) to the sum of the central pelvic external beam radiotherapy dose (EQD2) and the HDR IBT dose (EQD2).

high HDR IBT ratio. There was also no statistically significant relevance of total dose (EQD2) analyses. Variables such as pathology, pelvic lymph node involvement, SCC antigen or haemoglobin levels, overall treatment duration, total dose (EQD2), V1, and tumour asymmetry were not significant prognostic factors for DSS or PFS in patients with FIGO stage IIB cervical cancer. Their prognostic effects in matching FIGO stage patients may be attenuated although they were shown to be important for predicting survival in patients with locally advanced cervical cancer (8-10). This may have arisen from an association between FIGO stage and these variables, as well as the exclusion of patients who underwent radiotherapy field modification because of a bulky tumour, pelvic lymph node involvement, or high SCC antigen level. An older age of > 65 years was a significant predictor of poorer DSS in the univariate analysis. However, this finding is in disagreement with a previous study (11), which revealed comparable treatment outcomes for elderly and non-elderly patients. This could be because the group with low HDR IBT ratio included more patients aged > 65 years compared to that with high HDR IBT ratio. Moreover, six out of nine patients (66.7%) who had received inadequate second-line chemotherapy after progression were aged > 65 years, whilst two out of eight patients (25.0%) who did

receive adequate second-line chemotherapy after progression were aged ≤ 65 years ($p > 0.05$).

Previous reports supported the notion that brachytherapy can improve the survival rate of patients with cervical cancer (2-4). Therefore, we hypothesised that elevated HDR IBT ratios might be relevant to improving treatment outcomes in these patients. This strategy might be effective for the prevention of DMs, as well as the suppression of local progression. If patients with both local progression and DMs are also considered as DM, there tended to be differences in the HDR IBT ratio (23.4% vs. 8.7%; $p = 0.100$). The reason why active use of HDR IBT influences DM may be explained with respect to cancer and immunity. HDR IBT may induce cancer cell death more rapidly than conventional fractionated central pelvic EBRT through the precise delivery of high doses during a short interval (12). EQD2 calculated by a linear quadratic model might partially reflect the radiobiological effect of HDR IBT. However, HDR IBT might be more effective for relatively late responsive cancer cells (alpha/beta ratio of < 10.0 Gy at point A) than central pelvic EBRT because not all cancer cells are early responsive (alpha/beta ratio of 10 Gy at point A). Late-responsive cancer cells would increase during central pelvic EBRT because the CPD favours the eradication of early-responsive

Table IV. Univariate and multivariate analyses of patients with stage IIB cervical cancer.

	OS			PFS		
	HR	95% CI	p-Value	HR	95% CI	p-Value
Univariate factors ^a						
Age at diagnosis (>65 years)	4.27	1.42-12.83	0.010*	2.41	0.92-6.36	0.074
Histology (ADSC/ADC)	1.48	0.019-11.38	0.704	1.06	0.14-7.92	0.964
Pelvic lymph node involvement	0.57	0.19-1.30	0.153	0.62	0.24-1.64	0.339
Haemoglobin level (>11 g/dl)	0.44	0.15-1.27	0.130	0.46	0.18-1.22	0.119
SCC antigen level (>4.4 ng/ml)	2.68	0.84-8.54	0.096	2.78	0.98-7.90	0.055
Overall treatment duration (>56 days)	0.83	0.23-3.01	0.775	0.75	0.24-2.32	0.620
Total dose (EQD2) (>70 Gy)	1.48	0.52-4.23	0.467	1.57	0.60-4.07	0.358
Pre-treatment tumour volume (V1 >50 cc)	1.96	0.63-6.09	0.243	2.44	0.88-6.74	0.085
Tumour asymmetry (anterior/posterior)	0.56	0.15-2.05	0.378	0.58	0.18-1.81	0.347
HDR IBT ratio (>0.43)	0.17	0.04-0.63	0.008*	0.23	0.07-0.073	0.013*
Multivariate factors						
Age at diagnosis (>65 years)	3.09	0.99-9.62	0.052	2.23	0.74-6.64	0.152
SCC antigen level (>4.4 ng/ml)	2.04	0.62-6.67	0.240	2.55	0.80-8.08	0.111
Pre-treatment tumour volume (V1 >50 cc)	-	-	-	2.62	0.90-7.59	0.076
HDR IBT ratio (>0.43)	0.26	0.06-1.02	0.053	0.25	0.06-0.96	0.043*

ADSC, Adenosquamous carcinoma; ADC, adenocarcinoma; CI, confidence interval; EQD2, equivalent dose in 2 Gy fractions using an alpha/beta ratio of 10 Gy at point A; HDR, high-dose rate; HR, hazard ratio; IBT, intracavitary brachytherapy; OS, overall survival; PFS, progression-free survival; SCC, squamous cell carcinoma. ^aFactors with a value of $p < 0.1$ from the univariate analysis were included in the multivariate analysis.

*Significantly at $p < 0.05$.

cancer cells. Therefore, escalation of the HDR IBT dose (EQD2) might reduce the risk of DMs and local progression by reducing late-responsive cancer cells, which could be sustained if they were treated with central pelvic EBRT. In addition, recent studies have demonstrated that lymphopenia during central pelvic EBRT was associated with a poor response and shorter survival times in various types of cancer (13-16). These studies were supported by increasing evidence of a link between tumour-infiltrating lymphocytes and cancer prognosis (17). Central pelvic EBRT may reduce circulating lymphocytes, as well as cancer cells, and this may be related to a poor survival (18). In contrast, HDR IBT is more likely to sustain peripheral lymphocytes due to its physical properties and this could complement central pelvic EBRT-related lymphopenia. Furthermore, HDR IBT may increase tumour-specific immune responses as in the case of prostate cancer (19). Nevertheless, the systemic effect of HDR IBT in the treatment of cervical cancer is poorly understood and requires further investigation.

Our findings demonstrate that an important factor in reducing late complications is increased HDR IBT doses (EQD2) relative to the total dose (EQD2). All late complications requiring intervention occurred in patients with low relative HDR IBT doses (EQD2). These patients were treated with a total dose of ≥ 75.0 Gy (EQD2), including a CPD of > 44.0 Gy (EQD2). This was consistent with previously published studies in which patients with FIGO

stage IIB cervical cancer treated with a CPD of 40.0-45.0 Gy (EQD2) and high relative low-dose-rate IBT had the lowest complication rates (2, 20), considering the similarity between low-dose-rate IBT and HDR IBT in the development of severe complications. We might infer that irradiation of a large volume of the rectum and bladder by EBRT could be more significant in treating morbidity than the irradiation of a small volume of the pericervical organ by HDR IBT.

Consequently, it may be advantageous for survival to administer HDR IBT as much as possible instead of central pelvic EBRT for primary tumour control. According to this result, we might consider HDR IBT at 3-4 weeks to increase the HDR IBT ratio if the dose coverage for HDR IBT of the primary tumour was retained despite a poor response to central pelvic EBRT. In this case, MRI-guided HDR IBT may help to increase the HDR IBT ratio (21).

Although, as far as we are aware, this study is the first to demonstrate the clinical significance of the HDR IBT ratio in FIGO stage IIB cervical cancer, there are several limitations. Firstly, we were unable to establish whether a wide range of HDR IBT ratios would aid in improving clinical outcomes, because our study did not include HDR IBT ratios > 0.48 . Secondly, this was a retrospective study of a relatively small number of patients. Therefore, future prospective studies are warranted. Despite its limitations, this study has merit in analyzing a homogeneous group of patients treated with full cycles of cisplatin-based CCRT

followed by HDR IBT (EQD2) and in revealing that there are no significant differences in conventional prognostic factors between groups with high and low HDR IBT ratios.

In conclusion, a high HDR IBT ratio can improve DSS and PFS rates in patients with FIGO stage IIB cervical cancer. Increasing HDR IBT use in determining clinical total doses (EQD2) also reduces disease progression. Active administration of HDR IBT beyond previously accepted levels may be necessary for the treatment of locally advanced cervical cancer. Therefore, future prospective studies are warranted to further investigate this.

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