대한방사선종양학회지 2008;26(1):24~34

Accelerated Hyperfractionated Radiotherapy for Locally Advanced Uterine Cervix Cancers

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Purpose: To assess the efficacy of the use of accelerated hyperfractionated radiotherapy (AHRT) for locally advanced uterine cervix cancers.

Materials and Methods: Between May 2000 and September 2002, 179 patients were identified with FIGO stage IIB, IIIB, and IVA cancers. Of the 179 patients, 45 patients were treated with AHRT (AHRT group) and 134 patients were treated with conventional radiotherapy (CRT group), respectively. Patients undergoing the AHRT regimen received a dose of 30 Gy in 20 fractions (1.5 Gy×2 fractions/day) to the whole pelvis. Subsequently, with a midline block, we administered a parametrial boost with a dose of 20 Gy using 2 Gy fractions. Patients also received two courses of low-dose-rate brachytherapy, up to a total dose of 85~90 Gy to point A. In the CRT group of patients, the total dose to point A was 85~90 Gy. The overall treatment duration was a median of 37 and 66 days for patients that received AHRT and CRT, respectively. Statistical analysis was calculated by use of the Kaplan-Meier method, the log-rank test, and Chi-squared test.

Results: For patients that received cisplatin-based concurrent chemotherapy and radiotherapy, the local control rate at 5 years was 100% and 79.2% for the AHRT and CRT group of patients, respectively (p=0.028). The 5-year survival rate for patients with a stage IIB bulky tumor was 82.6% and 62.1% for the AHRT group and CRT group, respectively (p=0.040). There was no statistically significant difference for severe late toxicity between the two groups (p=0.561).

Conclusion: In this study, we observed that treatment with AHRT with concurrent chemotherapy allows a significant advantage of local control and survival for locally advanced uterine cervix cancers.

Key Words: Uterine cervix carcinoma, Hyperfractionation, Acceleration, Radiotherapy, Concurrent chemoradiotherapy

Introduction

In Korea, carcinoma of the uterine cervix is the fourth most common malignant neoplasm in women, after stomach, breast, and colorectal cancer. The incidence is on the decrease, but there are still a large number of patients. From 1999 to 2001, about 13,000 cases of carcinoma of the uterine cervix were reported to have developed over 3 years.[1)]

Submitted December 12, 2007, accepted February 27, 2008
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According to several previous reports, most patients with stage IIB tumors are treated with conventional fractionation radiation therapy (CRT) and intracavitary brachytherapy. The 5-year survival rate is 58% to 73.4% and the pelvic failure rate ranges from 10% to 50%.[2-5)] For a stage IIIB carcinoma, the 5-year survival rate ranges from 25% to 48%, and pelvic failure rates range from 38% to 50%.[3,6,7)] Although the rate of local failure is high in locally advanced uterine cervix cancers, the dose of radiation to the pelvis cannot be escalated recklessly to improve local control because of a significant correlation between dose escalation and complications of the bladder and rectum.[8,9)] Thus, the use of altered fractionated radiotherapy may be an attractive modality.

With the development of modern radiobiology, radiation

oncologists have recognized that the use of conventional fractionation radiotherapy is not universally the most optimal treatment method.[10-12] The induction of late toxicity is more sensitive to changes in fraction size. In studies of the mouse kidney, Williams and Denekamp reported that small dose fractions spare late responding normal tissues like the kidney relative to tumors and acutely reacting normal tissues.[12] The use of small dose fractions allows higher total doses to be administered without an increase of late toxicity in normal tissue, resulting in a higher biologically effective dose to the tumor.

There have been many attempts to improve clinical results by the use of altered fractionation radiotherapy. Withers indicated "if high doses can be given in a shortened overall treatment duration, using doses per fraction less than conventional, accelerated hyperfractionation should be, theoretically, a better regimen than either hyperfractionation or accelerated fractionation alone, and better than conventional treatment".[10]

In accelerated hyperfractionated radiotherapy (AHRT), the total dose is unchanged, and the size of the dose fraction and overall treatment time is reduced. A reduction in the overall treatment time decreases the opportunity for tumor cell regeneration during treatment, and therefore, increases the probability of tumor control for a given total dose.[13] Saunders et al. have shown an improvement of local control and survival in a group of non-small cell lung cancer patients that had been treated by continuous, hyperfractionated, accelerated radiotherapy (CHART).[14,15]

There was a previous report indicating that the survival rate could be increased by improving local tumor control in uterine cervix and oropharyngeal cancer.[16] We expected that the survival rate would be increased if AHRT could improve local tumor control without an increase of late toxicity. This study was performed to assess the efficacy of AHRT for locally advanced uterine cervix cancers and to evaluate the late complications of normal tissue.

Materials and Methods

1. Patients

Between May 2000 and September 2002, 179 patients with a previously untreated carcinoma of the uterine cervix in FIGO (International Federation of Gynecology and Obstetrics) stage IIB, IIIB, IVA were treated by definitive radiotherapy in our hospital. We analyzed these patients retrospectively. In these patients, 45 patients that provided fully informed consent were treated with an AHRT schedule and 134 patients who had not want to be treated with AHRT were treated with CRT.

Eligibility included patients with biopsy-proven carcinoma of the uterine cervix. Patients were required to have had no other evidence for metastatic disease outside the pelvis (to other organs or para-aortic lymph nodes) and had no specific medical contraindication to the administration of full-dose chemotherapy or radiotherapy. Pretreatment evaluations included a history and physical examination, chest x-ray, and magnetic resonance imaging (MRI) or computer tomography (CT) scan of the pelvis to delineate the tumor volume. The para-aortic region and distant metastatic lesions were to be evaluated by CT, MRI, or positron emission tomography (PET).

Patient characteristics are shown in Table 1. The duration of follow-up ranged from 3 to 89 months (median 68 months). A censor was defined as the date of death or last follow-up date. The overall treatment duration ranged from 33 to 40 days (median 37 days) for AHRT and from 49 to 93 (median 66 days) for CRT.

2. Treatment

Patients undergoing AHRT received a dose of 30 Gy in 20 fractions (two fractions of 1.5 Gy each day, 6 hours apart between fractions each day, 5 days a week) to the whole pelvis. Then, with a midline block, a parametrial boost was administered with a total dose of 20 Gy using 2 Gy fractions. Patients received two courses of low-dose-rate brachytherapy (LDR) up to total dose of 85～90 Gy to point A and 65～70 Gy to point B. The first LDR was given within 1 week after the final external irradiation and an interval of 1 week was permitted between the two courses of LDR. Fig. 1 is a diagram of treatment schedule of AHRT.

Patients undergoing CRT received 40～59.4 Gy in 20～33 fractions (one fraction of 1.8～2 Gy each day, 5 days a week) to the whole pelvis. The patients then received a parametrial boost with a total dose of 5.4～21.6 Gy using 1.8～2 Gy fractions. Patients received one or two courses of low-dose-rate brachytherapy (LDR) up to total dose of 85～90 Gy to point A and 70～75 Gy to point B. All external radiotherapy was performed in a prone position. Patients in both groups

Table 1. Patient Characteristics

	AHRT* (n=45)	CRT† (n=134)
Age (years)	30~73 (median 51)	24~81 (median 60)
<50	18	30
50~60	17	33
≥60	10	71
Stage		
IIB	37	104
IIIB	5	23
IVA	3	7
Pathology		
Squamous	39	113
Adenocarcinoma	3	14
Adenosquamous	0	5
Glassy cell	3	1
Small cell	0	1
Tumor size (cm)	3~8 (median 5)	2~15 (median 4)
<5	18	76
≥5	27	58
Lymph node		
Positive	23	72
Negative	22	62
ECOG‡ performance status		
1	5	46
2	38	78
3	2	10
CCRT§		
Yes	23	66
No	22	68
Duration of radiotherapy (day)		
Range	33~40	49~93
Median	37	66
Follow-up duration (month)	7~87 (median 75)	3~87 (median 68)

*accelerated hyperfrationated radiotherapy, †conventional fractionated radiotherapy, ‡Eastern Cooperative Oncology Group, §concurrent chemotherapy and radiotherapy

received one or two courses of low-dose-rate brachytherapy (LDR) up to total dose of 85~90 Gy to point A and 65~70 Gy to point B. The external beam radiotherapy was delivered to the whole pelvis using a 10-MV Linac with the four-field box technique. To reduce the volume of the small bowel in the field, a small bowel displacement device was used. After the midline block, patients were treated with AP/PA fields.

Twenty three patients that were given AHRT and 66 patients that received CRT received concurrent RT (external-beam RT plus brachytherapy) plus triweekly administration of 75 mg/m^2 cisplatin intravenously (3 cycles). Chemotherapy was started at the initiation of radiotherapy. Twenty-two patients that were given AHRT and 68 patients that received CRT had refused cisplatin-based concurrent chemotherapy and radiotherapy (CCRT). These patients were treated with only radiotherapy.

3. Statistical analysis

Survival data were calculated by the Kaplan-Meier method. The statistical significance was analyzed using the log-rank test and Chi-squared test. Overall survival was calculated by taking into consideration all of the death events. Local control was calculated by consideration of only events of local recurrence in the radiation field. Toxicity was assessed according to the RTOG/EORTC Radiation Morbidity Scoring Criteria.

Results

1. Prognostic factor

Table 2 summarize prognostic factors. By univariate analysis, stage and ECOG performance status were statistically

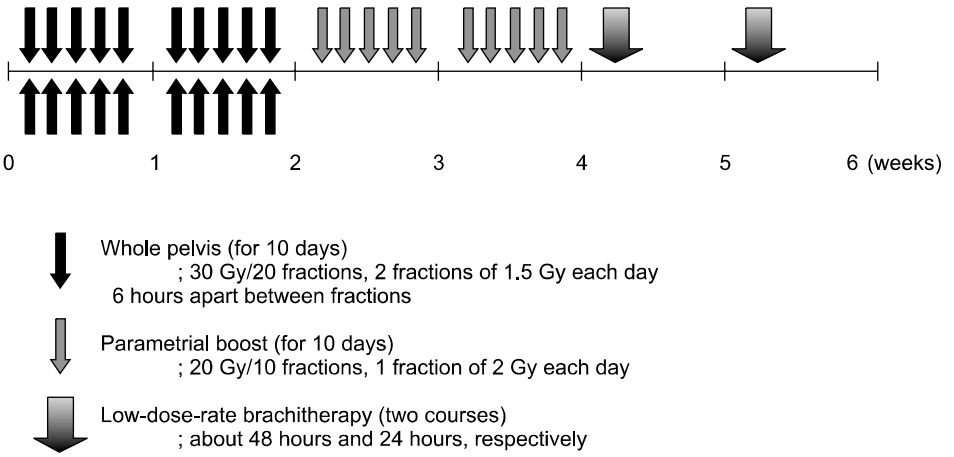

Fig. 1. The schedule of accelerated hyperfractionated radiotherapy.

significant factors affecting the overall survival. Stage, ECOG status, and age were statistically significant factors for local control. By multivariate analysis, stage and ECOG performance status were statistically significant factors affecting the overall survival. ECOG performance status, and age were statistically significant factors for local control. The other factors (chemotherapy, lymphadenopthay, tumor size, level of squamous cell carcinoma antigen, level of carcinoembryonic antigen, and hemoglobin level) were not statistically significant for overall survival and local control.

As determined by chi-squared analysis, we compared differences of prognostic factors between the groups of AHRT and CRT patients that received concurrent chemoradiotherapy (Table 2). There was a statistically significant difference in ECOG performance status and tumor size. The rate of ECOG grade 1, 2, and 3 were 13% (3/23), 87% (20/23), and 0% (0/23) in AHRT group and 48.5% (32/66), 45.5% (30/66), and 6.1% (4/66) in CRT group, respectively (p=0.002). The rate of bulky tumor were 82.6% (19/23) in AHRT group and 55.4% (36/66) in CRT group, respectively (p=0.020). In patients that received concurrent chemoradiotheray, CRT group had relatively higher proportion of good prognostic factors than AHRT group.

Table 2. Prognostic Factors for Survival and Comparison of Prognostic Factors between AHRT and CRT Group that Received Concurrent Chemoradiotherapy

Prognostic factors	p-value		CCRT*		
	Univariate	Multivariate	AHRT† (%)	CRT‡ (%)	p-value
ECOG performance status	0.000	0.002			0.002
Grade 1			13.0 (3/23)	48.5 (32/66)	
Grade 2			87.0 (20/23)	45.5 (30/66)	
Grade 3			0 (0/23)	6.1 (4/66)	
Stage	0.000	0.023			0.582
IIB			78.3 (18/23)	71.2 (47/66)	
IIIB			13.0 (3/23)	22.7 (15/66)	
IVA			8.7 (2/23)	6.1 (6/66)	
Bulky tumor	0.150	0.196	82.6 (19/23)	55.4 (36/66)	0.020
Chemotherapy	0.738	(−)	(−)	(−)	(−)
Lymphadenopathy	0.099	(−)	(−)	(−)	(−)
SCC§ level	NS#	(−)	(−)	(−)	(−)
CEA‖ level	NS	(−)	(−)	(−)	(−)
Hb¶ level	NS	(−)	(−)	(−)	(−)
Age	NS	(−)	(−)	(−)	(−)

*concurrent chemotherapy and radiotherapy, †accelerated hyperfrationated radiotherapy, ‡conventional fractionated radiotherapy, §squamous cell carcinoma antigen, ‖carcinoembryonic antigen, ¶hemoglobin level, #not significant

Table 3. Comparison of Survival, Local Control, and Distant Metastasis between AHRT and CRT Group

	5-yr*-survival (%)		p†	5-yr-local control (%)		p	Distant metastasis (%)		p
	AHRT‡	CRT§		AHRT	CRT		AHRT	CRT	
Overall	71.1	65.7	NS‖	92.4	82.4	NS	37.0	27.0	0.017
Stage IIB	77.9	71.2	NS	94.4	87.0	NS	35.1	20.2	NS
Stage IIIB, IVA	37.5	50.0	NS	80.0	64.6	NS	50.0	20.0	NS
CCRT	82.6	62.1	0.040	100.0	79.2	0.028	26.1	24.2	NS
CCRT stage IIB	84.2	59.5	NS	100.0	82.9	NS	22.7	25.5	NS
Non-CCRT	59.1	69.1	NS	84.0	86.1	NS	50.0	16.2	0.001

*year, †p-value, ‡accelerated hyperfrationated radiotherapy, §conventional fractionated radiotherapy, ‖not significant

2. Survival

Table 3 summarize the survival rates. The overall survival rate at 5 years was 71.1% for the AHRT group of patients and 65.7% for the CRT group of patients (p=0.377). In stage IIB, the 5 year survival rates were 77.9% and 71.2% for the AHRT and CRT group of patients, respectively (p=0.499). In stage IIIB and IVA, the 5 year survival rates were 37.5% and 50.0% for the AHRT and CRT group of patients, respectively (p=0.630).

In the patients that received cisplatin-based concurrent chemotherapy and radiotherapy, the 5 year survival rate was 82.6% for patients that received AHRT and 62.1% for patients that received CRT (p=0.040, Fig. 2) and the 5 year survival for stage IIB was 84.2% and 59.5%, respectively (p=0.062).

In the patients with bulky tumors (over 5 cm in diameter), the overall survival rate at 5 years was 70.2% for patients that received AHRT and 55.2% for patients that received CRT (p=0.150). However, for the subgroup of patients with bulky tumors in the CCRT group, the 5 year survival was 83.3% for patients that received AHRT and 55.3% for patients that received CRT respectively (p=0.044).

These findings indicate that AHRT is more effective than CRT in CCRT group of patients, resulting in improvement in patient survival. For patients with bulky tumors, patients that received AHRT showed better survival than patients that received CRT for the CCRT group of patients.

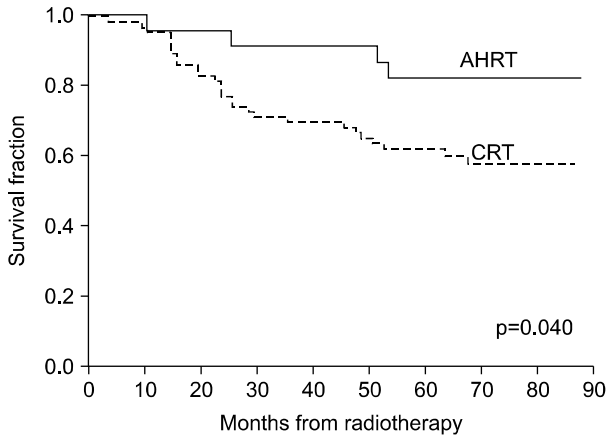

Fig. 2. Survival after AHRT and CRT for patients that received CCRT. For the subgroup of patients that received CCRT, the 5 year survival rate was 82.6% for patients that received AHRT and 62.1% for patients that received CRT (p=0.040).

3. Local control and distant metastasis

Table 3 and 4 summarizes the local control and distant metastasis. Local recurrence was defined as a recurrence in the irradiated field and distant metastasis was defined as a metastasis to outside of the irradiated field.

At 5 years, 6.7% (3/45) of patients in the AHRT group and 12.7% (17/134) of patients in the CRT group developed a local recurrence within the irradiated field. The local control rate at 5 years was 92.4% for the AHRT group of patients and 82.4% for the CRT group of patients (p=0.154).

For patients that received CCRT, 0% (0/23) of patients in the AHRT group and 13.6% (9/66) of patients in the CRT group developed a local recurrence. The local control rate at 5 years was 100.0% for the AHRT group of patients and 79.2% for the CRT group of patients (p=0.028, Fig. 3).

For the subgroup of patients that received AHRT, 0% (0/23) of patients in the CCRT group and 13.6% (3/22) of patients in the non-CCRT group developed a local recurrence.

For stage IIB, the local control rate at 5 years was 94.4% and 87.0% for the AHRT group of patients and CRT group of patients, respectively (p=0.320). For stage IIIB and IVA, the local control rate at 5 years was 80.0% and 64.6% for the AHRT group of patients and CRT group of patients, respectively (p=0.328).

Table 4. Patterns of Failure

	Treatment		CCRT‡		AHRT	
	AHRT* (%)	CRT† (%)	AHRT (%)	CRT (%)	CCRT (%)	Non-CCRT (%)
Local	6.7 (3/45)	12.7 (17/134)	0 (0/23)	13.6 (9/66)	0 (0/23)	13.6 (3/22)
Distant	37.8 (17/45)	20.1 (27/134)	26.1 (6/23)	24.2 (16/66)	26.1 (6/23)	50.0 (11/22)
Local & Distant	6.7 (3/45)	6.0 (8/134)	0 (0/23)	4.5 (3/66)	0 (0/23)	13.6 (3/22)

*accelerated hyperfrationated radiotherapy, †conventional fractionated radiotherapy, ‡concurrent chemotherapy and radiotherapy

Seventeen of 45 patients (37.8%) in the AHRT group and 27 of 134 patients (20.1%) in the CRT group developed a distant metastasis outside of the irradiated field (p=0.017, Table 3). Inthe patients that received CCRT, 26.1% (6/23) of patients in the AHRT group and 24.2% (16/66) of patients in the CRT group developed a distant metastasis (p=0.860). For the subgroup of patients that received AHRT, 26.1% of patients in the CCRT group and 50.0% of patients in the non-CCRT group developed a distant metastasis (p=0.098). For the subgroup of patients that received CRT, 16.2% of patients in the CCRT group and 24.2% of patients in the non-CCRT group developed a distant metastasis (p=0.245).

4. Complications

Table 5 summarizes the number of late toxicities that occurred as a result of the radiation therapy. In the AHRT group, 22.2% (10 of 45) of patients had a mild late toxicity (Grade 1 or 2) and 6.7% (3 of 45) of patients presented with severe late toxicity (Grade 3 or 4) requiring surgery. In the CRT group, 38.8% (52 of 143) of patients had a mild late toxicity and 4.5% (6 of 143) of patients presented with a severe late toxicity requiring surgery. There was a statistically significant decrease of mild late toxicity in the AHRT group as compared to the CRT group (p=0.043) but no significant difference of severe late toxicity (p=0.561). No patients had a severe acute toxicity in either the AHRT or CRT group. The incidence of mild acute toxicity was 20% (9 of 45) and 13.4% (18 of 134) for the AHRT group and the CRT group, respectively, and complications were tolerable for patients in both groups.

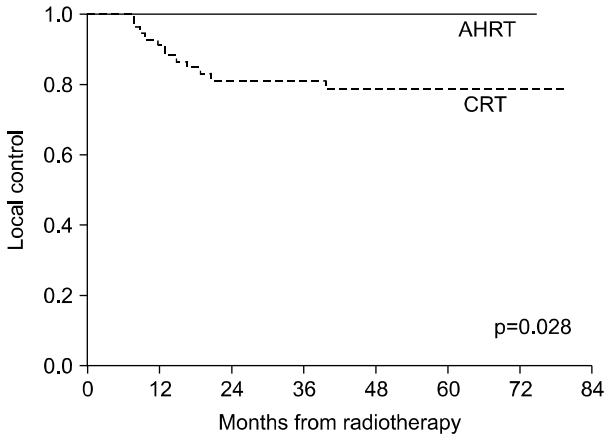

Fig. 3. Local control of tumors after AHRT and CRT for patients that received CCRT. For the subgroup of patients that received CCRT, the local control rate at 5 years was 100.0% for the AHRT group of patients and 79.2% for the CRT group of patients (p=0.028).

Discussion

Suit et al. have analyzed causes of failure in 1705 patients of uterine cervix cancer that were treated at the M.D. Anderson Cancer Center from 1954 to 1963. The total number of pelvic failures was 404 of 1705 patients (24%). The rate of deaths among patients with uncomplicated pelvic control was 14.8% (193 of 1,301 patients). If there were no pelvic failures, then the number of deaths among the 404 patients that had failed locally would be expected to be 404×0.148, or 59. In other words, 345 (404～59) additional survivors at five years would be expected. As a result, the 5-year survival rate would be increased from 65% to 85%. The study concluded that these predicted increases of survivors by improving local treatment methods are greater than would be predicted by improving treatment of distant disease, at least for patients with carcinoma of the uterine cervix and of the orocavity and oropharynx.[16)]

According to several previous reports, for stage IIB carcinomas, tumors are often treated with radiation alone and the pelvic failure rate ranges from 12.5% to 50%. For stage

Table 5. Late Complications of Radiation Therapy

	Mild (grade 1 & 2)		p-value	Severe (grade 3 & 4)		p-value
	AHRT*	CRT†		AHRT	CRT	
Urinary	2	15	(−)	0	5	(−)
Gastrointestinal	8	37	(−)	3	1	(−)
Total	10 (22.2%)	52 (38.8%)	0.043	3 (6.7%)	6 (4.5%)	0.561

*accelerated hyperfrationated radiotherapy, †conventional fractionated radiotherapy

IIIB carcinomas, pelvic failure rates range from 38% to 50%.[2-4,6,7] As the rate of local failure is still high in locally advanced uterine cervix cancers, efforts to improve local control should be required. For carcinoma of the uterine cervix, efforts to improve local control rates for this disease have included increasing the radiation dose,[17] the addition of hypoxic cell sensitizers,[18] the use of a combination of radiation and cytotoxic drugs,[19,20] the use of split courses of large fraction radiotherapy,[21] the use of fast neutron radiotherapy,[22] and the addition of hyperbaric oxygen.[23,24] However, there is no convincing evidence that these treatments have had a significant benefit on control of the local tumor, distant metastases, or survival.

We hypothesized that if AHRT improves local control in locally advanced uterine cervix cancers, an increase of survival would be expected. Actually in the present study, in the subgroup of patients that received CCRT, the local control rate at 5 years for patients that received AHRT was 100% and it was superior to the local control rate at 5 years of 79.2% for patients that received CRT (p=0.028). In addition, the 5-year survival rate of patients that received CCRT was 82.6% and 62.1% for patients that received AHRT and CRT, respectively (p=0.040).

AHRT can improve the therapeutic ratio by shortening the overall treatment time and can reduce the late toxicity of radiotherapy due to a small dose size per fraction.[13] A reduction in the overall treatment time decreases the opportunity for tumor cell regeneration during treatment. Withers has suggested that an accelerated repopulation of tumor cells during radiotherapy is an important cause of treatment failure in cancers of the head and neck.[25] Therefore, efforts will be necessary to reduce the overall treatment time. In the present study, the shortening of the total treatment time of AHRT (median 37 days) as compared to CRT (median 66 days) is prominent. Several reports have documented a decreased local control rate and even survival rate for cervix cancer with a prolongation of overall treatment time. Fyles et al. reported that the prolongation of the overall treatment time for carcinoma of the uterine cervix decreases the pelvic tumor control rate by 0.7% and less than 1.2% per day for patients with stage I/II and for stage III/IV, respectively.[26]

Perez et al., in a study of 1,330 patients treated with a definitive radiation treatment, reported that the prolongation of treatment time in patients with stage IB, IIA, IIB, and III carcinoma of the uterine cervix has a significant impact on pelvic tumor control and causes an increase in specific survival.[27] In the present study, we observed that the use of AHRT has significant advantages of local control and survival when the patients were treated with concurrent chemoradiotherapy. Previously, Withers also has indicated AHRT should be, theoretically, a better regimen than either hyperfractionation or accelerated fractionation alone, and better than conventional treatment.[10] The results of the use of AHRT in the present study were better than that of CRT and altered fractionated RT that were studied previously (Table 6). There have been several studies about the use of altered fractionated radiotherapy in uterine cervix cancers. Komaki et al. reported on 81 patients with bulky stage IB and IIA, IIB, III, and IVA carcinomas of the cervix that had been treated by hyperfractionated radiation therapy. A hyperfractionated dose of 1.2 Gy was administered to the whole pelvis twice daily; the total dose to the whole pelvis was 24~48 Gy. The external pelvic irradiation was followed by one or two intracavitary applications to deliver a total minimum dose of 85 Gy at point A. The first intracavitary application was given within 2 weeks after the final external irradiation and an interval of 2~4 weeks was permitted between the two intracavitary applications. The investigators found no increase in local control rates as compared with historical controls.[28] Compared to our study, the study by Komaki and colleagues had a long treatment time due to the long interval of brachytherapy and did not use current chemoradiotherapy. Although the study used hyperfractionated radiotherapy, the escalation of the radiation dose was not accomplished. MacLeod et al. reported on 61 patients with stage IIB carcinoma of the uterine cervix that were treated by accelerated hyperfractionated radiotherapy. An accelerated hyperfractionated dose of 1.25 Gy was administered twice daily to a total pelvic dose of 57.5 Gy. A boost dose of 3~30 Gy (median 27.5 Gy) was delivered to point A by low dose rate intracavitary brachytherapy.[29] The investigators were unable to obtain good results for local control and survival. The study of Macleod and colleagues study differs from our study in that most patients in their study were stage III and IV, except for two patients, and the patients did not receive

Table 6. Comparison with Other Previous Studies

	Tx*	Fraction size	Stage	No	5yr† survival (%)	5yr local control (%)	5yr local failure (%)	Distant metastasis (%)
Komaki[28]	HFX‡ (non-CCRT§)	1.2 Gy	IB-IIB	47	71 (3 yr)	60 (3 yr)	(−)	31.9
			IIIA-IVA	34	47 (3 yr)	47 (3 yr)	(−)	38.2
Chun[38]	MHRT‖	1.5 Gy	IIB	61	75.4	(−)	6.6	22.7
			IIB (≥4 cm)	54	(−)	(−)	7.4	22.2
MacLeod[29]	AHRT¶ (non-CCRT)	1.25 Gy	IIB-IVA	61	27	66	(−)	29.5
			IIB	2	50	(−)	(−)	(−)
Lanciano[39]	CRT# (CCRT)	1.8 Gy	IIB-IVA	159	68 (4 yr)	(−)	16 (4 yr)	18
Eifel[40]	CRT (CCRT)	1.8 Gy	IB-IVA	194	73	(−)	18	11.3
			IB-IIB	136	79	(−)	13	(−)
			IIIA-VIA	59	59	(−)	29	(−)
Saibishkumar[41]	CRT (CCRT)	2 Gy	IIB (≥4 cm)	18	50	61.1	(−)	(−)
			IIB-IIIB (≥ 4 cm)	57	45.6	57.9	(−)	(−)
Nakano[42]	CRT (Non-CCRT)	1.8~2 Gy	IB	146	88	(−)	7	6.8
			II	305	69	(−)	18	13.8
			III	554	56	(−)	24	24.7
			IVA, IVB	143	10, 21	(−)	39	58.0
Cho (Presents study)	AHRT	1.5 Gy	IIB-IVA	45	70.7	92.4	6.7	37.8
			IIB-IVA (≥5 cm)	27	70.2	96.0	3.7	37.0
			IIB	37	77.9	94.4	5.4	18.9
			IIB (≥5 cm)	20	79.7	94.7	5	35.0
			IIIA-IVA	8	37.5	80.0	12.5	50.0
	AHRT (CCRT)	1.5 Gy	IIB-IVA	23	82.6	100	0	26.1
			IIB-IVA (≥5 cm)	18	83.3	100	0	34.8
			IIB	19	84.2	100	0	26.3
			IIB (≥5 cm)	14	85.7	100	0	21.4

*treatment, †year, ‡hyperfractionated radiotherapy, §concurrent chemotherapy and radiotherapy, ‖modified hyperfractionated radiotherapy, ¶accelerated hyperfractionated radiotherapy, #conventional fractionated radiotherapy

concurrent chemoradiotherapy.

Previously, Perez et al. reported that the size of tumor is critical factor in prognosis, therapy efficacy, and evaluation of results for carcinoma of the uterine cervix.[30] Increased efforts are required to treat adequately bulky uterine cervix cancer. It is difficult in the case of bulky uterine cervix cancer to improve local control by the use of only conventional radiotherapy. For the treatment of a bulky tumor, isodose distribution of brachytherapy is not ideal and the hypoxic cells in the tumor are resistant to the radiation. In addition, the accelerated repopulation by the surviving tumor cells during fractionated radiation therapy contribute to the treatment failure.[25,31,32] In the present study, as compared with the use of CRT, AHRT had a better survival rate and local control for patients with bulky tumors in the CCRT group. The local control rate at 5 years for patients that received AHRT was 100% and it was superior to the local control rate at 5 years of 77.0% for patients that received CRT (p=0.038). In addition, the 5-year survival rate was 83.3% and 55.3% for patients that received AHRT and CRT, respectively (p=0.044).

The results presented in Tables 3 and 4 show that AHRT or CCRT alone cannot improve survival. However, patients that received AHRT with concurrent chemotherapy showed a statistically significant increase of local control and survival rate. In the subgroup of patients with a bulky tumor, the local control rates at 5 years were 96.0% and 71.1% for patients that received AHRT and CRT, respectively (p=0.044) but the 5 year survival rates were 66.7% and 55.2% for the AHRT and CRT group of patients, respectively (p=0.254). Although the local control rate showed a statistically significant difference between patients that received AHRT and CRT, the 5-year survival rate was not sufficiently high in the AHRT group of patients. We thought that the result originated from a high incidence of distant metastasis in patients that had received AHRT. The incidence of distant metastasis was 37.0% and 24.1% for the AHRT and CRT group of patients,

respectively (p=0.017). There have been many reports that both progression-free survival and overall survival had improved significantly when cisplatin-based chemotherapy was administered during radiation therapy for various stages of uterine cervix cancer.[33-37] Thus, for locally advanced uterine cervix cancers, an effort is required to control both local recurrence and distant metastasis.

Based on the results of the present study, we conclude that it is very important to increase the local control rate to increase the survival rate. However, it is difficult to accomplish a survival gain by an increase of local control alone. In addition, it would be less effective to control distant metastasis alone without an effort to increase the local control rate. When the control of distant metastasis accompanies the increase of local control, the efficacy of treatment will be maximized and survival gain will be achieved. The use of AHRT with current chemotherapy should be considered as a new treatment modality for patients with locally advanced uterine cervix cancers to increase the local control rate, with an expectation to increase the survival rate.

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대한방사선종양학회지 2008;26(1):24~34

국문초록

국소진행된 자궁경부암에서의 가속과분할 방사선치료

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목 적: 이 연구의 목적은 국소진행된 자궁경부암에서의 가속과분할 방사선치료의 효용성을 평가하기 위함이다.
대상 및 방법: 2000년 5월부터 2002년 9월 사이에 자궁경부암 병기 IIB, IIIB, IVA로 가속과분할 방사선치료를 받은 환자 45명과 같은 기간 동안 고식적 방사선치료를 받은 병기 IIB, IIIB, IVA 환자 134명이 비교 분석되었다. 가속과분할 방사선치료는 전골반에 대하여 총 30 Gy의 방사선을 1.5 Gy씩 하루 2회, 총 10일에 나누어 조사하였다. 전골반 조사 후 중심 차폐하여 자궁주위 조직에 대하여 총 20 Gy의 방사선을 2 Gy씩 하루 1회, 총 10일에 나누어 조사하였다. 외부방사선치료가 끝난 후 Cs-137을 이용한 저선량 근접치료를 Point A 기준 55~60 Gy의 방사선치료를 2회 시행하여, Point A 기준 총 85~90 Gy의 방사선 선량이 주어지도록 치료하였다. 고식적 방사선치료 또한 Point A 기준 총 85~90 Gy의 방사선 선량이 주어지도록 치료하였다. 총 치료기간은 가속과분할 치료군의 경우 중앙값이 37일이었으며, 고식적 치료군은 중앙값 66일이었다. 통계적 분석은 Kaplan-Meyer 법, log-rank test, 그리고 Chi-square test를 통해 이루어졌다.
결 과: 항암치료를 시행했던 환자군에서, 5년 국소제어율은 각각 100.0%와 79.2%로 가속과분할 치료군이 고식적 치료군에 비해 통계적으로 유의하게 우수한 성적을 보였고(p=0.028), 5년 생존율은 병기 IIB의 큰 종양군에서 가속과분할 치료군이 82.6%으로 고식적 치료군의 62.1%에 비해 통계적으로 유의하게 우수한 성적을 보였다(p=0.074). 두 군간에 있어서 방사선치료로 인한 후기 합병증의 차이는 없었다(p=0.561).
결 론: 항암치료와 동반된 가속과분할 방사선치료는 국소진행된 자궁경부암에서 생존율 및 국소제어율을 높이는데 효과가 있을 것으로 판단된다.

핵심용어: 자궁경부암, 가속, 과분할, 방사선치료, 동시 화학방사선요법