Investigation of the optimal combination of external beam radiotherapy and high-dose-rate intracavitary brachytherapy in definitive radiotherapy for uterine cervical cancer patients

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Investigation of the optimal combination of external beam radiotherapy and high-dose-rate intracavitary brachytherapy in definitive radiotherapy for uterine cervical cancer patients

Directed by Professor Yong Bae Kim

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Kyung Hwan Kim

<TABLE OF CONTENTS>

LIST OF FIGURES

LIST OF TABLES

ABSTRACT

Investigation of the optimal combination of external beam radiotherapy and high-dose-rate intracavitary brachytherapy in definitive radiotherapy for uterine cervical cancer patients

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Purpose: Intracavitary brachytherapy (ICBT) and external beam radiotherapy (EBRT) are both essential components of definitive radiotherapy for patients with uterine cervical cancer. From previous phase II trials, reduced cumulative central dose using midline block (MLB) did not compromise the treatment outcome while reducing late toxicity rate compared to other studies. However, no randomized evidence is available and long term results are needed to confirm the efficacy and safety of this treatment approach. We aimed to assess the efficacy and toxicity of low cumulative central dose using MLB during EBRT.

Patients and Methods: Between January 1988 and December 2010, a total of 1559 patients with uterine cervical cancer (FIGO stage IB 410, stage IIA 133, stage IIB 1016) who received definitive radiotherapy (n = 1054, 67.6%) or platinum-based

chemoradiotherapy (n = 504, 32.4%) consisting of EBRT and high-dose-rate intracavitary brachytherapy (HDR-ICBT) were retrospectively analyzed. The median EBRT dose was 45.0 Gy (range, 30.6–60.0 Gy) in 1.8 Gy per fraction and median HDR-ICBT dose prescribed at point A was 30 Gy (range, 12–63 Gy) in median 5 Gy (3.0–6.0 Gy) per fraction. During EBRT, tumor response was checked every week and when sufficient response was achieved to place the ICBT applicator, MLB of 4 cm width and 8–10 cm in height was placed (n = 1195, MLB group). For patients with slow tumor response during EBRT, full dose was applied without MLB (n = 364, non-MLB group). MLB was performed after ≤ 27 Gy (n = 229), > 27 Gy and ≤ 36 Gy (n = 847), or > 36 Gy (n = 119) of EBRT. The rectal and bladder doses were estimated using doses at the International Commission on Radiation Units and Measurements points. To calculate the cumulative dose from EBRT and ICBT, the biologically equivalent dose in 2-Gy fractions (EQD2) using the linear quadratic model was used (α/β value of 3 for normal tissue and 10 for tumor). Propensity score matching was also performed to balance the characteristics between MLB and non-MLB group.

Results: Median follow-up period was 89.0 months (range, 2.4-320.2 months). The 10-year overall survival (OS), progression-free survival (PFS), regional recurrence (RR), and local recurrence (LR) rates were 82.3%, 74.7%, 2.6%, and 9.5%, respectively. The 10-year OS, PFS, RR, and LR (all *P*s <0.05) were significantly superior in the MLB group compared to the non-MLB group. The MLB group was older in age, had smaller tumor size, lower FIGO stage, higher pelvic and para-aortic lymph node metastases rate than the non-MLB group. $EQD2_{point\ A}$ (72.9 Gy vs. 86.4

Gy), $EQD2_{rectal}$ (64.5 Gy vs. 74.8 Gy), and $EQD2_{bladder}$ (67.4 Gy vs. 75.9 Gy) were all significantly lower in the MLB group (all *P*s <0.05). Grade ≥2 late rectal toxicity was significantly lower in MLB group (8.1% vs. 11.5%, $P = 0.045$). There was no significant difference in late genitourinary and small bowel toxicity. After all patient and tumor characteristics were well balanced using propensity score matching, the 10-year OS, PFS, RR, and LR were similar between the MLB and non-MLB group (all Ps >0.05) despite the lower $EQD2_{point\ A}$ (72.9 Gy vs. 86.4 Gy; P <0.001).

Conclusion: Lowering the cumulative central dose using EBRT with MLB according to tumor response may reduce rectal toxicity without compromising treatment outcome. The efficacy of MLB should further be evaluated in prospective trials.

Key words: uterine cervical cancer, midline block, radiotherapy, high-dose-rate, intracavitary brachytherapy

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I. INTRODUCTION

Uterine cervical cancer is the seventh most common cancer worldwide and the tenth leading cause of cancer mortality.[1] However, it is the second most common and third leading cause of cancer mortality in developing countries.[2] Definitive radiotherapy (RT) and concurrent chemoradiotherapy (CRT) has been the standard treatments for early stage and locally advanced uterine cervical cancer.[3,4] Standard RT for uterine cervical cancer consists of external beam RT (EBRT) and intracavitary brachytherapy (ICBT). Recently high-dose-rate ICBT (HDR-ICBT) is taking over the place of low-dose-rate ICBT[5-7] and the dose schedules of EBRT and HDR-ICBT largely differ among various countries and institutions.[5,6,8] The optimal dose schedule

is yet to be established.

ICBT plays a major role in definitive treatment of patients with uterine cervical cancer. The impact of ICBT on survival was reported from two population based studies, which showed significantly higher overall survival in patients who received ICBT compared to those who did not.[9,10] One of the concerns in utilizing HDR-ICBT would be its late toxicity. The late toxicity rate of rectum and bladder would increases in correlation to the increasing radiation dose delivered to both organs. From a previous report from our institution, keeping the biological effective dose of point A not higher than 90 Gy was associated with lesser late rectal and bladder complications.[11] More recent studies showed that the dose volume parameters of the rectum and bladder were associated with the rate of late toxicity.[12,13] Therefore to enhance the therapeutic ratio, the establishment of an optimal dose schedule of HDR-ICBT and EBRT is necessary.

In an attempt of reducing the central dose, using the midline block (MLB) during EBRT was tested in a prospective multi-institutional study from Japan delivering biologically equivalent dose in 2-Gy fractions (EQD2) of 52–65 Gy to point A.[14,15] They reported a comparable outcome and lower incidence of late toxicity compared to other studies that used higher point A doses. However, the median follow-up period was relatively short in both studies. In our institution, we have adopted MLB during EBRT since 1988 for the last three decades. The initial results were reported previously and showed that the results were comparable to other reports that used global dose schedules not using MLB.[16] Here we present the long-term

follow-up data on treatment outcome and toxicity of using MLB during EBRT in conjunction with HDR-ICBT.

II. MATERIALS AND METHODS

1. Patients

The study included patients with histologically confirmed FIGO stage IB–IIB uterine cervical carcinoma treated with definitive RT or CRT using EBRT and HDR-ICBT between January 1988 and December 2010. Sixty-five patients were excluded due to double primary cancer (n = 15), small cell histology (n = 5), ICBT refusal (n = 13), previous hysterectomy (n = 2), and distant metastases (n = 30). Eventually, data of 1559 patients were retrospectively analyzed.

The staging evaluation routinely included physical examination, complete blood count, liver function test, sigmoidoscopy, cystoscopy, intravenous pyelogram, and chest radiographs. Either computed tomograghy (CT) scans (n = 1234) or magnetic resonance imaging (MRI) (n = 409) were performed to evaluate lymph node involvement for all patients. Lymph nodes larger than 1 cm in the short-axis dimension or with central necrosis were considered metastatic. Since 2004, 18F-fluorodeoxyglucose positron emission tomography (FDG-PET) was commonly performed and 158 patients underwent FDG-PET.

2. Radiotherapy

The treatment protocol at Yonsei Cancer Center has been described previously.[16-18] RT consisted of a combination of EBRT and HDR-ICBT. EBRT included the whole pelvis and was delivered by a 10-MV linear accelerator using the four-field box technique. The upper border of the pelvic field was L4/5 and lower

border was below the obturator foramen or 2 cm inferior to the caudal margin of tumor. The lateral borders were 1.5 cm beyond the lateral margin of bony pelvis for the anteroposterior (AP)-posteroanterior (PA) portals. The anterior border was placed at the anterior margin of symphysis pubis and the posterior border was placed at the posterior surface of the second sacrum. For patients with paraaortic lymph node involvement, extended field RT to T11/12 or T12/L1 was performed.[19] In patients with pelvic lymph node involvement near the aortic bifurcation, a semi-extended field was used which the superior border had extended to the upper margin of L2. EBRT was delivered 5 days per week to a total dose of 45–50.4 Gy in 1.8 Gy per fraction. MLB was placed after a sufficient tumor regression was achieved for ICBT applicator insertion which was checked by weekly pelvic examination (MLB group, n = 1195). The MLB usually were 4-cm wide and covered the inserted tandem. However, patients with insufficient response received full dose EBRT without placing MLB (non-MLB group, n = 364). The portal arrangement was changed to the AP-PA technique after the MLB was inserted. Usually the MLB was placed after 27–36 Gy of EBRT and HDR-ICBT was immediately initiated. After completion of HDR-ICBT, EBRT with MLB was delivered. In cases without sufficient response after 45 Gy of EBRT, an additional boost to the primary tumor mass was attempted to a total dose of 60 Gy. Since 1979, the Ralstron 303 (Shimadzu, Kyoto, Japan), utilizing Co-60 sources, had been used three times per week at 3 Gy per fraction to a total dose of 39 Gy. Later, GammaMed II (Sauerwein, Haan, Germany) with Ir-192 was applied at 5 Gy per fraction to a total dose of 30 Gy since 1989. Applicator insertion could be

done easily on an outpatient basis without anesthesia, and the time required for each treatment was approximately 10 to 15 minutes. For HDR-ICBT planning, both orthogonal AP-PA and lateral X-ray films were taken and the position of point A, bladder point, and rectal point were defined according to the International Commission on Radiation Units and Measurements (ICRU) 38 recommendation. Lymph node boost of 5.4–14.4 Gy in 1.8 Gy per fraction was performed in cases with lymph node metastases. Parametrial boost with MLB was used for patients with suspected residual parametrial disease after the planned course of EBRT and HDR-ICBT.

EQD2 using the linear quadratic model was used (α/β value of 3 for normal tissue [Gy_3] and 10 for tumor [Gy_{10}]) to calculate the cumulative dose from EBRT and ICBT at point A ($EQD2_{pointA}$), bladder point ($EQD2_{bladder}$), and rectal point ($EQD2_{rectum}$). The equation used to calculate the EQD2 was as follows[20]:

$$EQD2_{total} = EQD2_{EBRT} + EQD2_{ICBT}$$

$$= N_{EBRT} d_{EBRT} \left(\frac{d_{EBRT} + \alpha/\beta}{2 + \alpha/\beta} \right) + N_{ICBT} d_{ICBT} \left(\frac{d_{ICBT} + \alpha/\beta}{2 + \alpha/\beta} \right)$$

where N_{EBRT} is the number of fractions delivered before placing MLB, d_{EBRT} is the fraction dose of EBRT, N_{ICBT} is the number of delivered fractions of ICBT, and d_{ICBT} is the fraction dose of ICBT.

3. Chemotherapy

Concurrent chemotherapy was applied in 505 patients and most of them received platinum-based chemotherapy (n = 484). The commonly applied regimens were combination of carboplatin and 5-fluorouracil or combination of cisplatin and 5-fluorouracil performed at first, fourth, and seventh weeks of RT or weekly administration of cisplatin during RT. For patients with adenocarcinoma a combination of cisplatin, cyclophosphamide, and adriamycin was used.[18]

4. Follow-up and toxicity evaluation

Treatment response was evaluated 3 months after completion of treatment. Complete remission (CR) was defined as 100% decrease, partial response (PR) as ≥50% decrease, and progressive disease (PD) as >25% increase in size of gross tumor on clinical evaluation or radiologic images. Follow-up examinations were performed every 3 months for the first two years, every 6 months for the next 3 years, and then once per year every year afterwards. Patients were evaluated for disease status and treatment related toxicity, which included complete physical examinations in addition to laboratory, radiologic tests, and biopsies, when clinically indicated. Recurrences involving the cervix, vagina, or parametrial tissue were classified as local and lymph node failures within the RT field were defined as regional recurrences. Lymph node or hematogeneous metastasis outside the RT field were defined as distant recurrences. Late toxicities were defined as those occurring 3 months after treatment and graded according to the Radiation Therapy Oncology Group and European Organization for

Research and Treatment of Cancer late radiation morbidity scoring scheme.[21] Late distal ureteral strictures due to RT were counted as late genitourinary (GU) toxicity and graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.0.

5. Statistical analysis

Categorical data were analyzed by using Fisher's exact test or $\chi 2$ analyses and continuous data were compared using Mann-Whitney U test between the two groups. The Kaplan-Meier method and log-rank test were used to estimate and compare rates of overall survival (OS) and progression-free survival (PFS). Rates of local recurrence (LR), regional recurrence (RR), and toxicity were estimated by means of the cumulative incidence method and were compared between the two groups with the use of the Gray's test.[22] OS, PFS, PC, and LC rates were measured from the date of treatment start to the date of death from any cause, date of recurrence or death, date of regional recurrence, and date of local recurrence, respectively. Only death was considered a competing risk for local recurrence, regional recurrence, or toxicity. To determine the optimal cut-off values for $EQD2_{rectum}$ and $EQD2_{bladder}$ in predicting late rectal and bladder toxicity, we applied receiver operating characteristic (ROC) curve analyses. The optimal cutoff values were established by determining the values with maximum Youden index (sensitivity + specificity –1). Logistic regression analyses was performed to analyze the dose-response relationship between the late toxicity rate and ICRU dose. To balance the patient and tumor characteristics (age,

histology, tumor size, FIGO stage, lymph node involvement, use of concurrent chemotherapy) between MLB and non-MLB group, propensity score matching was performed using the Match-it package for R software version 3.1.0.[23] P <0.05 was considered statistically significant. All analyses were performed using IBM SPSS version 20.0 (SPSS, Chicago, IL).

III. RESULTS

1. Patient and treatment characteristics

Patient and treatment characteristics are summarized in Table 1. MLB was performed after ≤ 27 Gy (n = 229), > 27 Gy and ≤ 36 Gy (n = 847), or > 36 Gy (n = 119) of EBRT. The MLB group presented with older age, lower FIGO stage, smaller tumor size, lower pelvic and para-aortic lymph node metastases rate, and higher complete response rate than the non-MLB group. More patients in the non-MLB group received a whole pelvis dose of >45 Gy. There was no significant difference in use of concurrent chemotherapy. The $EQD2_{rectum}$, $EQD2_{bladder}$, and $EQD2_{pointA}$ were significantly lower in the MLB group compared to the non-MLB group.

Table 1. Patient and Treatment Characteristics

	non-MLB group N = 364	MLB group N = 1195	
Characteristic	N (%)	N (%)	*P*
Age, median (range), years	53 (21–87)	57 (24–86)	<0.001
Histologic subtype			0.198
Squamous cell	330 (90.7)	1108 (92.7)	
Non-squamous cell	34 (9.3)	87 (7.3)	
FIGO stage			<0.001
IB	44 (12.1)	366 (30.6)	
IIA	28 (7.7)	105 (8.8)	
IIB	292 (80.2)	724 (60.6)	
Tumor size, cm			<0.001
<4.0	105 (28.8)	682 (57.1)	

Characteristic	non-MLB group N = 364 N (%)	MLB group N = 1195 N (%)	*P*
≥4.0	259 (71.2)	513 (42.9)	
Pelvic lymph node			<0.001
Negative	274 (75.3)	998 (83.5)	
Positive	90 (24.7)	197 (16.5)	
Paraaortic lymph node			0.005
Negative	347 (95.3)	1171 (98.0)	
Positive	17 (4.7)	24 (2.0)	
Chemotherapy regimen			0.230
Platinum based regimen	121 (23.2)	363 (30.5)	
Others	5 (1.4)	16 (1.3)	
Radiotherapy alone	238 (65.4)	816 (68.3)	
Radiotherapy field			0.001
Whole pelvis	320 (87.9)	1116 (93.4)	
Semi-extended field	25 (6.9)	55 (4.6)	
Extended field	19 (5.2)	24 (2.0)	
Complete response			<0.001
No	25 (6.9)	11 (0.9)	
Yes	339 (93.1)	1184 (99.1)	
EBRT dose			<0.001
≤45 Gy	324 (89.0)	1154 (96.6)	
>45 Gy	40 (11.0)	41 (3.4)	
$EQD2_{ICBT}$, median (range), Gy			
Point A dose, Gy_{10}	42.3 (16.3–77.9)	37.5 (26.0–62.0)	0.293
Bladder point dose, Gy_3	32.3 (8.1–100.9)	35.0 (7.1–102.2)	0.001
Rectal point dose, Gy_3	30.9 (4.1–103.3)	31.3 (1.9–160.0)	0.073
$EQD2_{EBRT+ICBT}$, median (range), Gy			
Point A dose, Gy_{10}	86.4 (54.9–122.2)	72.9 (51.7–98.0)	<0.001
Bladder point dose, Gy_3	75.9 (49.0–144.1)	67.4 (33.9–136.8)	<0.001
Rectal point dose, Gy_3	74.8 (47.3–160.3)	64.5 (29.3–198.0)	<0.001

Abbreviations: FIGO = International Federation of Gynecology and Obstetrics; MLB = midline block; EQD2 = biologically equivalent dose in 2-Gy fractions; EBRT = external beam radiation therapy; ICBT = intracavitary brachytherapy

2. Late toxicity rate with or without midline block

Table 2 summarizes the crude rate of grade ≥2 and of grade ≥3 late toxicity after RT according to MLB application.

Table 2. Late Toxicity Rates in the Midline Block (MLB) Group and non-MLB Group

	non-MLB group N = 364	MLB group N = 1195	
	N (%)	N (%)	*P*
Rectal toxicity			
Grade ≥2	42 (11.5)	97 (8.1)	0.045
Grade ≥3	17 (4.7)	24 (2.0)	0.005
Genitourinary toxicity			
Grade ≥2	26 (7.1)	65 (5.4)	0.225
Grade ≥3	6 (1.6)	13 (1.1)	0.394
Small bowel toxicity			
Grade ≥2	8 (0.8)	19 (1.6)	0.496
Grade ≥3	5 (0.5)	15 (1.3)	0.256

Abbreviations: MLB = midline block

The actuarial incidence of grade ≥2 late rectal, bladder, and small bowel

toxicity are shown in Figure 1.

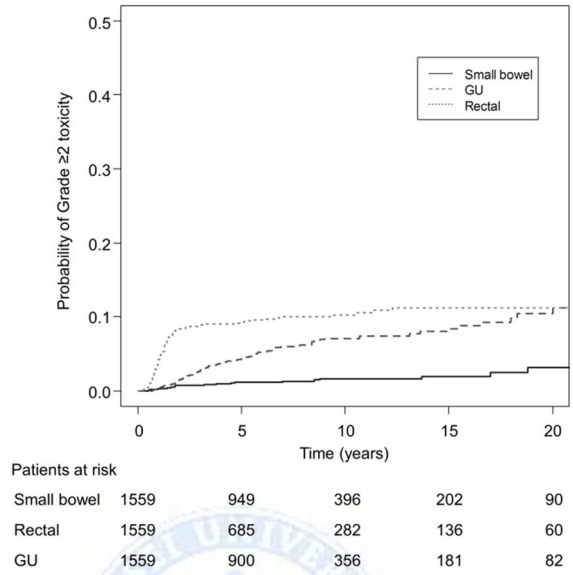

Fig. 1. Grade ≥2 late complication rates of rectum, genitourinary (GU), and small bowel.

The 10-year rate of grade ≥2 late rectal toxicities, late GU toxicities and late small bowel toxicities were 10.4% (95% confidence interval [CI], 8.8–12.3%), 7.2% (95% CI, 5.8–9.0%), and 1.7% (95% CI, 1.1–2.7%), respectively. Most of the rectal toxicity occurred within 2 years after treatment but the incidence of GU toxicity consistently increased throughout the follow-up period for more than 20 years (Fig 1). There was no difference in 10-year grade ≥2 late small bowel toxicity between the non-MLB and MLB groups (1.4% versus 1.8%, $P = 0.565$). The 10-year grade ≥2 late rectal toxicity rates were 13.5% (95% CI, 10.2–18.2%) and 9.4% (95% CI, 7.7–11.6%) for non-MLB and MLB groups, respectively ($P = 0.012$), and the difference was

consistent until 20 years (16.0% and 10.5%). The 10-year rates of grade ≥2 late GU toxicities were 8.5% (95% CI, 5.4–13.1%) and 6.8% (95% CI, 5.3–8.9%) for non-MLB and MLB groups, respectively (P = 0.158). Although the difference in grade ≥2 late GU toxicity rates between the two groups was not significant, it continued to increase after 10 years. At 20 years, the grade ≥2 late GU toxicity rate was 16.6% (95% CI, 9.8–28.1%) and 9.5% (7.0–13.0%), in the non-MLB and MLB groups, respectively. When GU toxicity was subdivided to bladder and distal ureteral strictures the 20-year rates of grade ≥2 late bladder toxicity and distal ureteral stricture rates were 10.4% (95% CI, 9.0 –12.1%) and 1.3% (95% CI, 0.04–4.4%). Although the difference in the 20-year rate of distal ureter stricture was not statistically different between the two groups (0.5% versus 1.5%, P = 0.339), the difference in 20-year rate of grade ≥2 late bladder toxicities was borderline significant (16.6% versus 8.3%, P = 0.070).

3. Association between the cumulative ICRU point dose (EQD2) and late toxicity rate

The median $EQD2_{rectum}$ was median 74.2 Gy_3 (range, 35.4–160.3 Gy) for patients who experienced grade ≥2 rectal toxicity and median 66.0 Gy_3 (range, 29.3–198.0 Gy_3) for those who did not (P <0.001). The median $EQD2_{bladder}$ of patients who experienced grade ≥2 GU toxicity was also significantly higher compared to the patients who did not (75.6 Gy_3 [range, 40.7–127.9 Gy_3] versus 69.5 Gy_3 [range, 33.9–144.1 Gy_3], P = 0.019). For grade ≥2 late rectal toxicity, $EQD2_{rectum}$ exhibited

significantly higher area under curve (AUC) of 0.65 than the line of no discrimination (defined as AUC = 0.50) (P <0.001). For grade ≥2 late GU toxicity, $EQD2_{bladder}$ exhibited an AUC of 0.57 which was also significantly higher than the line of no discrimination (P = 0.019). The optimal cutoff value of $EQD2_{rectum}$ was 63.3 Gy_3 for grade ≥2 late rectal toxicity and the optimal cutoff value of $EQD2_{bladder}$ was 74.3 Gy_3 for grade ≥2 late GU toxicity. The 10-year grade ≥2 late rectal toxicity rate for patients with $EQD2_{rectum}$ of ≤63.3 Gy_3 and >63.3 Gy_3 were 4.7% (95% CI, 3.2–6.9%) and 14.4% (95% CI, 12.0–17.3%), respectively (P <0.001). The 10-year grade ≥2 late GU toxicity rate for patients with $EQD2_{bladder}$ of ≤74.3 Gy_3 and >74.3 Gy_3 were 5.3% (95% CI, 4.0–7.1%) and 10.0% (95% CI, 7.4–13.5%), respectively (P = 0.001). The median $EQD2_{pointA}$ was significantly higher in patients who experienced grade ≥2 late rectal toxicity (77.0 Gy_{10} [64.1–99.6 Gy_{10}] versus 72.9 Gy_{10} [51.7–122.2 Gy_{10}], P <0.001) but no difference was observed between the patients who experienced grade ≥2 late GU toxicity and those who did not. ROC curve analysis revealed that $EQD2_{pointA}$ could predict grade ≥2 late rectal toxicity (AUC 0.61, P = 0.022). Using the optimal cutoff value of 74.0 Gy_{10}, the incidence of grade ≥2 late rectal toxicity was 12.9% (95% CI, 9.2–18.2%) in patients with $EQD2_{pointA}$ >74.0 Gy_{10} and 6.7% (95% CI, 4.6–9.6%) in patients with $EQD2_{pointA}$ ≤74.0 Gy_{10} (P <0.001). No significant differences in $EQD2_{rectum}$, $EQD2_{bladder}$, and $EQD2_{pointA}$ were observed between the patients who experienced grade ≥2 late small bowel toxicity and those who did not. ROC curve analyses revealed that $EQD2_{rectum}$ (P = 0.631), $EQD2_{bladder}$ (P = 0.490), and $EQD2_{pointA}$ (P = 0.596) were not able to predict grade ≥2 late small bowel toxicity.

A significant dose-response relationship between the ICRU dose and occurrence of grade ≥2 late rectal and GU toxicity was shown (Fig 2). The 5% and 10% probability EQD2rectum on grade ≥2 late rectal toxicity was 47.0 Gy3 (95% CI, 34.4–74.3 Gy3) and 75.1 Gy3 (95% CI, 54.9–118.7 Gy3), respectively and the 5% and 10% probability EQD2bladder on grade ≥2 late GU toxicity was 79.1 Gy3 (95% CI, 44.9–329.2 Gy3) and 126.3 Gy3 (95% CI, 71.8–526.2 Gy3).

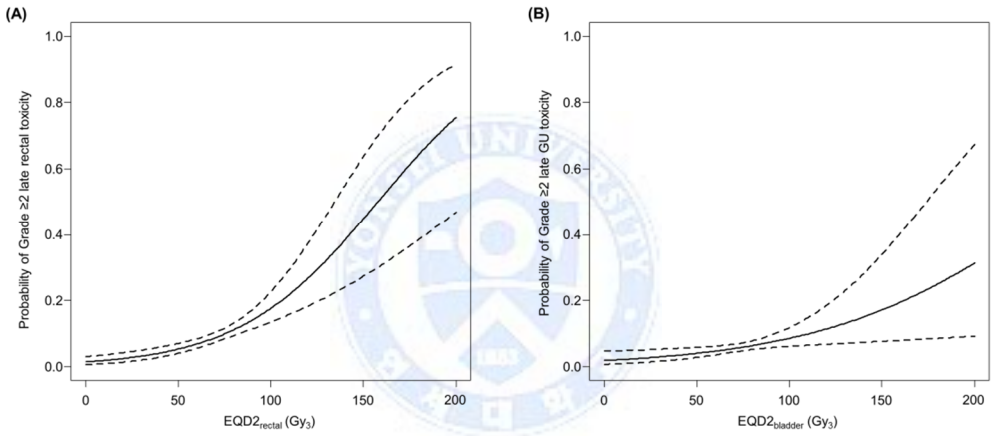

Fig. 2. Probability of grade ≥2 late rectal toxicity according to biologically equivalent dose in 2-Gy fractions (EQD2) of rectal point (A) and probability of grade ≥2 late genitourinary (GU) toxicity according to EQD2 of bladder point (B).

4. Treatment outcome according to midline block

The median follow-up period was 89.0 months (range, 2.4–320.2 months). The 10-year OS, PFS, LR, and RR rates were 82.3% (95% CI, 80.2–84.5%), 74.7% (95% CI, 72.2–77.2%), 9.5% (95% CI, 8.0–11.2%), and 2.6% (95% CI, 1.8–3.7%), respectively. The 10-year OS, PFS, LR, and RR rates of the MLB group were 83.4% (95% CI, 81.1–85.9%), 76.6% (95% CI, 73.9–79.4%), 8.3% (95% CI, 6.7–10.2%), and 2.3% (95% CI, 1.8–3.5%), respectively, and 78.5% (95% CI, 73.8–83.5%), 68.2% (95% CI, 62.6–74.2%), 13.5% (95% CI, 10.1–17.9%), and 3.4% (95% CI, 1.6–7.3%), respectively, for the non-MLB group (Fig. 3). All endpoints were significantly superior in the MLB group.

After propensity score matching, the patient and tumor characteristics were well balanced (Table 3). The 10-year OS, PFS, LR, and RR rates of the MLB group were 78.9% (95% CI, 74.4–83.8%), 70.3% (95% CI, 65.2–75.8%), 13.0% (95% CI, 9.6–17.5%), and 2.9% (95% CI, 1.5–5.4%), respectively. Despite the significantly lower $EQD2_{pointA}$ in the MLB group, all endpoints were similar compared to the non-MLB group (all *P*s >0.05).

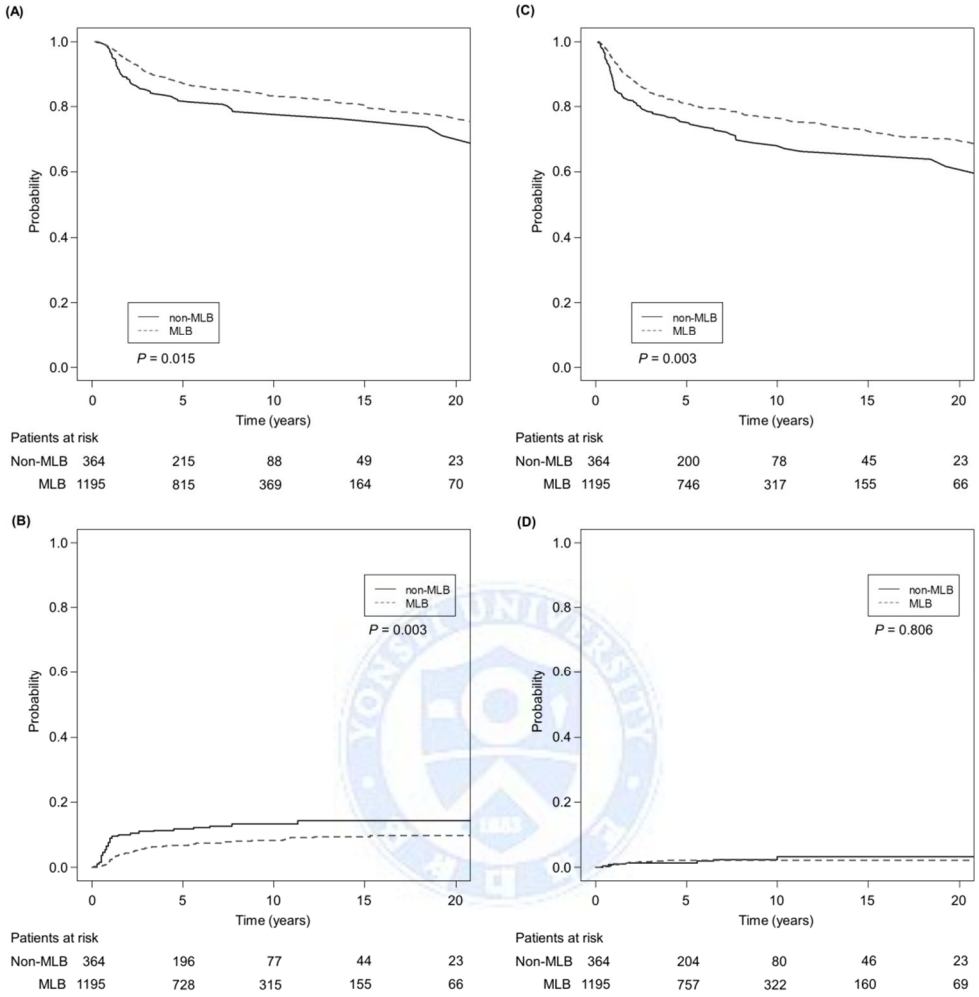

Fig. 3. Overall survival (A), progression-free survival (B), local recurrence (C), and regional recurrence (D) rates of the midline block (MLB) group and non-MLB group.

Table 3. Patient and treatment characteristics after propensity score matching

	non-MLB group N = 364	MLB group N = 364	
Characteristic	N (%)	N (%)	*P*
Age, median (range), years	53 (21–87)	54 (28–86)	0.418
Histologic subtype			0.222
Squamous cell	330 (90.7)	339 (93.1)	
Non-squamous cell	34 (9.4)	25 (6.9)	
FIGO Stage			0.916
IB	44 (12.1)	47 (12.7)	
IIA	28 (7.7)	26 (7.1)	
IIB	292 (80.2)	291 (79.9)	
Tumor size, cm			0.420
<4.0	105 (28.8)	115 (31.6)	
≥4.0	259 (71.2)	249 (68.4)	
Pelvic lymph node			0.542
Negative	274 (75.3)	281 (77.2)	
Positive	90 (24.7)	83 (22.8)	
Paraaortic lymph node			0.170
Negative	347 (95.3)	354 (97.3)	
Positive	17 (4.7)	10 (2.7)	
Chemotherapy regimen			0.786
Platinum based regimen	121 (23.2)	117 (32.1)	
Others	5 (1.4)	3 (0.9)	
Radiotherapy alone	238 (65.4)	244 (67.0)	
Radiotherapy field			0.088
Whole pelvis	320 (87.9)	327 (89.8)	
Semi-extended field	25 (6.9)	29 (8.0)	
Extended field	19 (5.2)	8 (2.2)	
Complete response			0.001
No	25 (6.9)	7 (1.9)	
Yes	339 (93.1)	357 (98.1)	

Characteristic	non-MLB group N = 364 N (%)	MLB group N = 364 N (%)	*P*
EBRT dose, Gy			<0.001
≤45	324 (89.0)	346 (95.1)	
>45	40 (11.0)	18 (4.9)	
$EQD2_{EBRT+ICBT}$, median (range), Gy			
Point A dose, Gy_{10}	86.4 (54.9–122.2)	72.9 (59.1–98.0)	<0.001
Bladder point dose, Gy_3	75.9 (49.0–144.1)	68.3 (33.9–136.8)	<0.001
Rectal point dose, Gy_3	74.8 (47.3–160.3)	66.1 (34.0–117.5)	<0.001

Abbreviations: FIGO = International Federation of Gynecology and Obstetrics; MLB = midline block; 5-FU = 5-fluorouracil; EQD2 = biologically equivalent dose in 2-Gy fractions; EBRT = external beam radiation therapy; ICBT = intracavitary brachytherapy

IV. DISCUSSION

This retrospective study is one of the largest series to date investigating the benefit and feasibility of using MLB for patients with cervix cancer who received definitive RT or CRT. The cumulative dose prescribed to point A in the MLB group was lower than the dose recommended in current guidelines, which recommends more than 80 Gy to $EQD2_{pointA}$.[24] Although the central dose was reduced, our results suggest that MLB based on response to EBRT may not compromise local control or survival and rather reduce the incidence of late rectal toxicity.

HDR-ICBT is a critical portion of treatment and use of ICBT is associated

with improved survival.[9,10] The role of EBRT, which is more limited compared to HDR-ICBT, is to 1) improve the geometry of the tumor for optimal ICBT by reducing the size of tumor and bringing the tumor volume within a higher dose portion of HDR-ICBT dose distribution, 2) sterilize disease in the parametrium and lymph nodes that cannot receive adequate dose by HDR-ICBT. Therefore in our institution we have blocked the central region as soon as the tumor regressed and the geometry of the tumor was appropriate for ICBT. The attempt to find the optimal fractionation schedule of EBRT and HDR-ICBT has been made but no clear conclusions were drawn.[25] The efficacy of reducing the cumulative central dose using MLB in FIGO stages IB to IIB, non-bulky tumors was investigated in a small prospective trial from Japan.[14] MLB was performed after 20 Gy of pelvic EBRT, and the cumulative dose prescribed to point A was EQD2 52 Gy_{10}. The results were promising with a 3-yr pelvic control rate of 96% and no grade ≥3 toxicity. Several retrospective studies with long-term follow-up using a low cumulative central dose protocols have also shown comparable results with other studies using higher dose protocols.[16,26] In our study, the MLB group showed better local control and survival compared to the non-MLB group. Since the MLB group presented with more favorable characteristics we performed propensity score matching. After matching the characteristics were well balanced and the local control and survival rate were similar between the two groups even though the median $EQD2_{pointA}$ was lower by 13.5 Gy_{10} in the MLB group.

However, the fore-mentioned studies including our study do not provide information on dose-volume parameters of tumor volume, which is also a critical

factor in addition to the prescribed dose. Recently Dyk et al. reported the results of using IMRT and HDR-ICBT.[27] During EBRT the cervix region received 20 Gy and the nodal region received 50 Gy in 28 fractions. MRI guided HDR-ICBT was performed in 6 weekly fractions of 6.5 Gy prescribed to point A. The minimum dose delivered to 100 and 90% of gross tumor volume (D100, D90) was significantly lower in the patients who experienced local failure compared to the patients who achieved local control. They estimated that the D100, D90 for ≥90% local control was 69 and 98 Gy_{10}. In a similar manner, the Vienna group has compared the spatial dose distribution within the high-risk clinical target volume (HR-CTV) for patients who failed locally and patients who achieved continuous complete remission.[28] The mean minimum point dose within the HR-CTV was 72 Gy_{10} for patients with local failure and 99 Gy_{10} in patients who achieved local control. It implies that patients with poor target coverage may more likely result in local recurrence. In our study the median dose prescribed to point A in the MLB group was 72.9 Gy_{10}. Although we cannot evaluate the dose-volume parameters, some possibilities can be brought up why the lower point A dose did not result in poorer local control. After significant tumor reduction during EBRT, the central dose from HDR-ICBT would be remarkably higher than the dose prescribed to point A. In addition, small tumors or bulky tumors that show a major response may not need as much radiation as large tumors without response after EBRT. This was observed from the data from the Vienna group. They showed that D90 and D100 of HR-CTV were correlated with local control.[29] However, small and large tumors with good response to EBRT did not show statistically

significant dependence on dose for local control. Recently, Mazeron et al. proposed a dose-response relationship for local control in patients treated with image guided pulsed-dose rate brachytherapy.[30] In this model, the HR-CTV volume had significant impact on the dose thresholds and D90 required to achieve a 90% local control was ≥92.0 Gy_{10} in cases of HR-CTV volume ≥30 cm^3 and ≥73.9 Gy_{10} in cases of HR-CTV volume <30 cm^3.

The 10-year actuarial rate of developing grade ≥2 late rectal, GU, small bowel toxicities were 10.4%, 7.2%, and, 1.7%, respectively. Although, it may not be appropriate to compare the toxicity rates among different studies due to the difference in patient population and the retrospective nature of this study, our results were comparable or lower compared to other studies.[14,31] Previous studies have shown that the ICRU rectal dose has a relatively better correlation with late rectal toxicity compared to ICRU bladder dose with late bladder toxicity.[13] In the era of 3D image-based ICBT, the dose-volume parameters such as D_{2cc} have been introduced in substitution to ICRU point doses in reporting dose delivered to organs at risk.[20] Considering the inhomogeneous dose distribution for organs near the source, dose-volume parameters seem more appropriate compared to single point dose assessment and several studies have reported on the predictability of dose-volume parameters on late rectal or bladder complications.[12,13] The Vienna group reported the predictive value of dose-volume parameters, such as the minimum EQD2 to the most exposed 2 cm3 (D2cc) that patients. Patients with rectal D2cc>75 Gy had a higher incidence of grade ≥2 rectal morbidity (12% versus 4%). In addition, patients with bladder

D2cc>100 Gy had a higher incidence of grade ≥2 bladder toxicity (13% versus 9%).[13] However, still a large portion of patients are planned in a conventional fashion[7,32] and dose-volume parameters may not be available. Previous reports showed that the ICRU rectal dose provided a good estimate of D_{2cc} for the rectum while the ICRU bladder dose did not.[33,34] In our study both ICRU rectal and bladder dose showed significant correlation with late rectal and bladder toxicities, respectively, though the correlation was weaker between ICRU bladder dose and late bladder toxicity. We have analyzed the optimal cutoff value for grade ≥2 late rectal ($EQD2_{rectum}$ = 63.3 Gy_3) and bladder toxicities ($EQD2_{bladder}$ = 74.3 Gy_3) and the dose of 10% probability in developing grade ≥2 late rectal ($EQD2_{rectum}$ = 75.1 Gy_3) and GU toxicities ($EQD2_{bladder}$ = 126.3 Gy_3).

The MLB is aimed to shield the centrally located rectum and bladder and eventually lower the dose delivered to these organs. Therefore the MLB group could be anticipated to have lesser late rectal and bladder toxicities. However, in our study, the MLB group and non-MLB group showed significant difference in the rate of late rectal toxicity but not in GU toxicity. The minimal difference in GU toxicity may be due to the higher ICRU bladder point dose delivered during HDR-ICBT in the MLB group (35.0 Gy_3 versus 32.3 Gy_3). The 2.7 Gy_3 difference seems small but it has been reported that ICRU bladder dose usually underestimates the D2cc of bladder[33,34] and the ICRU dose difference may have been underestimated. Although not statistically significant, the difference of 7% in the 20-year rate of grade ≥2 late GU toxicity rate may need some attention. With a longer median follow-up time the data may not only

show clinical but also statistical significance. We have also observed the fact that the bladder toxicity, which includes hematuria or vesicovaginal fistula, mainly contributed to the difference in GU toxicity and the difference in rate of distal ureteral stricture was minimal. Since the MLB covers 4 cm of the central region, the shielding effect to the distal ureter would have been minimal.

Some limitations of our study should be noted. First, this was an institution-based retrospective study for a long study period. However, a large volume of patients were treated with a consistent policy and a long-term follow-up was performed which was sufficient enough to evaluate late complications. Second, the baseline patient and tumor characteristics were different between the MLB group and non-MLB group. In attempt to reduce the difference in baseline characteristics we have performed propensity score matching. However, tumor response itself can be prognostic for further treatment outcome[30,35] and the different response to RT may represent the different tumor biology which is out of the scope of this study. Third, MLB has innate limitations that should be considered. The rectangular shape of MLB does not match the pear shaped HDR- ICBT dose line. In addition, until now, we have no way to precisely calculate the cumulative dose of HDR-ICBT and EBRT using MLB on 3-dimensional basis. Even in patients who underwent CT simulation, there are uncertainties in evaluating the cumulative dose delivered to tumor and organs at risk.[36] Fourth, we did not perform 3D image-based brachytherapy during the study period. The reduction of complications and improvement of treatment outcome by using image-based brachytherapy has been reported and we have also started image-

based brachytherapy since 2011.[37,38] To further evaluate the feasibility of our approach, patients who receive 3D image-based brachytherapy in addition to EBRT with MLB should be analyzed for their dose-volume parameters.

V. CONCLUSION

This single-institution retrospective study with a large patient volume and a long-term follow-up period investigated the safety and benefit of selectively applying MLB for uterine cervical cancer patients who showed response to EBRT. We found that the rectal toxicity was significantly lower in patients who received MLB and the positive dose-response relationship between cumulative ICRU doses and late rectal and GU toxicity. Additionally, the treatment outcome does not seem to be compromised in the MLB group even though the cumulative central dose was lower. These data should be confirmed in further prospective randomized trials comparing the treatment outcome and toxicity rates according to dose response relationship.

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ABSTRACT(IN KOREAN)

자궁경부암 환자의 근치적 방사선치료 시 외부방사선치료와 근접방사선치료의 최적조합 탐색

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목적: 자궁경부암 환자의 근치적 방사선 치료에는 자궁 내 근접 방사선 치료와 외부 방사선 치료가 모두 필수적인 요소이다. 이전 2상 전향적 연구들에서는 중앙 블록 (midline block) 을 통한 중심 선량의 감소를 통해 다른 연구들과 비교하여 부작용이 감소하고 치료 성적에는 차이가 없음을 보였다. 하지만 무작위 3상 연구가 이루어지지 않았고 더 긴 시간 추적관찰이 필요한 실정이다. 본 연구의 목적은 외부 방사선 치료 중 시행하는 중앙 블록을 통한 중앙 선량 감소가 주는 임상적 효용성과 독성을 살펴 보기 위함이다.

대상 및 방법: 1988년 1월에서 2010년 12월 사이에 자궁경부암으로 진단 받고 근치적 방사선 치료 (n = 1054, 67.6%) 받은 환자와 근치적 항암 방사선 치료 (n = 504, 32.4%) 시행 받은 1559명의 환자를 대상

으로 진행되었다. 환자들이 조사받은 외부 방사선 치료 선량의 중앙값은 45.0 Gy (범위, 30.6–60.0 Gy) 이었고 근접 방사선 치료 선량은 A 지점 기준으로 중앙값 30 Gy (범위, 12–63 Gy) 이었다. 외부 방사선 치료 중에 매주 종양 반응 평가가 이루어 졌고 근접 방사선 치료 기구가 설치 될 수 있을 만큼 감소한 경우 넓이 4cm 의 중앙 블록을 설치하였다 (n = 1195, 중앙 블록 설치군). 외부 방사선 치료 중 종양 감소가 충분히 되지 않은 환자의 경우에는 중앙 블록 없이 진행하였다 (n = 364, 중앙 블록 비 설치군). 직장과 방광에 조사되는 선량은 국제 방사선 단위 측정 위원회에서 정하는 지점을 가지고 추정 하였다. 외부 방사선 치료와 근접 방사선 치료의 선량을 합산 하기 위해 선형이차함수모델을 근거로 2-Gy 환산 선량을 구하였다. 정상 조직은 $\alpha/\beta = 3$, 종양은 $\alpha/\beta = 10$ 으로 가정하였다. 중앙 블록 설치군과 비 설치군의 특성을 맞추기 위해 성향점수맞춤 (propensity score matching) 기법을 이용하였다.

결과: 대상환자의 중앙추적조사기간은 89.0 개월 (범위, 2.4–320.2 개월) 이었다. 10년 생존율, 무병생존율, 골반제어율, 국소제어율은 각각 82.3%, 74.7%, 87.9%, 90.1% 이었다. 중앙 블록 설치군이 비 설치군에

비해서 10년 생존율, 무병생존율, 골반제어율, 국소제어율이 모두 통계학적으로 유의하게 높았다 (P <0.05). 환자 특성을 살펴 보았을 때 중앙 블록 설치군이 비 설치군에 비해서 비해 나이가 더 많고, 종양의 크기가 작았고, 병기가 낮았으며 골반 및 대동맥 림프절의 전이가 더 빈번하였다. A 지점, 직장 및 방광에 대한 2-Gy 환산 선량은 중앙 블록 설치군에서 통계학적으로 유의하게 낮았고 2등급 이상의 직장 독성이 중앙 블록 설치군에서 유의하게 낮았다 (8.1% 대 11.5%, P = 0.045). 방광 및 소장에 대한 독성에는 차이가 없었다. 성향점수맞춤을 통하여 양군간의 환자 특성을 동등하게 맞추었고 이때 10년 생존율, 무병생존율, 골반제어율, 국소제어율에 차이가 없었다.

결론: 외부 방사선 치료 중 중앙 블록을 통해 중심 선량을 감소 시킬 경우 치료 성적에 영향을 주지 않으면서 직장 독성을 줄일 수 있었다. 중앙 블록 사용에 대한 효용성은 향후 전향적 연구에서 검증이 되어야 할 것이다.

핵심 되는 말: 자궁경부암, 중앙 블록, 외부 방사선 치료, 고선량 자궁 내 근접 방사선 치료