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RADIATION THERAPY FOR STAGE IIIB UTERINE CERVICAL CANCER AT OUR INSTITUTION : TREATMENT OUTCOMES AND PROGNOSTIC FACTORS

Noriko Takagi[1)], Akira Anbai[1)], Yuki Wada[1)], Satoshi Kumagai[1)], Eriko Okuyama[1)], Kento Hatakeyama[1)], Naoki Sato[2)] and Manabu Hashimoto[1)]

[1)]*Department of Radiology and Radiation Oncology, Akita University Graduate School of Medicine*
[2)]*Department of Gynecology, Akita University Graduate School of Medicine*

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Abstract

Purpose

We examined the treatment outcomes, prognostic factors, and toxicities after radiotherapy for stage IIIB uterine cervical cancer.

Methods and Materials

We studied patients with stage IIIB uterine cervical cancer who were both diagnosed and treated with combined external beam radiotherapy (EBRT) and intracavitary brachytherapy (ICBT). We retrospectively analyzed the clinical characteristics (age, primary tumor size, lymph node metastasis, and chemotherapy), 5-year overall survival (OS) rate, progression-free survival (PFS) rate, and late toxicities over grade 3.

Results

A total of 25 patients were enrolled in this study. Overall 23 and 2 patients showed complete and partial response, respectively. The objective response was 100%. The 5-year OS and PFS were 73.4% (95% confidence interval [CI] 55.1-91.6%) and 69% (95% CI 49.5-88.0%), respectively. Primary tumor size ≥40 mm was a prognostic factor for poor OS and PFS (HR : 5.088, $p=0.024$ and HR : 5.088, $p=0.033$, respectively). Five patients (20%) developed late toxicities over grade 3 with related radiotherapy.

Conclusions

Local tumor control, OS, PFS, and late toxicity rate in this study were similar to those in previous reports. A bulky tumor was identified as a prognostic factor.

Key words : uterine cervical cancer, radiotherapy, brachytherapy

Introduction

Uterine cervical cancer is the fourth most common malignancy in women worldwide after breast, colorectal, and lung cancers, according to the World Health Organization (WHO)[1)]. An estimated 530,000 new cases and 270,000 deaths occur annually, accounting for 7.5% of all cancer-related deaths in female patients[1,2)]. In Japan, 10,500 new cases were diagnosed and 2,710 patients died from cervical cancer in 2016[3)].

Surgery and radiotherapy are considered standard treatments for stage IB-IIB cancers, but for stage IIIA-IVA cancers, only concurrent chemoradiotherapy (CCRT)

Correspondence : Noriko Takagi
Department of Radiology and Radiation Oncology, Akita University Graduate School of Medicine, Akita 010-8543, Japan
Tel : 81-18-884-6179
Fax : 81-18-836-2623
E-mail : tnoriko@med.akita-u.ac.jp

is recommended in Japanese guidelines[4]. Intracavitary brachytherapy (ICBT) is an integral component in the treatment of patients with advanced cervical cancer and is the standard treatment in combination with external beam radiotherapy (EBRT)[5]. The advantage of ICBT emanates from its dosimetry benefits, including the ability to deliver a locally high and conformal dose to the site of disease with a rapid dose fall-off, thereby sparing adjacent structures such as the bladder, rectum, sigmoid, and small bowel. It is well known that combined treatment with ICBT and EBRT results in good local tumor control than EBRT alone[6].

Purpose of this study was to retrospectively analyze treatment outcomes, prognostic factors, and toxicities of uterine cervical cancer patients treated with radiotherapy in our institution.

Patients and Methods

A total of 137 patients with uterine cervical cancer were treated with ICBT at the Akita University Hospital between April 2004 and March 2014 (Table 1). Among these patients, the medical records of patients with stage IIIB uterine cervical cancer who had undergone both EBRT and ICBT at our institution were retrospectively reviewed. Our institution has a high-dose-rate brachytherapy system unit, and it is the only institution with an after-loading treatment device in Akita prefecture. Thus, we receive several treatment consultations for ICBT from other hospitals. In this study, we excluded these patients because they were not treated using the same protocol of EBRT or chemotherapy as that in our institution.

All patients had biopsy-proven uterine cervical carcinoma. Clinical staging was performed according to the FIGO (International Federation of Gynecology and Obstetrics) classification[7] on the basis of medical history ; physical examination ; and imaging examinations, such as transvaginal ultrasound (US), computed tomography (CT), and magnetic resonance imaging (MRI). Stage IIIB was defined as a tumor extending to the pelvic wall and/or causing hydronephrosis or kidney dysfunction. The maximum tumor diameter was measured by US and stratified at 40 mm. A diameter of 40 mm is used in stage I and II FIGO classifications. Pelvic and para-aortic lymph node enlargement >10 mm in the short axis on CT was defined as metastasis.

All patients were treated with 3D conformal EBRT and 2D ICBT. The radiation treatment planning systems used for EBRT were FOCUS (Computerized Medical systems, St Louis, USA) and Eclipse (Varian Medical systems, California, USA). EBRT was delivered using a linear accelerator with 10 MV X-ray photons. Initially, patients were treated with a combination of the 4-field (2 opposed anterior-posterior and posterior-anterior [AP-PA] and 2 lateral fields) box technique of irradiation and received 17 fractions of external radiotherapy, with a daily dose of 1.8 Gy, 5 times per week. After 30.6-41.4 Gy to whole pelvic with EBRT, The patients received 2 opposing AP-PA technique with midline shield which covered the uterine side in order not to over irradiate the uterine with combined EBRT and ICBT. They were treated with ICBT immediately. Eventually patients received total doses of 50.4 Gy with EBRT. The initial EBRT

Table 1. Patients of uterine cervical cancer treated with radiotherapy at Akita University Hospital between April 2004 and March 2014

Patients belong	I*	II*		III*		IV*		unknown
		A	B	A	B	A	B	
Akita University Hospital ***n*=40**	2 5.0%	0 0%	7 17.5%	1 2.5%	25 62.5%	4 10.0%	1 2.5%	0 0
Another Hospitals ***n*=97**	8 8.2%	11 11.3%	12 12.4%	3 3.1%	28 28.9%	8 8.2%	1 1.0%	26 26.8

*FIGO staging for carcinoma of the vulva, cervix, and corpus uteri.

area covered the gross disease, parametrium, uterosacral ligaments, sufficient vaginal margin from the gross disease (at least 3 cm), presacral nodes, and other elective pelvic nodal volumes at risk.

ICBT treatment was administered using the 192-Iridium high dose rate brachytherapy system Varisource (Varian Medical systems, California, USA). ICBT was administered in 2-6 fractions once per week, and a total dose of 10-30 Gy was delivered at point A in the Manchester method. We used a Fletcher or Henschke type applicator for ICBT. Point A is 2 cm superior and lateral to the cervical os (Figure 1).

Chemotherapy was performed concurrently with radiotherapy and included 5 courses of nedaplatin (30 mg/m^2, administered intravenously over 2-4 hours) administered weekly.

The treatment effect was evaluated by CT, US, and body examination 1 month later. After the first examination, patients were evaluated every 3 months for the first 3 years, every 6 months during the fourth and fifth years, and then annually. Disease status and the degree of treatment-related toxic effects were assessed by history taking, physical examination, and appropriate laboratory and CT imaging. Suspected cases of persistent or recurrent disease were confirmed by biopsy whenever possible.

Therapeutic effects were evaluated by physical, imaging, and pathological examinations. The response evaluation criteria were based on RECIST guidelines[8]. The overall survival and disease-free survival rates were calculated from the beginning of EBRT.

We examined several patient-, tumor- and treatment-related characteristics (age, primary tumor size, lymph nodes metastasis, chemotherapy, radiation). We estimated survival curves using the Kaplan-Meier method by univariate analyses (Log-rank test) and multivariate analyses (Cox proportional hazards regression model). P-values <0.05 were considered significant.

All analyses were performed using statistical software IBM SPSS Statistics version 24 (IBM, Armonk, New York, USA).

Acute and late toxicities associated with CCRT were evaluated using the National Cancer Institute CTCAE (Common Terminology Criteria for Adverse Events) version 4.03[9] and RTOG (Radiation Therapy Oncology Group) /European Organization for Research and Treat-

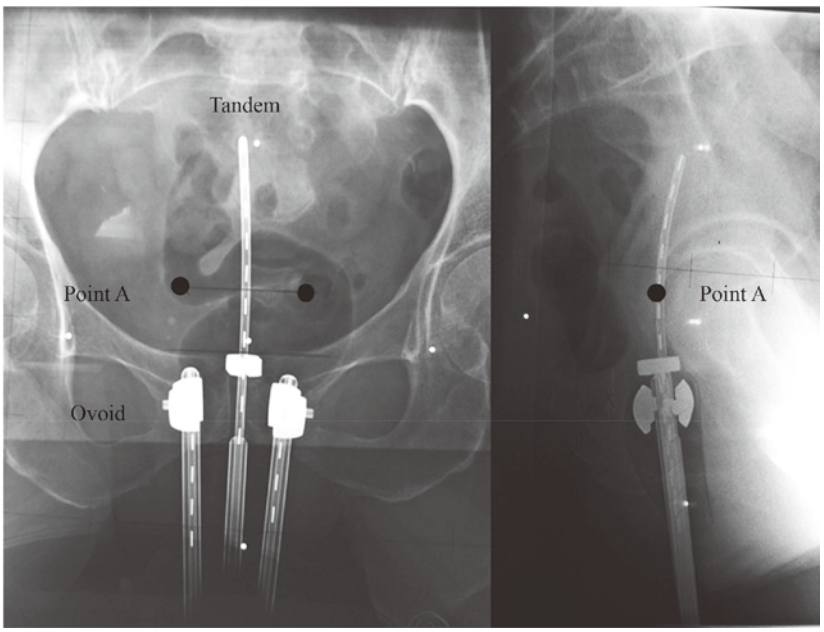

Figure 1. Point A using the plain X-ray films

ment of Cancer late radiation morbidity scoring scheme[10].

Results

We enrolled 25 patients in this study. A summary of the patients' characteristics and tumor features is shown in Tables 2 and 3. The median age was 59 years (range, 39–90 years). Histopathological examination showed adenocarcinoma in 1 patient and squamous cell carcinoma in the other 24 patients. The primary tumor size ranged from 22 to 100 mm ; 22–39 mm in 14 patients, 40–100 mm in 8 patients, and was unknown in 3 patients (these patients were diagnosed on the basis of observation of a tumor extending to the pelvic wall on physical examination). No patient had hydronephrosis. Five patients had lymph nodes metastasis, 3 patients had pelvic lymph nodes metastasis, 1 patient had abdominal para-aortic lymph nodes metastasis, and 1 patient had both pelvic and abdominal para-aortic lymph nodes metastasis.

Eighteen patients were treated with CCRT and 7 patients were treated with radiotherapy alone. Seven patients did not receive chemotherapy, including 5 patients who had renal dysfunction and 2 patients aged 80 years or older.

Total irradiation doses of EBRT were 50.4 Gy for all patients. The median total irradiation dose with ICBT was 25 Gy : 1 patient was irradiated with 30 Gy ; 18 patients, with 25 Gy ; 3 patients, with 20 Gy ; 1 patient with 15 Gy ; and 2 patients with 10 Gy along with ICBT.

The median follow-up period was 68 months (range,

Table 2. Patient and tumor characteristics

Number of patients	*n*=25	
Age (years)		39–90
Median		59
Histology		
Squamous cell carcinoma	24	96%
Adenocarcinoma	1	4%
Primary tumor size (maximum diameter)		
0–39 mm	14	56%
40–100 mm	8	32%
unknown	3	12%
Lymph nodes metastasis		
Pelvic lymph node	3	12%
Para-aortic lymph node	1	4%
Both region	1	4%
None	20	80%
Hydronephrosis		
Yes	0	0%
No	25	100%
Concurrent chemotherapy		
Yes	18	72%
No	7	28%
Total dose of EBRT		
50.4 Gy	25	100%
Total dose of ICBT		
10–20 Gy	6	24%
25–30 Gy	19	76%

Abbreviation ; EBRT : external beam radiotherapy, ICBT : intracavitary brachytherapy

Table 3. Patients' characteristics and tumor features.

No.	Age	Primary tumor size (mm)	Histology	Chemo-therapy	Point A (Gy)	Total ICBT dose (Gy)	Total EBRT dose (Gy)	Initial response	Survival times	Late toxicity (grade 3, 4)
1	74	unknown	SCC	No	5	20	50.4	CR	68	Urinary retentions
2	75	unknown	SCC	No	5	20	50.4	CR	10	
3	77	24	SCC	No	5	25	50.4	CR	127	
4	56	35	SCC	Yes	5	25	50.4	CR	147	Sigmoid colon fistula
5	82	54	SCC	No	5	25	50.4	CR	47	
6	70	unknown	SCC	Yes	5	15	50.4	CR	12	Ileum perforation
7	56	33	SCC	Yes	5	20	50.4	CR	75	
8	41	31	SCC	Yes	5	30	50.4	CR	126	Vaginal adhesion, hematuria
9	83	35	SCC	Yes	5	25	50.4	CR	79	
10	61	22	SCC	Yes	5	25	50.4	CR	116	
11	46	39	SCC	Yes	5	25	50.4	CR	95	
12	47	56	SCC	Yes	5	25	50.4	CR	20	
13	53	33	SCC	Yes	5	25	50.4	CR	44	
14	48	47	SCC	Yes	5	10	50.4	CR	33	
15	84	34	SCC	No	5	10	50.4	PR	23	
16	58	27	SCC	Yes	5	25	50.4	CR	102	
17	52	39	SCC	Yes	5	25	50.4	CR	90	
18	38	31	SCC	Yes	5	25	50.4	CR	99	
19	45	38	SCC	Yes	5	25	50.4	CR	67	
20	74	30	SCC	Yes	5	25	50.4	CR	96	Rectal bleeding and stenosis
21	68	62	SCC	Yes	5	25	50.4	CR	80	
22	65	66	Adeno-carcinoma	No	5	25	50.4	PR	14	
23	39	70	SCC	Yes	5	25	50.4	CR	25	
24	59	100	SCC	Yes	5	25	50.4	CR	75	
25	90	50	SCC	No	5	25	50.4	CR	28	

Abbreviation ; SCC : squamous cell carcinoma, ICBT : intracavitary brachytherapy, EBRT : external beam radiotherapy, CR : complete response, PR : partial response

Table 4. Recurrence during the follow-up period

	Number of patients
Local recurrence within radiation field	
Primary tumor progression	2
Pelvic lymph node metastasis	2
Both lesion	1
Distant metastasis outside radiation field	
Para-aortic and Virchow's lymph node metastasis	2
Liver metastasis	1
Lung metastasis	2
Value of SCC antigen evaluation	3

Abbreviation ; SCC antigen : Squamous cell carcinoma related antigen

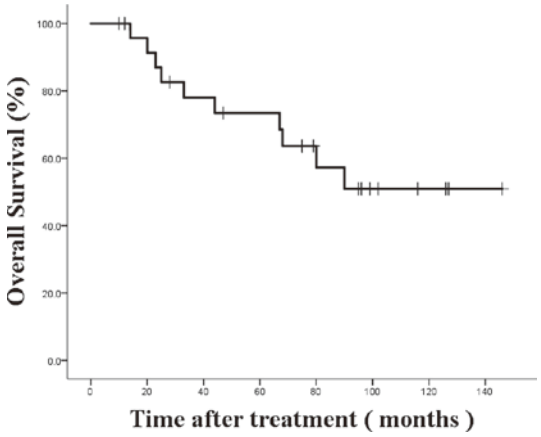

Figure 2. Overall survival rate in patients with stage IIIB uterine cervical cancer treated with radiotherapy

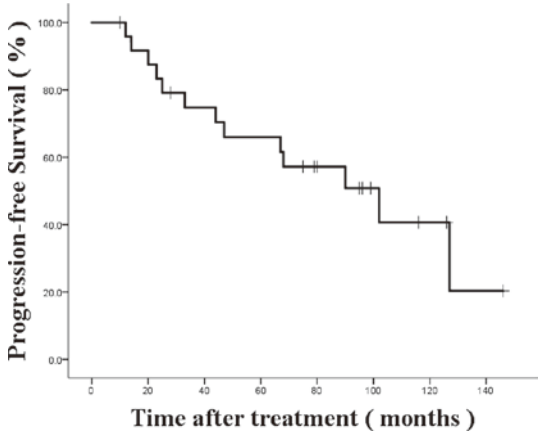

Figure 3. Progression-free survival rate in patients with stage IIIB uterine cervical cancer treated with radiotherapy

10-147 months). Table 3 shows the initial treatment response. In all, 23 patients achieved a complete response (CR), and 2 patients achieved a partial response (PR). The objective response rate (CR and PR) was 100%. However, 13 patients developed recurrence during the follow-up period (Table 4). Five patients had local recurrence within the radiation field ; 2 patients had re-progression of the primary tumor, 2 patients had pelvic lymph node metastasis, and 1 patient had both lesions. Five patients had distant metastasis outside of the radiation field, and 2 patients had both para-aortic lymph node and Virchow's lymph nodes metastases. One patient had liver metastasis, and two patients had lung metastasis. Three patients only had elevated

Table 5. Univariate analyses for 5-year outcomes according patients, tumor characteristics and treatment

	n	OS (%)		PFS (%)	
Age (years)					
<59	12	66.7	$p=0.762$	66.7	$p=0.988$
≥ 59	13	81.8		65.6	
Primary tumor size					
<40 mm	14	85.7	**$p=0.011$**	84.6	**$p=0.017$**
≥ 40 mm	8	46.9		40.0	
unknown	3				
Lymph nodes metastasis					
Positive	5	40.0	$p=0.227$	40.0	$p=0.130$
Negative	20	83.0		77.0	
Chemotherapy					
Yes	18	76.5	$p=0.297$	76.5	$p=0.126$
No	7	66.7		44.4	
Total dose of ICBT					
< 25 Gy	6	50.0	$p=0.090$	50.0	**$p=0.037$**
≧ 25 Gy	19	78.6		73.0	

Abbreviation ; OS : Overall survival rate, PFS : Progression-free survival rate

squamous cell carcinoma antigen levels.

The 5-year OS and PFS rates were 73.4% (95% confidence interval [CI] 55.1-91.6%) (Figure 2) and 69% (95% CI 49.5-88.0%), respectively (Figure 3). Ten patients died because of uterine cervical cancer during the follow-up period. There was no mortality associated with treatment.

Table 5 and Figures 4-13 show results of univariate analyses of 5-years outcomes according patient, tumor and treatment characteristics. Patients with a primary tumor size ≥40 mm had significantly poorer OS and PFS than did patients with a primary tumor size <40 mm. Patients receiving <25 Gy with ICBT had significantly poorer PFS than patients receiving ≥25 Gy, but there was no significant difference in OS. There was no significant difference in OS and PFS in the patients according to age, lymph nodes metastasis, and chemotherapy.

Table 6 shows the results of multivariate analysis of prognostic factors. Primary tumor size ≥40 mm was a

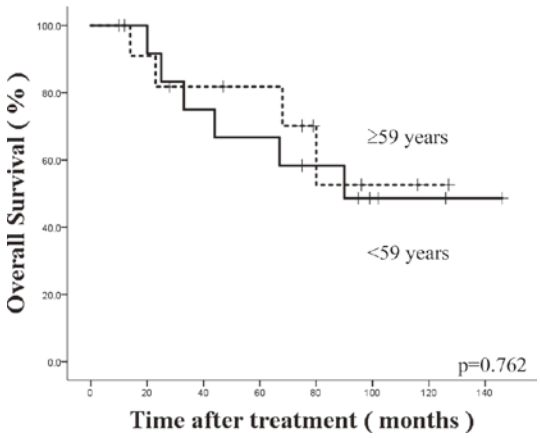

Figure 4. Kaplan-Meier curve estimates of overall survival for patients treated with radiotherapy in the age groups < 59 years and ≥ 59 years (p=0.762).

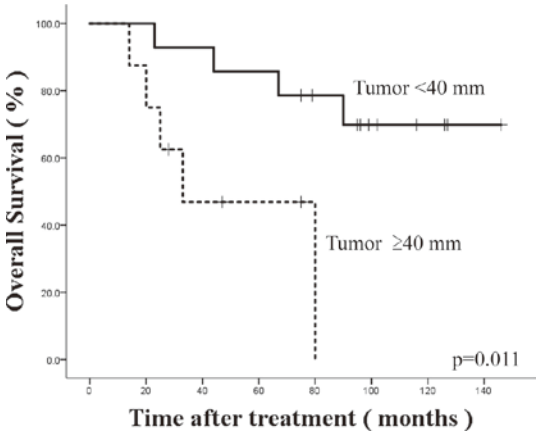

Figure 6. Kaplan-Meier curve estimates of overall survival for patients treated with radiotherapy according to primary tumor size : < 40 mm and ≥ 40 mm (p=0.011).

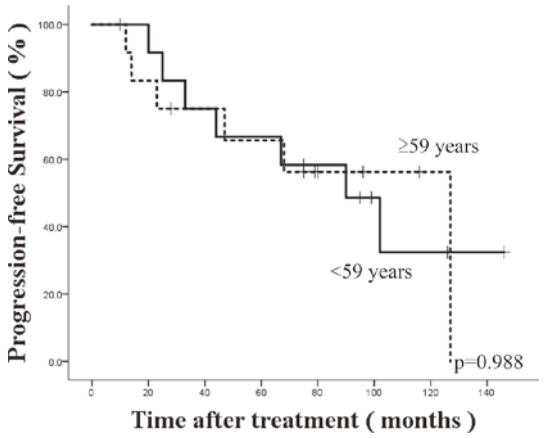

Figure 5. Kaplan-Meier curve estimates of progression-free survival for patients treated with radiotherapy in the age groups < 59 years and ≥ 59 years (p=0.988).

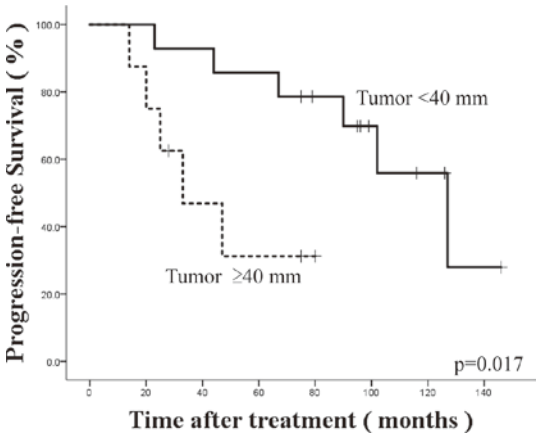

Figure 7. Kaplan-Meier curve estimates of progression-free survival for patients treated with radiotherapy according to primary tumor size : < 40 mm and ≥ 40 mm (p=0.017).

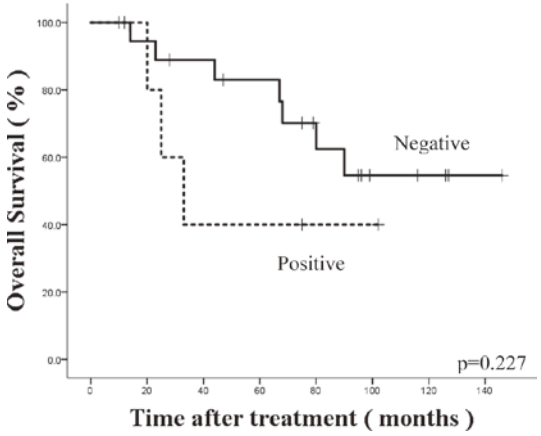

Figure 8. Kaplan-Meier curve estimates of overall survival for patients treated with radiotherapy according to the presence (positive) or absence (negative) of lymph node metastasis ($p=0.227$).

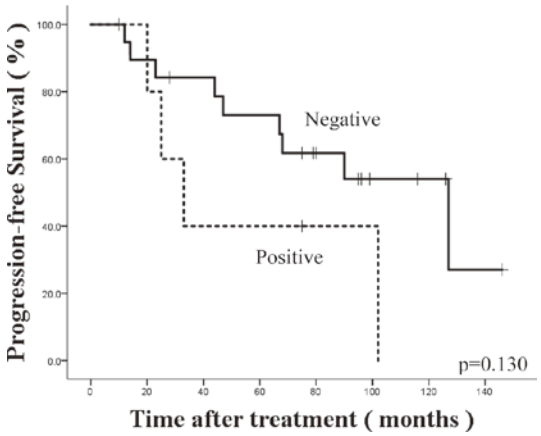

Figure 9. Kaplan-Meier curve estimates of progression-free survival for patients treated with radiotherapy according to the presence (positive) or absence (negative) of lymph node metastasis ($p=0.130$).

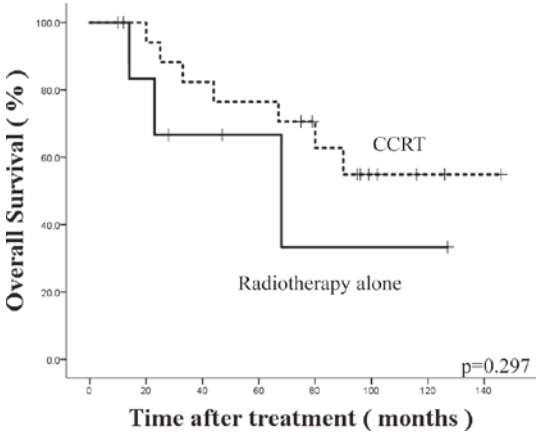

Figure 10. Kaplan-Meier curve estimates of overall survival for patients treated with radiotherapy alone or on conccurent chemoradiotherapy (CCRT) ($p=0.297$).

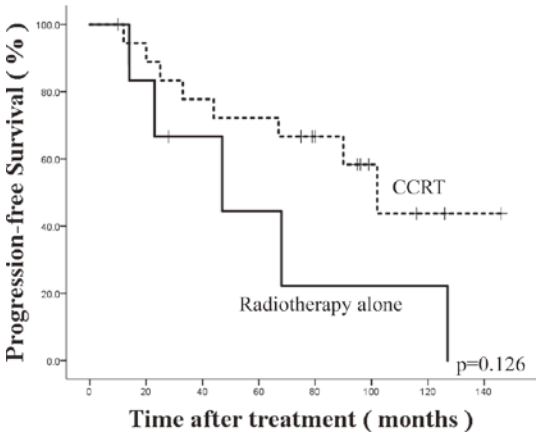

Figure 11. Kaplan-Meier curve estimates of progression-free survival for patients treated with radiotherapy alone or on conccurent chemoradiotherapy (CCRT) ($p=0.126$).

significant poor prognostic factor (hazard ratio (HR) for OS was 5.588 (95% CI 1.251-24.95, $p=0.024$) and for PFS was 5.088 (95% CI 1.166-22.20, $p=0.030$).

There were no severe acute blood and lymphatic system toxicities causing interruption of treatment. Tables 3 and 7 shows severe late toxicities. Five patients developed late toxicities higher than grade 3 and were administered related therapy. Grade 3 rectal bleeding and stenosis occurred in 1 patient. One patient had grade 3 ileum perforation and one patient had grade 3 urinary retentions. Moreover, one patient had grade 3 vaginal adhesion and hematuria. One patient had a grade 4 sigmoid colon fistula, and she was treated with colostomy.

Discussion

There have been many reports on concurrent chemoradiotherapy for uterine cervical cancer since 1990. In

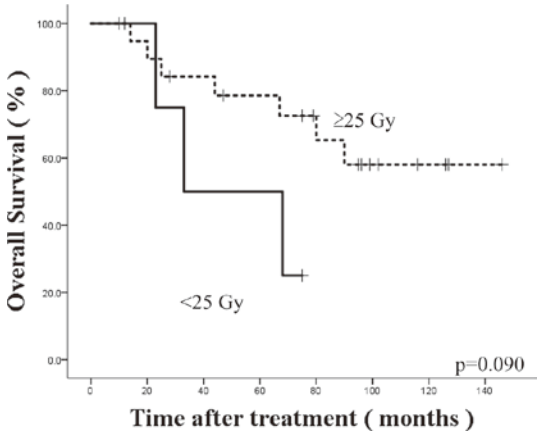

Figure 12. Kaplan-Meier curve estimates of overall survival for patients treated with intracavitary radiotherapy (ICBT) doses <25 Gy and ≥25 Gy (p=0.090).

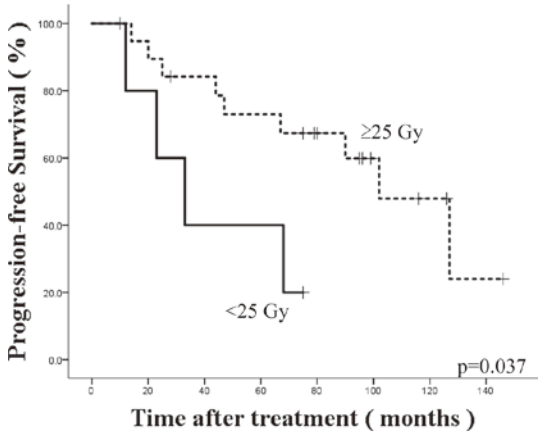

Figure 13. Kaplan-Meier curve estimates of progression-free survival for patients treated with intracavitary radiotherapy (ICBT) doses <25 Gy and ≥25 Gy (p=0.037).

Table 6. Multivariate analyses for outcomes according to prognostic factors

	OS (%)			PFS (%)		
	HR	95% CI	*p* value	HR	95% CI	*p* value
Primary tumor size	5.558	1.251-24.95	**0.024**	5.088	1.166-22.20	**0.030**
Total dose of ICBT	0.323	0.059-1.758	0.191	0.213	0.066-1.831	0.213

Abbreviation ; HR : hazards ratio, CI : confidence interval, OS : overall survival, PFS : Progression-free survival

Table 7. Late toxicities over grade 3 with related therapy according to the Radiation Therapy Oncology Group (RTOG) late Radiation Morbidity Scoring Scheme

Late toxicities	Number of patients
Grade 4	
Sigmoid colon fistula	1
Grade 3	
Ileum perforation	1
Rectal bleeding and stenosis	1
Urinary retention	1
Vaginal adhesion	1

1999, the National Cancer Institute (NCI) reported the efficacy of concurrent chemoradiotherapy (CCRT) using cisplatin against uterine cervical cancer[11-13]. Compared with radiation monotherapy, CCRT had a hazard ratio of 0.52[12], drastically lowering the mortality rate. Thereafter, the use of CCRT with cisplatin increased rapidly as a standard treatment. According to a Japanese guideline, CCRT is a therapeutic option used parallel to surgery and is recommended for stage III and IV cases[4].

Our therapeutic outcomes for CCRT with 2D-IGBT for stage IIIB uterine cervical cancer were a CR of 92% and a five-year survival rate of 73.4%. Another facility reported that the five-year survival rate of stage IIIB uterine cervical cancer was 40-60%[4], which is similar to our result. In terms of adverse events, there were three cases of grade 3 or higher late-stage adverse events in the gastrointestinal tract (3/25 cases, 12%), which is higher than that noted in a previous report (grade 3 or higher, rectum, 2.5%)[13].

The five-year survival rate of stage IIIB uterine cervical cancer in the present study was similar to that reported previously. In the present study, tumor diameter of 40 mm or more was a poor prognostic factor. In the pre-

vious report, tumor diameter, lymph node metastasis, and chemotherapy were reported as prognostic factors[14–16].

A reason for tumor diameter being a prognostic factor is the limitation in the setting of the dose prescription point in the Manchester method[17]. With the Manchester method, plans are prepared based on bi-plane X-ray imaging, but X-ray cannot identify the tumor. Therefore, left and right bilateral points 2 cm each from the vertical line that runs from the external os of the uterus along the uterine axis at 2 cm in the rostral direction were stipulated as point A, and were defined as the dose reference point in ICBT. This point A dose is an index for the therapeutic dose for the primary lesion and injury dose for the bladder and the rectum. If the tumor diameter is over 40 mm, that is, if the distance between the uterine axis to the tumor edge is 20 mm or more, it is easy to recognize that tumor exists beyond point A. With large tumors, there is insufficient dose beyond point A, which is a likely cause of the poor performance of the Manchester method. By introducing a three-dimensional method at our hospital, we discovered that when the tumor diameter is especially large, even if the applicator appeared to have been fully inserted into the fundus, the tip of tandem may be snagged by the tumor, thus not reaching the base. However, since we were unable to accurately determine the positional relationship between the tandem and the fundus of the uterus, inaccurate insertion of the tandem might have contributed to poor dose distribution. Past reports suggested that tumor diameter is a poor prognosis factor not only for the control rate of primary lesion, but also for the rate of distant metastasis and recurrence[17–19]. Improving dose distribution for tumors with large diameter is critical in improving therapeutic result for stage IIIB uterine cervical cancer.

In the present examination, the number of grade 3 or higher late-stage adverse events in the gastrointestinal tract was higher (3/25 : 12%) compared to the past report (grade 3 or more, rectum, 2.5%)[13]. In one of these cases, insertion of the tandem was shallow at 3 cm, thus, ovoid dose contribution increased leading to dose distribution that spread in the rectum. Therefore, a wide range of the rectum was irradiated with a high dose. There was no image or record of tumor diameter. In two of these cases, the maximum diameter of tumor was 40 mm or less, and the tandem was inserted at least 5 cm. ICBT had a point A dose of 5 Gy completed five times, and the cause could not be identified.

As discussed earlier, to improve OS, dose distribution needs to be enhanced, especially when the tumor diameter is large, and to reduce side effects, the dose on the rectum must be regulated. In recent years, both domestically and internationally, there is transition to 3D-IGBT that utilizes CT and MRI[20–23]. For 3D-IGBT, CT and MRI imaging are performed after inserting the applicator, and the treatment plan is proposed on the basis of the 3D images obtained. Even if the tumor shrinks drastically during the treatment, on the basis of the tumor size and positional relationship with surrounding organs during intracavitary brachytherapy, excessive exposure of surrounding organs can be avoided. As the positional relationship between the applicator, uterus, and tumor can be three-dimensionally understood, the accuracy of the position of the applicator tip can be assured. As such, with 3D-IGBT, dose distribution across the tumor is secured regardless of the tumor size, allowing for reduction in the dose on the rectum and bladder and contributing to improvement in treatment results. In past reports on 3D-IGBT, OS could not be extensively compared to 2D-IGBT. However, some subgroup analyses had reported OS improvement with 3D when tumor diameter was large[24,25]. These results are consistent with our report that showed that although the Manchester method assures tumor dose for tumors of small diameter, dose might be insufficient when tumor diameter is large.

A limitation of the present report is the small number of cases. In previous reports, in addition to the tumor diameter, lymph node metastasis and chemotherapy were reported as prognostic factors[15,16]. In the present report, there were trends in lymph node metastasis (OS of 40% vs. 83% and PFS of 40% vs. 70%) as a prognosis factor, but a longer observation period and a larger number of cases are necessary.

The second limitation relates to retrospective nature of the study. There is no control group, and especially chemotherapy could introduce selection bias by therapist.

The third limitation is the concurrent chemotherapy using nedaplatin instead of cisplatin, which makes direct

comparison with other studies difficult.

Conclusion

Treatment outcomes of the Manchester method of CCRT for stage IIIB uterine cervical cancer at our hospital were 92% CR and a five-year survival rate of 73.4%. Specifically, the result was poorer when the tumor was large and there were late-stage adverse events in the gastrointestinal tract. However, these issues should be improved with 3D-IGBT. Thus, we plan to switch to a three-dimensional method to improve treatment outcomes.

Conflict of Interest : COI

The authors have no conflicts of interest to declare.

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