Cancinoma of Uterine Cervix Treated with High Dose Rate Intracavitary Irradiation:

1. Patterns of Failure

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226 patients with carcinoma of the uterine cervix treated with curative radiation therapy at the Department of Therapeutic Radiology, Dongsan hospital, Keimyung university, School of medicine, from July, 1988 to May, 1991 were evaluated. The patients with all stages of the disease were included in this study. The maximum and mean follow up durations were 60 and 43 months. The radiation therapy consisted of external irradiation to the whole pelvis (2700~4500 cGy) and boost parametrial doses (for a total of 4500~6300 cGy) with midline shild (4×10 cm), and combined with intracavitary irradiation irradiation (5700~7500 cGy to point A). The distribution of patients according to the stage was as follows: stage IB 37 (16.4%), stage IIA 91 (40.3%), stage IIB 58 (25. 7%), stage III 32 (13.8%), stage IV 8 (3.5%).

The overall failure rate was 23.9% (54 patients). The failure rate increased as a function of stage from 13.5% in stage IB to 15.4% in stage IIA, 25.9% in stage IIB, 46.9% in stage III, and 62. 5% in stage IV. The pelvic failure alone were 32 patients and 11 patients were as a components of other failure, and remaining 11 patients had distant metastasis only. Among the 43 patients of locoregional failure, 28 patients were not controlled initially and in other words nearly half of total failures were due to residual tumor.

The mean medial paracervical (point A) doses were 6700 cGy in stage IIB, 7200 cGy in stage IIA, 7450 cGy in stage IIB, 7600 cGy in stage III and 8100 cGy in stage IV. The medial paracervical doses showed some correlation with tumor control rate in early stage of disease (stage Ib, IIA), but there were higher central failure rate in advanced stage in spite of higher paracervical doses. In advanced stage, failure were not reduced by simple increment of paracervical doses. To improve a locoregional control rate in advanced stages, it is necessary to give additional treatment such as concomitant chemoradiation.

Key Words: Cervix, High dose rate, Brachytherapy, Patterns of failure

INTRODUCTION

Among the malignant tumors, the uterine cervical cancer is one of the tumors that is curable with radiation therapy alone. So Radiation therapy has been the major modality for patients with carcinoma of the uterine cervix for several decades[1~4]. Intracavitary brachytherapy at low dose rate (LDR) and external beam radiotherapy has long been considered the standard method of treatment because of acceptable curability and complications. In recent years, there has been a trend to move towards high dose rate brachytherapy, in which there are some important advantages to treat patient such as: (a) patient convenience and cost; (b) excellent treatment reproducibility[5~7]. A number of papers comparing low dose rate versus high dose rate regimens have reported similar results in tumor control and complications[8~11]. We obtained 5-year results of treatment with carcinoma of cervix treated with high dose rate therapy and observed patterns of failure, and also analyzed some treatment factors to know the effect on treatment failure.

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MATERIALS AND METHODS

1. Patients Characteristics

From July 1988 to August 1991, 276 patients with histologically proven carcinoma of cervix were treated with radiation at the Department of therapeutic radiology, Dongsan Hospital, Keimyung University. The present study is based on 226 patients who were treated by external beam irradiation and high dose rate intracavitary therapy completely. The remaining 50 patients were excluded from the study since they received postoperative external irradiation alone or incomplete treatment. Patients were initially evaluated with physical examinations, routine blood count, chemistry profiles, chest X-ray, intravenous pyelogram, cystoscopy, sigmoidoscopy, pelvic CT scanning and occasionally pelvic MRI scanning. Punch biopsies of the uterine cervix were obtained on all patients. Staging was performed according to FIGO classification system at the time of initial examination.

Clinical characteristics of patients are listed in Table 1. The age range of patients was from 28 to 78 years old. The majority of patients were in the 41~70 age groups and the mean was 53.6 years old. The distribution of patient according to FIGO staging was as follows: stage IB 16.4%, stage IIA 40.3%, stage IIB 25.7%, stage III 14.2%, and stage IV 3.5%. Most of stage III patients were stage IIIB, and stage IVB were included in the this study. In tumor histology, the most common cell type was squamous cell carcinoma (92.5%).

Although general treatment polices have been followed, therapy was somewhat individualized, depending on the disease extent, geometry of the pelvic organ, performance and age of patient.

2. External Beam Irradiation

Patients were treated with 6 or 20 MV high-energy photon beams through Box-technique fields. The ususal field sizes were 15×15 cm or 18×15 cm for stage I and II. For patients with stage III, IV or nearly all patients who had visible pelvic or paraaortic lymph nodes on CT scanning, the irradiation fields were extended up to the T11~12 level, if patients could tolerate the treatment. For patients with stage IIIA or inguinal lymph node metastasis, both inguinal area were treated with electron beams. The external irradiation dose ranges 4500~6300 cGy according to disease stages. Midline shilding was applied with 4×10 cm sized rectangular block after 2700 cGy in stage IB, 3600 cGy in stage IIA, and 4500 cGy in stage IIB or above. Thus the usual lateral pelvic dose was 4500 cGy in stage IB and IIA, and 5400 cGy in stage IIB or above. And the patient with persistent parametrial induration after 5400 cGy or visible pelvic node (s) on initial CT scan or physical examination, boost dose with reduced field size to ipsilateral pelvis, were delivered up to 6300 cGy. The paraaortic irradiation dose was 4500 cGy in most cases, but in case of paraaortic enlargement boost doses were delivered up to 5400 cGy.

3. Intracavitary Irradiation

After completion of external beam irradiation, intracavitary brachytherapy was performed as soon as possible, usually within 7 days. We used Buchler remote afterloading system. High dose rate brachytherapy using Co-60 source was performed twice per week, with 500 cGy per fraction to point A, delivering 3000 to 3500 cGy within 3 and a half weeks to the all stages of patients. And if there noted persistent hypertrophy or residual hard induration in the cervix, one or two times of boost application of brachytherapy was performed with

Table 1. Characteristics of Patients

		No. of patients (%)
No. of patients: 226, Jul, 1988~May. 1991		
Age (years)*	≦40	26 (11.5)
	41~50	59 (26.1)
	51~60	80 (35.4)
	61~70	55 (24.3)
	71≧	6 (2.7)
Histologic type	Squa. C.C.	209 (92.5)
	Adenoca.	13 (5.8)
	Small C.C.	1 (0.4)
	Adenosq.	3 (1.3)
Stage	IB	37 (16.4)
	IIA	91 (40.3)
	IIB	58 (25.7)
	III	32 (14.1)
	IV	8 (3.5)
Mean paracervical dose** by stage	IB	6700
	IIA	7200
	IIB	7450
	III	7600
	IV	8100

*mean age: 53.6 years old.
**dose in cGy.

weighting of dose on the cervical area.

The mean total doses to point A (paracervical dose) according to stage is presented in Table 1.

4. Statistical Analysis

Factors contributing to treatment failures such as stage, histology, total doses, age, and hemoglobin were analyzed in univariate and multivariate methods. Survival duration and time to recurrence were calculated from the date of the first treatment. Survival was calculated with life table method, and evaluation of statistical significance was assessed by Cox proportional hazard method.

RESULTS

Patients were followed periodically by both the staff of radiotherapy and that of gynecology departments until lost to follow-up or death. The mean follow-up duration was 43 months, maximum 60 months and minimum 24 months. Location of the first failure is presented on Table 2. Tumor control was defined when complete response sustained excess of 6 months. Of the 226 evaluable patients, 172 patients (76.1%) were remained disease-free through the entire period of observation, but remaining 54 patients (23.9%) were failed treatment. Of the 54 patients of treatment failure, 32 patients were locoregional alone. The locoregional failure rate increased as a function of the stage, from 10.8% for stage IB to 50% for stage IV. Distant metastasis only was the first sign of failure in 11 patient. In the remaining of 11 patients, both of locoregional and distant metastasis were occurred concomitantly. Among the 43 patients of local failure, 28 patients were not controlled initially, and that occupied more than half of total failures. Therefore, we thought that initial local tumor control was very important for treatment of uterine cervical cancer.

And we also analyzed several treatment factors to know the relation on treatment failure and to determine the contribution on disease control and survivals.

1. Stage

The overall failure rate increased as a function of stage of the disease. The overall recurrence rate were 23.9% for the entire group and 13.5%, 15.4%, 25.9%, 46.9%, 62.5% for stages I, IIA, IIB, III, and IV, respectively (Table 2).

2. Histology

There were no preponderance of histologic type according to stages. Both cell types were distributed evenly throughout the stages. The majority of nosquamous cell were adenocarcinoma (3/17), of which 6 patients were failed (46.1%). Overall failure rate of nonsquamous cell carcinomas were more prominent than squamous cell carcinomas. Their failure rate were 22.0% for squamous cell and 47.1% for nonsquamous cell carcinomas (Table 3).

3. Treatment Dose

These data should be interpreted with caution, since this is not a dose-seeking study but a retrospective review in which, from a clinical judgement, patients with larger tumors of those with less tumor regression were given higher doses of irradiation. The paracervical dose represents the sum of the external beam to the whole pelvis (not included the doses after midling shielding) plus the intracavitary doses, and grouped into four dose levels from below 6500 cGy to above 8500 cGy with 1000 cGy

Table 2. Patterns of Failure

Stage	Site			Failure rate (*/**)
	L.F	D.M	L.F+D.M	
IB	3 (1)	1	1 (1)	5/ 37 (13.5%)
IIB	7 (3)	5	3 (3)	14/ 91 (15.4%)
IIB	8 (6)	3	4 (2)	15/ 58 (25.9%)
III	10 (6)	1	4 (3)	15/ 32 (46.9%)
IV	4 (4)	1	0 (0)	5/ 8 (62.5%)
Total	32 (20)	11	11 (8)	$54^{+}/226^{++}$ (23.9%)

( ) number of initially not controlled patients.

*/**: sum of failure patients/total number of patients in corresponding stage.

+/++: total number of failure patients/total number of evaluable patients.

Table 3. Failure by Histology

Stage / Histology	IB	IIA	IIB	III	IV	Total (*/**)
Sq. C.C.	(4)/35	(12)/84	(13)/53	(12)/29	(5)/8	46/209
Adenoca.	(1)/ 2	(0)/ 4	(2)/ 4	(3)/ 3		6/ 13
Small C.C.		(1)/ 1				1/ 1
Adenosq C.C.		(1)/ 2	(0)/ 1			1/ 3
Total	(5)/37	(14)/91	(15)/58	(15)/32	(5)/8	54/226

*/**: sum of failure patients/total number of patients in corresponding histology.
( ): No. of failure.

Table 4. Failures by Dose Level

Stage / Doses	IB	IIA	IIB (*/**)	III	IV	Total
~6500	1/14	1/ 6		1/ 1		3/ 21
6501~7500	4/20	11/70	11/53	9/21	2/3	37/167
7501~8500	0/ 3	2/15	4/ 5	5/10	3/4	14/ 37
8501~					0/1	0/ 1
Total	5/37	14/91	15/32	5/8	54/226	

*/**: number of failures/total number of patients in corresponding dose and stage.

Table 5. Failure by Age Group

Stage / Age	IB	IIA	IIB	III	IV	Total (*/**)
~40	(1)/ 4	(3)/11	(3)/ 8	(1)/ 1	(1)/2	9/ 26
41~50	(3)/14	(5)/18	(5)/13	(7)/12	(1)/2	21/ 59
51~60	(0)/12	(2)/36	(4)/16	(6)/13	(2)/3	14/ 80
61~70	(1)/ 7	(4)/23	(3)/18	(1)/ 6	(1)/1	10/ 55
71		(0)/ 3	(0)/ 3			0/ 6
Total	(5)/37	(14)/91	(15)/58	(15)/32	(5)/8	54/226

*/**: sum of failure patients/total number of patients in corresponding age group.
( ): No. of failure.

intervals. As shown in table 4, there was a trend of better locoregional control with higher doses of irradiation receiving over 7500 cGy compared to less doses in stage IB and IIA. But there were no significant correlation between the dose levels and the probability of locoregional control in advanced stage of IIB, III, and IV. There were rather progressively increased rates of failure in those stages, in spite of receiving higher doses.

4. Age

The age distribution of failure patients were similar to general distribution found for this disease, being in the 41~60 age groups. An analysis of the age distribution according to the stage of disease revealed no significant relations between them. If the age were divided into two large groups at the age of 50, 30 of the 85 patients (35.3%) who were younger than 50 years old were failed, but only 24 of the 141 patients (17.0%) were failed in the older age group (Table 5).

5. Hemoglobin Level

All patients were classified into two groups according to hemoglobin level, below and above the 11.0 mg/dl. Although there was a tendency for patients with advanced stage to show a lower hemoglobin level, the difference of locoregional failure rate between two groups were rather apparent, 26 of 81 patients (32.1%) in below and 28 of 145 patients (19.3%) in above 11.0 mg/dl groups were failed (Table 6).

Table 6. Failure by Hemoglobin Level

Hg \ Stage	IB	IIA	IIB	III	IV	Total (*/**)
≦11.0	(0)/ 9	(6)/25	(8)/23	(9)/18	(3)/6	26/ 81 (32.1%)
>11.1	(5)/28	(8)/66	(7)/35	(6)/14	(2)/2	28/145 (19.3%)
Total	(5)/37	(14)/91	(15)/58	(15)/32	(5)/8	54/226 (23.9%)

*/**: sum of failure patients/total number of patients in corresponding Hg level.
( ): No. of failure.

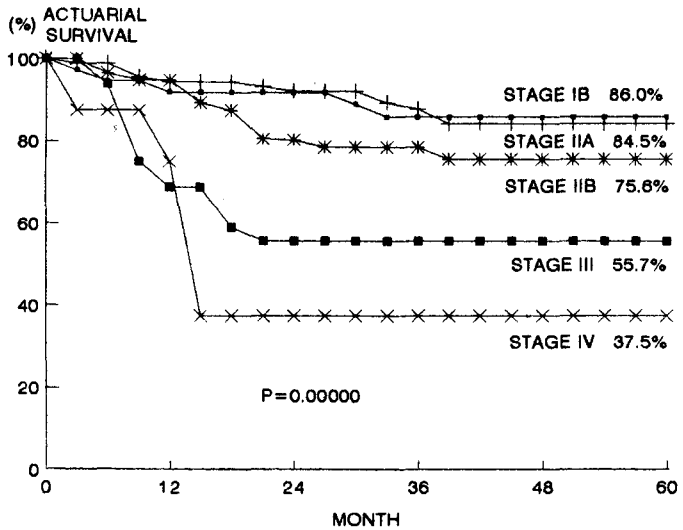

Fig. 1. Overall survival by stage.

Table 7. Factors Related to Control and Survival

Factors	Control		Survival	
	Uni.	Multi.	Uni.	Multi.
Stage	0.0000*	0.0122	0.0000	0.0130
Histology	0.0005	0.0144	0.0020	0.0125
Dose	0.0011	0.6145	0.0009	0.4578
Age	0.0011	0.0107	0.0029	0.6890
Hemoglobin	0.0001	0.0375	0.0052	0.9790

Uni.: univariate analysis.
Multi.: multivariate analysis.
*: p-value

Statistical analysis of treatment factors on the control and survival were performed. Univariate analysis revealed all of above factors to be significant with respect to tumor control and survival (Table 7). In the multivariate analysis of disease control, disease stage (p=0.0122), histology (p=0.0144), age (p=0.0107) and hemoglobin level (p=0.0375) had significance, but treatment dose had no significance. And with respect to survival rate, only stage (p=0.0130) and histology (p=0.0125) revealed to be significant factors in multivariate analysis.

As shown in Fig. 1, the acturial 5-year survivals of stage IB, IIA, IIB, III, and IV were 86.0, 79.3, 75.6, 55.7 and 37.5% respectively. Survivals between stage IIA and IIB were not significantly different, whereas survival of patients with stage IIB disease was significantly better than that for stage III.

DISCUSSION

Most effective form of treatment in carcinoma of cervix has been considered to combine external irradiation and low dose rate intracavitary therapy. In recent years, high-dose-rate intracavitary irradiation technique has been developed[4]. But any new

treatment modality has to meet the therapeutic standards of the conventionally established methods. Currently reported results of high dose rate therapy from several centers are similar to or better than low dose rate brachytherapy both in terms of the local control and survival[8~11]. In those reports, they used nearly similar technique with some variation in fraction dose, number of fractions, intervals between treatments, and total dosage[8,12~14]. So far, there has been no evidence that one regimen is significantly superior to another with respect to local tumor control or complication rate. In addition, the high dose rate brachytherapy had a number of advantages for the treatment of carcinoma of cervix[5~7]. So there has been a trend to move towards high dose rate brachytherapy recently.

In this study, 23.9% (54/226) of the patients were failed. The analysis of the site of the first manifestation of failure showed that the majority of the patients, 19% of the treated patients, had recurrence within treated field. In 4.9% of the patients, the first manifestation of recurrence was distant metastases alone, and 11 patients (4.9%) had both of locoregional and distant metastases. The overall frequency of failure in this study are relatively low compared with other reports, which may be due to short follow-up duration and small numbers of analyzed patients, but distribution of failures is similar to other reports. And among the locoregional failure 65.1% of failures (28/43) were not controlled initially, which was not closely related to paracervical doses, because most of initial failure were received higher doses. To improve survival rate, it is very important to obtain initial local control. It is not effective to increase irradiation doses simply, but more aggressive approches such as concomitant chemo-radiation or invasive interstitial implantation at the involved parametrial region must be considered to obtain local control[5,6,15~17]. In addition, half of distant metastases, they also had local failure. So improvement of local control may be one way to reduce distant metastasis.

The 5-year survival rate of stage IB was 86.0%, which was comparable to other reports treated with high dose rate intracavitary brachytherapy[2,5~7]. Like other institution, most of our patients with cervical cancer in early stage or favorable condition underwent surgery. Consequently, the patients treated with irradiation had poor general conditions. If taking into the consideration of these points, our result is compatible with or better than those of operation[10,12,14,18]. The five-year survival of stage IIA, IIB, and III were 84.5%, 75.6% and 55.7%, respectively. These results are comparable with other reported results[10,11,14,15,18]. The 5-year survival rate of stage IV of this study were very high. But this has no statistical significance due to small number of the patients.

In the statistical analysis of factors related to disease control and survival rates, both stage and histology were most significant predictor of pelvic control and survival in this study. But in the histology, there have been many controversies about the adenocarcinoma. In recent days, there were many papers reporting to show poor control rate of adenocarcinoma of cervix, especially treated with high dose rate intracavitary brachytherapy[19~21]. Although the number of our patients with adenocarcinoma were too small to compare, the control rate was poorer than squamous cell carcinoma (53.8% versus 90.4%). So it is our treatment policy to perform extrafascial hysterectomy after radiotherapy in nonsquamous cell carcinoma of cervix, especially adenocarcinoma.

Patient's age has variously been reported either to have no influence on survival or to have modest influence on prognosis[22]. Usually younger patients seemed to have bulky tumor or advanced stage of disease. In this study, age revealed relatively high sinificance level ($p=0.0107$) on disease control, showing to be poor in younger patients group (below the 50 years old), but it had no influence on survival rate in multivariate analysis ($p=0.6890$).

Hemoglobin level have been shown to be predictors of pelvic control and survival[23]. But patients with larger tumors or advanced disease usually tended to present with lower hemoglobin level, and it may cause relative intratumoral hypoxia. Under this hypothesis, blood transfusion has been requsted before or during the treatment in many institutes, and reporting better results on pelvic control and survival rates, but there are many controversies about the transfusion. The analyzed data of our results could also confirmed above general observations, and it had influence on pelvic control, but not on survival in multivariate analysis.

Treatment dose is dependent upon the several factors such as tumor size, extent of disease, inherent cellular radiosensitivity, and purpose of treatment. So patients who have locally advanced or bulkier diseases usually received a higher dose of irradiation, but it was fairly common to find out higher failure rate in these patients in clinical prac-

tice, in spite of higher dose. And the results in term of survival and local control still remain unsatisfactors. They are not effectively treated with simple increment of total dose. Recently many authors suggest that concomitant chemotherapy and radiation may play a important role in improving the control rate of the locoregional lesions and extrapelvic lesion[16,17]. Nevertheless, it seems that higher dose of radiation to pelvis may be associated with improved pelvic control rate[24].

In conclusion, high dose rate intracavitary radiation therapy is a useful modality for cervical cancer and has many advantages for clinical practice. Initial primary control is very important to improve patient survival, and local control itself may reduce distant metastasis. For improvement of local control rate, other modalities such as concomitant chemoradiation or altered fractionated radiation should be considered in case of locally advanced or bulky primary lesions.

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═국문초록═

자궁경부암의 고선량율 강내치료후 실패양상에 대한 고찰

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1988년 7월부터 1991년 5월까지 계명대학교 의과대학 동산의료원 치료방사선과에서 완치목적으로 고선량율 강내조사장치로 치료한 226명의 자궁경부암 환자를 대상으로 하여 치료후의 실패양상을 관찰하고자 하였다. 대상환자는 전병기에 고르게 분포하고 있으며, 최장 및 평균 추적관찰기간은 각각 60개월, 43개월이었다. 방사선치료는 외부조사를 먼저 시행하였으며, 가능한 단기간내에 강내치료를 시작하였다. 먼저 외부조사로써 대개의 환자에서 4500~6300 cGy를 골반부에 조사하였으며, 병기에 따라서 2700~4500 cGy부터 골반중앙부를 차폐하였다. 강내치료는 A점을 기준으로 전체 조사선량이 최소한 5700~7500 cGy가 되도록 하였으며, 병기별로 A점에 조사된 평균선량은 IB 6700 cGy, IIA 7200 cGy, IIB 7450 cGy, III 7600 cGy, IV 8100 cGy이었다. FIGO 병기에 따른 환자 분포는 IB 37명(16.4%), IIA 91명(41.3%), IIB 58명(25.7%), III 32명(13.8%), IV 8명(3.5%)이었다.

총 재발환자는 226명 중 54명으로 23.9%이었으며, 각 병기별 재발율은 IB 13.5%, IIA 15.4%, IIB 25.9%, III 46.9%, IV 62.5%로 병기가 진행됨에 따라서 재발율이 증가하는 것으로 나타났다. 또 재발부위별 양상은 54명의 재발환자 중 32명에서 골반내 단일재발이었으며, 11명은 골반재발과 원격전이가 동시에 나타났다. 그리고 나머지 11명에서 원격전이만 보였다. 43명의 국소재발의 반이상을 차지한다. 그리고 조사선량과 재발율과의 관계는 초기환자(IA, IIA)에서는 다소 유의하게 보였으나, 진행된 병기의 환자에서는 조사선량이 많았으나 치료실패율이 현저하게 높았다. 따라서 이들 환자들을 효과적으로 치료하기 위하여 단순히 치료선량을 증가시키는 것보다 다른 보조적치료, 즉 약물치료와의 병용치료 등이 절실히 요구되며, 또한 국소재발의 억제가 원격전이를 감소시킬 수 있는 한 방법일 수 있다.