Bowel Complication after Radiotherpy of Uterine Cervix Carcinoma

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Five hundred and fifty patients treated for carcinoma of the uterine cervix at the Department of Therapeutic Radiology, Seoul National University Hospital from 1979 to 1986, were analyzed retrospectively for late rectal complications. Of them, 468 patients received primary radiotherapy for the cervix cancer in intact uterus, and the other eighty two patients were treated postoperatively. The cumulative incidence of radiation induced rectal complication of grade 2 or 3 was 6.7% at five years. The mean rectal dose for the group of patients with complication was higher than the group without complication, and the difference was statistically significant ($p<0.01$). But relationship between mean rectal dose and severity of complication was not found. The frequency of complication (grade 1, 2, 3) increased as a function of radiation dose to rectum; from 16.1% for patients with rectal dose less than 6,000 cGy to 71.2% for patients with rectal dose higher than 8,000 cGy. Among various factors analyzed, history of diabetes mellitus, number of intracavitary irradiation, size of ovoid, retroflexion of uterus and the total dose delivered to rectum turned out to have significant effect on the complication.

Key Words: Radiotherapy, Cervix cancer, Rectum, Complication, Dose

INTRODUCTION

The results of radiation therapy for the treatment of carcinoma of the uterine cervix have been improved with the development of high energy megavoltage beams and intracavitary irradiation techniques. But one obstacle to the improvement is the occurrence of late complications in the irradiated organs such as bladder and rectum. So, the goal of treatment can be said as obtaining maximum tumor control with minimum complications.

Among factors affecting the complications, the radiation dose and the volume treated is known to be most important. Pourquier et al reported a correlation of dose with complication, and they showed dosimetric guidelines for prevention of late rectal and rectosigmoid complications[1]. Esche et al showed that the frequency and severity of proctitis increased with cumulative rectal doses and volumes treated[2]. Perez et al have reported on the correlation of dose with genitourinary and rectosigmoid complications, showing that maximum total dose upto 8,000 cGy was relatively safe with grade 2 and 3 complication incidence less than 5%[3].

Other factors, such as hypertension, diabetes, age, previous pelvic surgery, and pelvic inflammatory disease have been known as responsible for development of complications[4~8].

We analyzed the 550 patients with carcinoma of the uterine cervix retrospectively to evaluate the relationship between late rectal complications and some factors considered to influence the development of late complications.

MATERIALS AND METHODS

Between January 1979 and December 1986, 651 patients of histologically proven carcinoma of the uterine cervix were treated with radiation therapy at the Department of Therapeutic Radiology, Seoul National University Hospital. Among them, 101 patients were excluded from this study because they were treated incompletely or treated partially at other hospital. The remaining 550 patients were treated with a combination of external beam and intracavitary irradiation and constitute the basis for this study. Most of the patients were initially evaluated with physical and pelvic examination, complete blood count, chest X-ray, intravenous pyelogram, sigmoidoscopy and cystoscopy as a routine pretreatment staging workups. Computerized tomography of pelvis was done in some patients with advanced diseases.

The patient characteristics are shown in Table 1. The age ranged from 21 to 81 and two hundred

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thirty eight patients (43.3%) were staged as IIb. Most of the patients had squamous cell carcinoma (93.5%). Four hundred and sixty eight patients were irradiated with curative intent on intact uterus and remaining 82 patients were initially operated and irradiated for positive resection margin in 43 patients, for recurrent disease in 31 patients and for stump cancer in 8 patients.

Table 1. Patient Characteristics

Characteristics	No. of patients (%)
Age	
<30	10 (1.8)
30~39	54 (9.8)
40~49	153 (27.8)
50~59	219 (39.8)
60~69	88 (16.0)
>70	26 (4.8)
Stage	
Ib	63 (11.4)
IIa	111 (20.2)
IIb	238 (43.3)
IIIa	7 (1.3)
IIIb	118 (21.4)
IVa	13 (2.5)
Histology	
squamous cell ca.	514 (93.5)
adenocarcinoma	13 (2.4)
adenosquamous ca.	9 (1.6)
no information	14 (2.5)
Treatment	
primary RT	468 (85.1)
postop. RT	82 (14.9)

Details of our treatment protocol has been previously reported[9~14]. All the patients received external beam irradiation of 40~50 Gy to whole pelvis (plus para-aortic field if indicated) with megavoltage beams (Co-60, 6 or 10 MV photon) and one or two courses of intracavitary radiotherapy with Fletcher-Suit afterloading applicators. The daily dose were 175~180 cGy with five fractions per week and intracavitary irradiation was done about 2 weeks after completion of external beam irradiation and intracavitary irradiations were separated by a two week gap.

Intracavitary applicators were applied under spinal anesthesia and orthogonal X-ray films were taken. And then Cs-137 was loaded manually in a specially designed room for radiation protection. The doses at point A, point B, bladder and rectum were calculated. The maximum rectal dose was calculated at the closest point of rectum from the Cesium source by placing Foley catheter balooned with contrast material in the rectum. The dose rate of A point was 55~60 cGy per hour and the total dose was 80~85 Gy to point A in patients treated with curative intent, or 85~90 Gy to vaginal surface in patients treated postoperatively. After the completion of external and intracavitary irradiation, external beam boost irradiation was given to one or both parametrium with 4 cm wide rectangular midline block upto a total dose of 60~65 Gy to point B.

Minimum follow up period was 2 years and the status at last follow up was informed by clinical

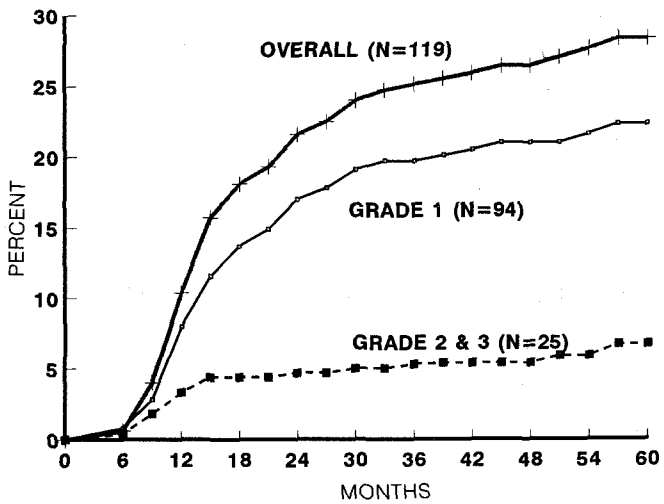

Fig. 1. Five year actuarial incidence of rectal complication by grade.

examination in 67.8%, by mail in 20.6% and by telephone in 11.6% of patients.

Rectal complications were assessed and classified according to their severity. In this grading system, the grade 1 complication represents rectal bleeding which developed after 3 months of initiation of radiotherapy and subsided spontaneously without medical management. Grade 2 is defined as rectal bleeding which required hospitalization for diagnosis and medical treatment such as transfusion. And grade 3 include the cases in which operation was necessary.

We reviewed the doses delivered by external beam and intracavitary irradiation at each point of interest, and we could calculate cumulative radiation dose in cGy, TDF, and CRE unit respectively[15-22].

Five year incidence of late rectal complication was calculated by the actuarial method and T-test was done for comparison of dose between complicated and non-complicated groups which was also applied in comparing the groups with different severity of complications[23]. We also tested some factors which are considered to affect the incidence of complication by Cox proportional hazard model[24].

RESULTS

One hundred nineteen patients developed rectal complications showing 21.6% of the overall frequency. Most of the patients expressed mild self limited grade 1 complications (17.1%), and twenty five patients (4.5%) developed grade 2 or 3 complications (Table 2).

The five year actuarial incidence of rectal complication is shown in figure 1, showing 22.3% incidence of grade 1, and 6.7% of grade 2 or 3 complication.

Five year actuarial incidences of rectal complication were 24.5% in stage I, 27.9% in stage IIa, 25.6% in stage IIb, 33.4% in stage IIIa, 40.3% in stage IIIb, and 23.8% in stage IVa.

Details on patients with grade 3 complications are described in table 3. Six patients showed rectovaginal fistulae and four of them had locoregional recurrence before or at the same time with fistula development. Three patients showed intestinal obstruction or adhesion and two of them were treated postoperatively. Two patients developed

Table 2. Actuarial 5 Year Incidence of Rectal Complication by Stage

Stage	Number of patients	Grade 1, 2 (%)	Grade 3 (%)	Total (%)
Ib	63	24.5	–	24.5
IIa	111	26.1	1.8	27.9
IIb	238	23.1	2.5	25.6
IIIa	7	33.4	–	33.4
IIIb	118	37.8	2.5	40.3
IVa	13	16.5	7.7	23.8
Total	550	107 (19.5)	12 (2.2)	119 (28.3%)

Table 3. Details on Patients with Grade 3 Complications

No.	Stage	Rectal dose	Cx.	Time interval	Treatment	Status		
1	IIa	7227	RVF	7M	Conservative	DOD	LR	9M
2	IIa	7281	RVF	14M	Conservative	DOD	LR	16M
3	IIb	5656	RVF	44M	Conservative	DOD		49M
4	IIb	8155	RVF	20M	Operation	DOD	PAN	63M
5	IIIb	6369	RVF	13M	Conservative	DOD		13M
6	IVa*	8840	RVF	9M	Conservative	DOD	LR	11M
7	IIb	6431	Int. Obs	11M	Conservative	DOD	L	11M
8	IIb	6730	Int. Obs	4M	Operation	ADF		24M
9	IIb	8384	Int. Adh	15M	Operation	ADF		44M
10	IIb	6711	Col. Obs	17M	Operation	DOD	L	23M
11	IIIb	9069	Col. Obs	9M	Conservative	AWD		11M
12	IIIb	8304	R. Perfo	51M	Operation	ADF		53M

*Patients with bladder invasion

〈Abbreviation〉

Cx=complication, RVF=rectovaginal fistula, Int. Obs=intestinal obstruction, Adh.=adhesion, Col.=colon, R. Perfo=rectal perforation, DOD=died of disease, ADF=alive disease free, AWD=alive with disease, LR=locoregional, PAN=paraaortic node, L=local

colon obstruction and one patients experienced rectal perforation.

Table 4 represents the relationship of radiation dose and complication. The mean rectal doses in cGy, TDF, and CRE for the group with complications were all higher than those of the group without complication, and the differences came mainly

Table 4. Significance of Dose to Rectal Complication

	Complication status		
	No	Yes	p-value*
Whole pelvis dose			
cGy	4626±658	4731±554	N.S.
TDF	70± 10	72± 8	N.S.
CRE	1442±175	1476±165	p=0.06
Rectal dose by ICR			
cGy	2312±881	2650±928	p<0.01
TDF	39± 18	48± 21	p<0.01
CRE1*	920±324	1072±378	p<0.01
CRE2*	1334±468	1554±543	p<0.01
Total rectal dose			
cGy	6946±717	7424±834	p<0.01
TDF	106± 16	117± 18	p<0.01
CRE1*	1609±216	1752±232	p<0.01
CRE2*	1905±298	2110±350	p<0.01

*T-test.
*CRE1, CRE2: Normalization constant K=0.53 and 0.77 respectively in brachytherapy

Table 5. Significance of Dose by Severity of Complication

	Grade 1 (Mean±S.D.)	Grade 2 or 3 (Mean±S.D.)	p-value*
Whole pelvis dose			
cGy	4710±586	4809±421	N.S.
TDF	72± 9	72± 6	N.S.
CRE	1480±176	1462±121	N.S.
Rectal dose by ICR			
cGy	2668±959	2585±821	N.S.
TDF	49± 22	45± 18	N.S.
CRE1*	1095±387	991±335	N.S.
CRE2*	1585±555	1440±487	N.S.
Total rectal dose			
cGy	7437±819	7378±900	N.S.
TDF	118± 18	114± 20	N.S.
CRE1*	1756±224	1739±261	N.S.
CRE2*	2119±340	2079±388	N.S.

*T-test.
*CRE1, CRE2: Normalization constant K=0.53 and 0.77 respectively in brachytherapy

Table 6. Factors Affecting Complication

Factors		Coeff./S.E.*			
		cGy	TDF	CRE1	CRE2
Age	increasing	N.S.	N.S.	N.S.	N.S.
Stage	advancing	N.S.	N.S.	N.S.	N.S.
Pelvic operation	yes	N.S.	N.S.	N.S.	N.S.
PID	yes	N.S.	N.S.	N.S.	N.S.
PAN treatment	yes	N.S.	N.S.	N.S.	N.S.
Acute symptom	yes	N.S.	N.S.	N.S.	N.S.
Diabetes mellitus	yes	2.26	2.26	2.22	2.21
Hypertension	yes	−1.44	−1.61	−1.57	−1.56
Chemotherapy after RT	yes	N.S.	N.S.	N.S.	N.S.
ICR	2 times	−2.15	−1.46	−0.23	−0.21
Interval between Ext. RT & ICR	increasing	N.S.	N.S.	N.S.	N.S.
Whole pelvis dose†	increasing	N.S.	N.S.	N.S.	N.S.
ICR dose to rectum†	increasing	N.S.	N.S.	N.S.	N.S.
Total rectal dose†	increasing	2.26	2.24	2.82	2.96
Tandem No.	1 vs 2 vs 3	N.S.	N.S.	N.S.	N.S.
Tandem position	central vs Ant. vs Post.	N.S.	N.S.	N.S.	N.S.
Uterus	AVF vs RVF	2.35	2.28	2.14	2.29
Ovoid distance	increasing	N.S.	N.S.	N.S.	N.S.
Ovoid size	mini vs standard vs ovoid cap	−3.33	−3.42	−3.45	−3.45

*Statistically significant at 5% risk, if Coeff./S.E.≧1.96
†Radiation dose expressed in cGy, TDF, CRE1, CRE2.

from the dose distributed by ICR. The severity of complications did not correlate with rectal dose (Table 5). The incidence of complication increased with total rectal dose and this was common whether the rectal dose was expressed in cGy, TDF, or CRE (Fig. 2). As can be seen in these figures, the frequency of complication rose from below 20% for patients receiving less than 7,000 cGy to above 50% for patients who received more than 8,000 cGy. And the incidence was higher when ICR was performed only once.

Multivariate analysis was performed with several factors that may be related with complication and the results are summarized in table 6. Of the patient factors, presence of diabetes mellitus was the only factor related with complication. The patients who were treated with external and one intracavitary irradiation showed higher complication rate than those treated with two times of ICR, and the differences was statistically significant in analysis with cGy unit (Table 6). Increasing total rectal dose, retroflexion of uterus and smaller size of ovoid were closely correlated with rectal complication ($p < 0.05$). The frequency of complication was not related with factors such as age, stage, pelvic operation, pelvic inflammatory disease, paraaortic node irradiation, hypertension or acute symptoms of rectum.

DISCUSSION

Many authors reported the overall frequency of complication between 3 and 15% after treatment of cervix cancer, the rectal or rectosigmoid areas being the most frequent site[1,3,6,25,26,27]. The incidence of 6.7% (Grade 2 and 3) is comparable to that of others. Half of 12 grade 3 complications were rectovaginal fistulae.

Most of the complications appeared within 30 months and then the steepness of the increase was decreased irrespective of its severity. This is the same as the report of Perez et al, where eighty percent of the rectosigmoid complications were observed within 30 months from initial therapy[3].

Horiot et al found that grade 3 complication rates are higher in stage IIb and III than in stage I and IIa, but we could not find any correlation of complication with stage[26]. The overall crude inci-

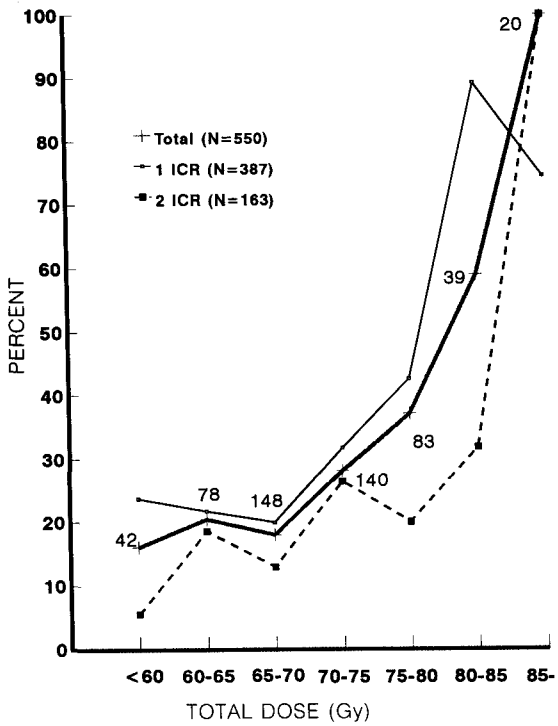

Fig. 2-a. Five year actuarial incidence of rectal complication by total dose (Gy).

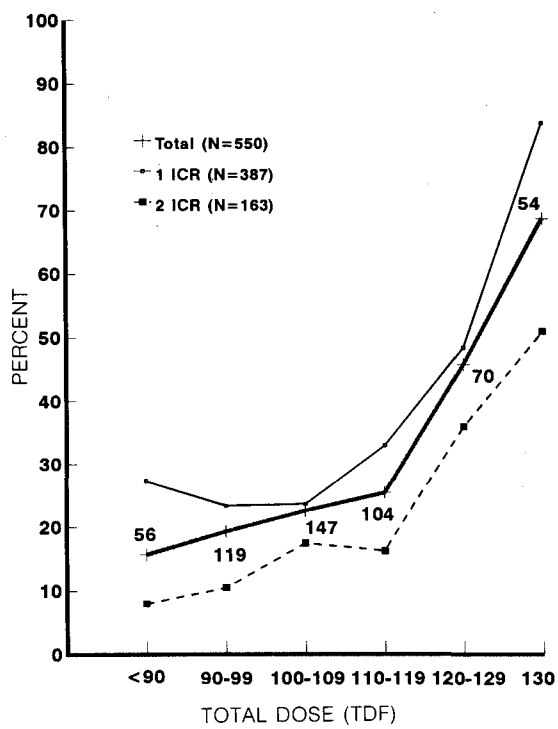

Fig. 2-b. Five year actuarial incidence of rectal complication by total dose (TDF)

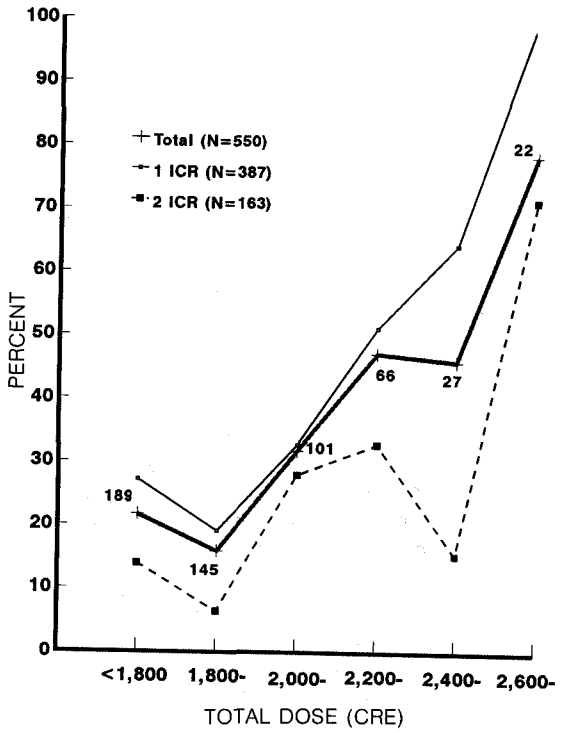

Fig. 2-c. Five year actuarial incidence of rectal complication by total dose (CRE, K=0.77).

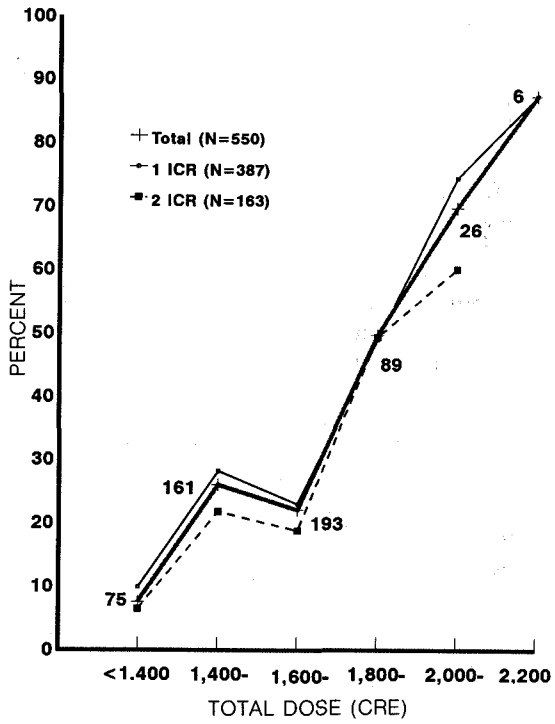

Fig. 2-d. Five year actuarial incidence of rectal complication by total dose (CRE, K=0.53).

dence ranges from 20 to 30 percent and the 5 year actuarial frequency 23.8% to 40.3%. Though the complication rate was a little higher in stage IIIb, this was not statistically significant.

Among various factors affecting the complications, the radiation dose and the volume treated is most important. Pourquier et al reported that there is a correlation of dose with complications, and they showed dosimetric guidelines for prevention of late rectal and rectosigmoid complications[1]. By using the concepts of maximum rectal dose and mean cumulative dose, they could elicit a conclusion that the maximum and cumulative mean rectal dose should be strictly calculated on the anterior surface of the rectum by the addition of external and intracavitary irradiation dose. Esche et al also noted that the frequency and severity of proctitis increased with cumulative rectal doses and volumes treated[2]. In their study, the majority of rectosigmoid complications occurred with cumulative doses in excess of 7,000 cGy. Perez et al have reported similar results demonstrating the correlation of doses with genitourinary and rectosigmoid complications, showing that maximum total dose upto 8,000 cGy was relatively safe with grade 2 and 3 complication incidence less than 5%[3]. The relationship of radiation dose and complication was also observed in our study. The mean rectal doses in cGy, TDF, and CRE for the group with complications were higher than those of without complications. And there exists a positive correlation of radiation dose and 5 year actuarial incidence of complication. And of these various methods used in comparing total dose to rectum, CRE using 0.53 as the normalization constant looks best matches in this analysis.

Hamberger et al reported significant increase in complication of bladder and rectum with increasing whole pelvis dose[6]. They observed 3.1% incidence of severe complication with 4,000 rad whole pelvis dose, 10% incidence with 5,000 cGy and 20% incidence with 6,000 cGy whole pelvis dose. Pourquier et al also emphasized the whole pelvis dose, demonstrating that the highest risk of complication occurred above 45 Gy external dose to whole pelvis[1]. But Kottmeier et al and Perez et al indicated that total dose contributed by both external and intracavitary irradiation to a given organ have a

greater predictive value in correlation with frequency of major complication than the dose by either modality alone[3,27]. In our study, dose delivered to whole pelvis did not correlate with the incidence of late rectal complication, but total rectal dose did. Estimating the total rectal dose, TDF and CRE was used in addition to cGy and all these estimates showed similar correlation. But the rectal dose and the severity of complication was not well correlated, possibly because of small number of cases with complication.

Kagan et al, and Cunningham et al have correlated the high dose areas in the rectum, bladder or vagina with the development of clinically significant injuries, and they suggested that complications can be prevented by modifying the loading of the applicators according to the dose distribution previewed by computer assisted calculation system[28,29]. These methods were applied to our patients, resulting in a comparable outcome to other reports. In addition, the importance of vaginal gauze packing and vaginal flexiblity should be emphasized because the optimal source geometry could be obtained through the careful gauze packing in competent vagina.

Combs et al analyzed the influence of major pathologic condition such as marked overweight, hypertension and previous abdominopelvic surgery and reported that these classic factors of poor tolerance to radiotherapy were not correlated with control rates but clearly influenced the incidence of complication[30]. But we could not find such a result, and the diabetes mellitus was the only factor that influenced the complication rate significantly (relative risk=2.5). Patients with hypertension also showed higher complication rate, but it was not statistically significant.

Kottmeier and Gray in an analysis of 500 patients with invasive carcinoma of the uterine cervix treated with radiotherapy noted that there was no correlation between rectal injuries and retroflexion of uterus or previous history of pelvic surgery[27]. They explained this by the fact that the radium dosage was routinely decreased in high risk patients. We had also modulated the cesium dosage but the poor geometry could not be corrected fully as in retroflexed uterus. In our multivariate analysis, the retroflexion of the uterus was a statistically significant factor that can influence the risk of complication.

In this analysis, the ovoid size appeared as the most significant factor. That can be explained as: when the vagina was too narrow to insert a standard ovoid, we could not help inserting a miniovoid, which was also accompanied by difficulty in packing the gauze sufficiently. Thus a longer length of rectum was included in the high dose area.

Perez et al noted that in patients receiving a total dose of 6,000 cGy to the bladder or rectum, higher complication rate was noted when only one intracavitary insertion was performed, compared with two or three insertions[25]. That was consistent with our results, showing complication rate about two times higher in patients treated with one intracavitary irradiation.

In summary, large area of anterior rectal wall is in relative close proximity to the intracavitary applicators, which results in a great portion of anterior rectal wall being encompassed in a high dose volume. Although we cannot alter the anatomical relationship, we can calculate the dose distribution around the rectum. If one can obtain the dose distribution in three dimension, it would be more likely that one can predict and prevent the complication more accurately.

CONCLUSION

A multivariate analysis was performed on 550 patients of carcinoma of the uterine cervix treated at the Department of Therapeutic Radiology, Seoul National University Hospital from 1979 through 1986 to evaluate the factors affecting late complication of rectum.

Cumulative incidence of radiation complication of grade 2 or 3 were 6.7% in rectum at five years of follow up. The mean rectal dose for the group of patients with complication was higher than that of the group without complication. The difference of mean dose according to the severity of complication was not statistically significant. The incidence of complication was affected by the factors such as the history of diabetes mellitus, the number of intracavitary irradiation, flexion of uterus, ovoid size and total dose to rectum. And in estimation of total dose, the CRE using 0.53 as a normalization constant looks better in our analysis.

APPENDIX

* TDF calculation procedure by Orton

TDF (fractionated) $= nd^{1.538} x^{-0.169} 10^{-3}$

TDF (continuous) $= 4.76\ r^{1.35} T\ 10^{-3}$

Decay factor $= (T/T+R)^{0.11}$

n : number of fraction given
d : dose per fraction (cGy)
x : average interval between fraction (days)
r : dose rate (cGy per hour)
T : overall treatment time (days)
R : rest period (days)

* CRE calculation procedure by Kirt

CRE (fractionated) $= D\ N^{-0.24}\ T^{-0.11}$

CRE (continuous) $= K\ D\ T^{-0.29}$

Decay factor $= e^{-0.008R}$

D : total dose
N : number of fraction
T : overall treatment time
K : normalization constant
K=0.53, suggested by Orton
K=0.77, suggested by Kirk
R : rest period

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= 국문초록 =

자궁경부암의 방사선치료후 대장 및 직장합병증에 대한 분석

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1979년부터 1986년까지 자궁경부암으로 진단되어 외부방사선 및 강내 방사선 치료를 함께 받은 550명의 환자를 대상으로 직장 합병증과 방사선량에 대한 후향적 분석을 시행하였다. 전체 환자 550명 중 468명은 근치적 목적으로 방사선 치료를 받았으며, 82명은 수술후에 추가적인 방사선 치료를 받았다. 이들 82명 중 43명은 수술절제연 양성으로, 31명은 원발질환의 재발로, 8명은 stump cancer로 방사선 치료를 받았다.

Grade 2와 3를 포함하는 직장 합병증의 발생률은 5년에 6.7%였다. 합병증이 생긴 환자군의 직장에 조사된 방사선량은 7424±834 cGy이었으며, 이는 합병증이 발생하지 않은 환자군의 6946±717 cGy 보다 많았고 통계학적 유의성이 있었다($p<0.05$). 직장합병증의 정도에 따른 방사선량의 차이는 통계학적 유의성이 없었다($p>0.05$). 전체 합병증의 발생률은 직장에 조사된 방사선량에 따라 증가하였는데, 6,500 cGy 이하에서는 5년 합병증 발생률이 15.6%이었으며 8,000 cGy 이상 조사된 환자군에서는 71.2%이었다. 직장 합병증에 영향을 줄 수 있는 요인들을 Cox의 방법에 의해 다변량 분석한 결과 당뇨가 있는 경우 합병증 발생률이 증가하였으며, 강내 방사선치료는 한번 시행한 경우보다 두번 시행한 환자군에서 합병증 발생률이 더 적었다. 또한 자궁의 후방만곡은 ovoid의 크기와 함께 분석된 경우에 통계적으로 중요한 의미를 나타내었고, ovoid의 크기는 이번 분석에서 합병증 발생에 가장 중요한 인자로 나타났다. 직장에 조사된 방사선량도 중요한 요소로서 방사선량이 많아질수록 합병증 발생률은 증가하였다($p<0.05$). TDF와 CRE 단위로 분석하였으며 선량과 합병증의 관계는 cGy 단위의 결과와 같았다.