

# The Relationship between Radiation Dose and Late Complication of Bladder in Carcinoma of the Uterine Cervix

Sung Whan Ha, M.D., Woong Ki Chung, M.D. and Jong Hoon Kim, M.D.

*Department of Therapeutic Radiology, College of Medicine, Seoul National University, Seoul, Korea*

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 bladder complications. Of them, 468 patients received primary radiotherapy for the cervix cancer in intact uterus, and the other 82 patients were treated postoperatively. The cumulative incidence of radiation induced bladder complication of grade 2 or 3 was 2.5% at five years. The mean bladder dose for the group of patients with complication was higher than that of the group without complication, and the difference was statistically significant ( $p < 0.01$ ). But relationship between mean bladder dose and severity of complication was not found. The frequency of complication (grade I, II, III) increased as a function of radiation dose to bladder from 5.0% for patients with bladder dose less than 6,500 cGy to 27.7% for patients with bladder dose higher than 8,000 cGy. Among various factors, the age of patient and the distance between ovoids turned out to have significant effect on the complication.

**Key Words:** Radiotherapy, Cervix cancer, Bladder, Complication, Dose

## INTRODUCTION

Radiation therapy is a well known effective modality in the treatment of carcinoma of the uterine cervix. But the occurrence of late complication in the irradiated organs such as bladder and rectum has been the obstacle to the successful treatment. Among factors affecting the complications, the radiation dose and the volume are the most important. 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%<sup>1)</sup>. Lee et al have demonstrated that hot spots on the bladder and rectum can be the site of clinically significant injuries to these organs<sup>2)</sup>. Montana et al also showed the correlation of severity of cystitis and bladder dose<sup>3)</sup>.

Other factors, such as hypertension, diabetes, age, previous pelvic surgery, and pelvic inflammatory disease have been known as responsible for development of complications<sup>4~8)</sup>.

We analyzed the 550 patients with carcinoma of the uterine cervix retrospectively to evaluate the relationship between late bladder complications

and some factors considered to influence the development of late complications.

## MATERIALS AND METHODS

Between January 1979 and December 1986, 651 patients with 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 work-ups. 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 238 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 recur-

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rent disease in 31 patients and for stump cancer in 8 patients.

Details of our treatment protocol has been previously reported<sup>9-14</sup>. All the patients received external beam irradiation to whole pelvis (plus para-aortic field if indicated) and one or two courses of intracavitary radiotherapy with Fletcher-Suit afterloading applicators. The maximum bladder dose was calculated at the closest point of bladder

Table 1. Patient Characteristics

Characteristics	No. of patients (%)
<b>Age</b>	
< 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)
<b>Stage</b>	
Ib	63 (11.4)
IIa	111 (20.2)
IIb	238 (43.3)
IIIa	7 ( 1.3)
IIIb	118 (21.4)
IVa	13 ( 2.5)
<b>Histology</b>	
squamous cell ca.	514 (93.5)
adenocarcinoma	13 ( 2.4)
adenosquamous ca.	9 ( 1.6)
no information	14 ( 2.5)
<b>Treatment</b>	
primary RT	468 (85.1)
postop. RT	82 (14.9)

from the cesium source on orthogonal X-ray films by placing Foley catheter balooned with contrast material in the bladder.

Minimum follow up period was 2 years and the status at last follow up was informed by clinical examination in 67.8%, by mail in 20.6% and by telephone in 11.6% of patients.

Bladder complications were assessed and classified according to their severity. In this grading system, the grade 1 complication represents hematuria which developed after 3 months of initiation of radiotherapy and subsided spontaneously without medical management. Grade 2 is defined as hematuria 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 calculated cumulative radiation dose in cGy, TDF, and CRE unit<sup>15-22</sup>.

Five year incidence of late bladder 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<sup>23</sup>. We also tested some factors which are considered to affect the incidence of complication using Cox proportional hazard model<sup>24</sup>.

## RESULTS

Seventy patients developed bladder complica-

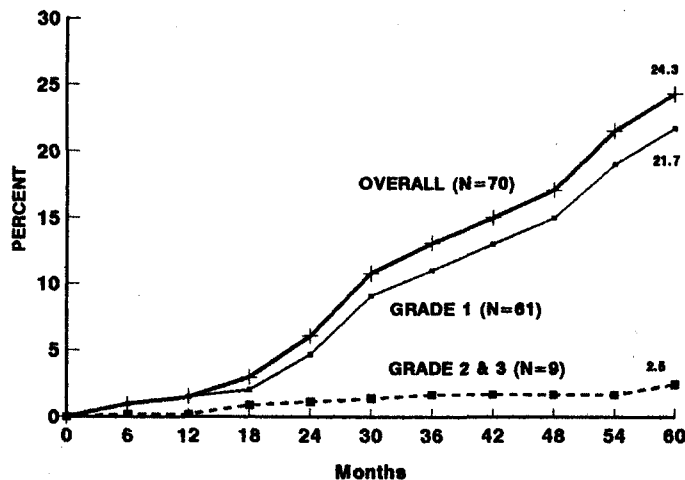


Fig. 1. Five year actuarial incidence of bladder complication by grade.

tions showing 12.7% of overall frequency. Most of the patients (61) expressed mild self limited grade 1 complications (11.1%), and only 9 patients (1.6%) developed grade 2 or 3 complications. The five year actuarial incidence of bladder complication is shown in Figure 1, showing 21.7% incidence of grade 1, and 2.5% of grade 2 or 3 complication.

Five year actuarial incidences of bladder complication were 23.3% in stage I, 17.5% in stage IIa, 26.9% in stage IIb, 38.6% in stage IIIa, 30.4% in stage IIIb, and 23.9% in stage IVa (Table 2).

Details on patients with grade 3 complications are described in table 3. Three patients showed vesicovaginal fistulae and two of them had locoregional recurrence.

Table 4 represents the relationship of radiation dose and complication. The mean bladder 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 from the dose distributed by ICR. The severity of complications did not correlate with bladder dose (Table 5). The incidence of complication increased slightly with total bladder dose and this tendency was common whether the bladder dose was expressed in cGy, TDF, or CRE (Fig. 2). As can be seen in these figures, the frequency of complication did not correlate with bladder dose significantly. And the number of ICR did not show any influence on the development of complications.

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, the age of patient was the only factor related with complication. The frequency of complication was not affected by factors such as stage, urinary tract infection, hydronephrosis, bladder invasion, pelvic operation, paraaortic node irradiation, acute symptoms of bladder, and hypertension.

**Table 2. Actuarial 5 Year Incidence of Bladder Complication by Stage**

Stage	Number of patients	Number with complication	%
Ib	63	8	23.3%
IIa	111	9	17.5%
IIb	238	36	26.9%
IIIa	7	2	38.6%
IIIb	118	14	30.4%
IVa	13	2	23.9%
Total	550	71	24.3%

**Table 3. Details on Patients with Grade 3 Complication**

No.	Stage	Bladder dose	Cx.	Time interval	Status
1	IIIb	7640	UVF	15M	LR 15M
2	IVa	7544	VVF	4M	LR 6M
3	IIb	7522	VVF	74M	NED 79M
4	IIIb	7726	VVF	21M	LR+DM 25M

Cx=complication, UVF=urethrovaginal fistula, VVF=vesicovaginal fistula, LR=locoregional, DM=distant metastasis

**Table 4. The Relationship between Radiation Dose and Presence or Absence of Bladder Complication.**

	Complication status		p-value*
	No	Yes	
Whole Pelvis Dose			
cGy	4644±643	4685±610	N.S.
TDF	70±10	71±9	N.S.
CRE	1446±171	1469±186	N.S.
Bladder Dose from ICR			
cGy	2500±874	2811±948	p<0.01
TDF	40±20	51±21	p<0.01
CRE1*	1007±354	1112±430	p<0.05
CRE2*	1480±618	1631±612	p=0.06
Total Bladder Dose			
cGy	7150±808	7487±768	p<0.01
TDF	112±17	120±23	p<0.01
CRE1*	1679±229	1751±291	p<0.05
CRE2*	2011±331	2136±373	p<0.05

\* T-test

\* CRE1, CRE2: Normalization constant K=0.53 and 0.77 respectively in brachytherapy

Table 5. The Relationship between Radiation Dose and Severity of Bladder Complication.

	Grade 1 (Mean±S.D.)	Grade 2 or 3	p-value <sup>#</sup>
Whole Pelvis Dose			
cGy	4669 ± 632	4791 ± 440	N.S.
TDF	71 ± 10	73 ± 7	N.S.
CRE	1468 ± 194	1479 ± 126	N.S.
Bladder Dose from ICR			
cGy	2797 ± 1001	2911 ± 473	N.S.
TDF	50 ± 22	52 ± 11	N.S.
CRE1*	1105 ± 457	1160 ± 161	N.S.
CRE2*	1623 ± 650	1686 ± 234	N.S.
Total Bladder Dose			
cGy	7456 ± 803	7701 ± 437	N.S.
TDF	120 ± 24	121 ± 13	N.S.
CRE1*	1753 ± 290	1738 ± 315	N.S.
CRE2*	2137 ± 376	2131 ± 377	N.S.

\* T-test

\* CRE1, CRE2: Normalization constant K=0.53 and 0.77 respectively in brachytherapy

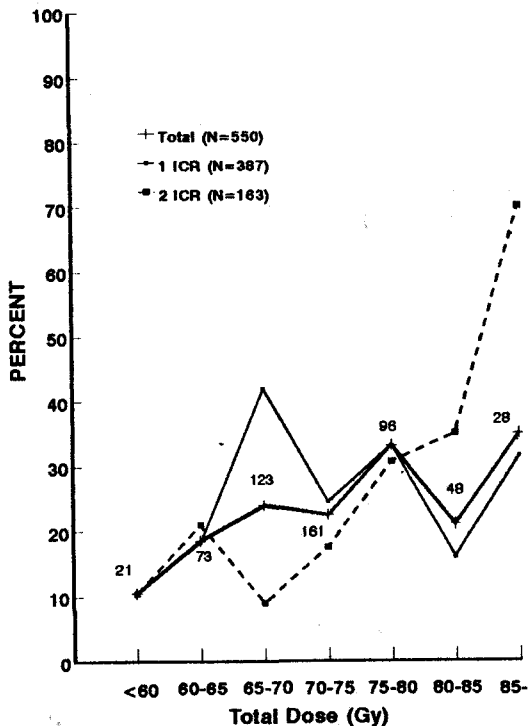


Fig. 2-a. Five year actuarial incidence of bladder complication by total dose (Gy).

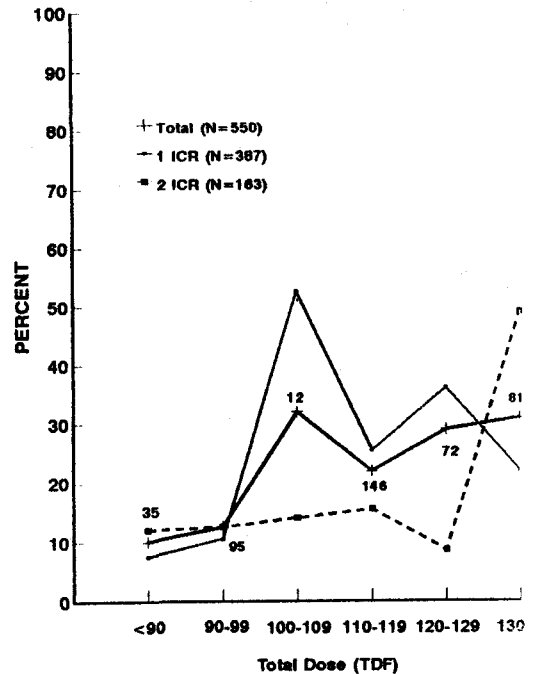


Fig. 2-b. Five year actuarial incidence of bladder complication by total dose (TDF).

The flexion of uterus and diabetes mellitus showed some correlation with the incidence of complications, but they did not show statistical significance which was present in our previous study on rectal

complication<sup>25</sup>). And decreasing distance between ovoids was the other factor that was closely correlated with bladder complications. The whole pelvis dose was a factor that showed marginal significance on analysis with CRE units.

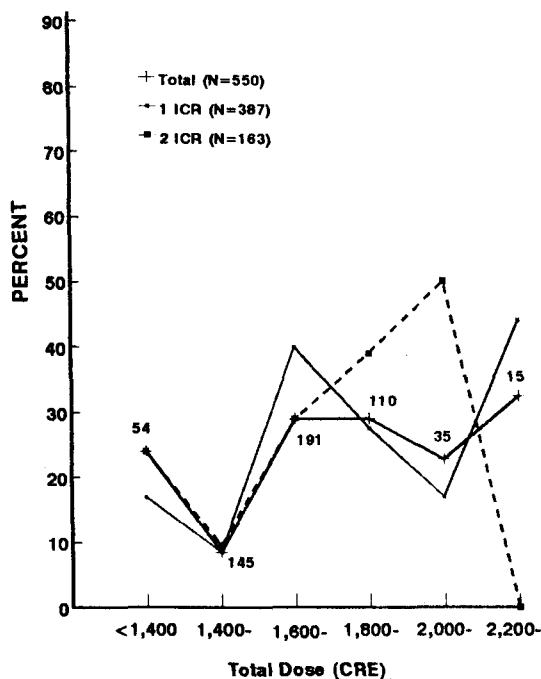


Fig. 2-c. Five year actuarial incidence of bladder complication by total dose (CRE, K=0.53).

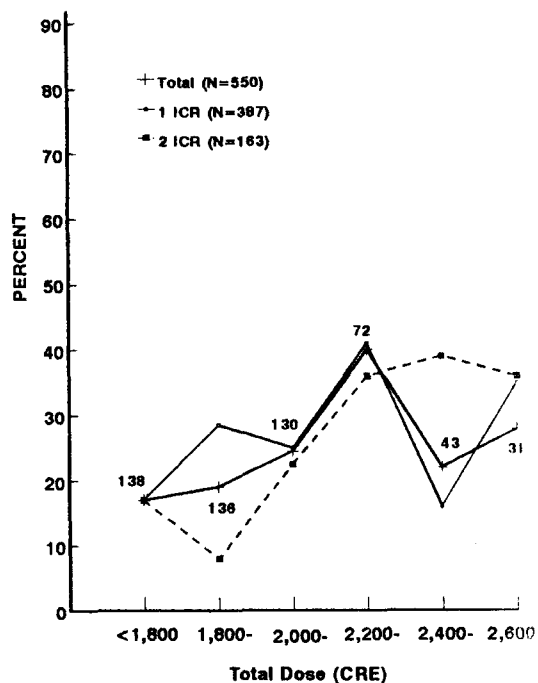


Fig. 2-d. Five year actuarial incidence of bladder complication by total dose (CRE, K=0.77).

Table 6. Factors Affecting Complication

Factors		Coeff./S.E.*			
		cGy	TDF	CRE1	CRE2
Age	increasing	-2.80	-2.70	-2.88	-2.89
Stage	advancing	N.S.	N.S.	N.S.	N.S.
Urinary tract infection	yes	N.S.	N.S.	N.S.	N.S.
Hydronephrosis	yes	N.S.	N.S.	N.S.	N.S.
Bladder invasion	yes	N.S.	N.S.	N.S.	N.S.
Pelvic operation	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	1.53	1.09	1.42	1.44
Hypertension	yes	N.S.	N.S.	N.S.	N.S.
Chemotherapy after RT	yes	N.S.	N.S.	N.S.	N.S.
ICR	2 times	N.S.	N.S.	N.S.	N.S.
Interval between Ext. RT & ICR	increasing	N.S.	N.S.	N.S.	N.S.
Whole pelvis dose <sup>§</sup>	increasing	N.S.	N.S.	1.80	1.92
ICR dose to bladder <sup>§</sup>	increasing	N.S.	N.S.	N.S.	N.S.
Total bladder dose <sup>§</sup>	increasing	N.S.	N.S.	N.S.	N.S.
Tandem No.*	1 vs 2 vs 3	N.S.	N.S.	N.S.	N.S.
Tandem position*	central vs Ant. vs Post.	0.65	0.59	0.66	0.65
Uterus*	AVF vs RVF	N.S.	N.S.	N.S.	N.S.
Ovoid distance	increasing	-2.11	-2.29	-2.40	-2.27
Ovoid size	mini vs standard vs ovoid cap	N.S.	N.S.	N.S.	N.S.

\* Statistically significant at 5% risk, if |Coeff./S.E.| ≥ 1.96

<sup>§</sup> Radiation dose expressed in cGy, TDF, CRE1, CRE2

\* Analyzed in 455 patients with intact uterus

## DISCUSSION

This study revealed the grade 2 and 3 bladder complication rate of 2.5% which is lower than that of previous report on rectal complication rate (6.7%)<sup>25</sup>. Although the reason for such difference in complication rates between bladder and rectum is not certain, Montana et al explained these finding by the difference in the anatomical relationship of bladder and of the anterior rectal wall to the uterus, and the bacterial contamination of the rectal wall<sup>3</sup>. Orton explained in different ways. He thought that a significant proportion of patients who might be expected to develop bladder complications would not survive long enough for the symptoms to be observed and this might result in an underestimate of the rate of induction of bladder injuries<sup>9</sup>. But our study estimated the incidence in a life table method and so this explanation cannot be applied.

Most of the complications appeared after 18 months, and the gradual increase of complication continued until 5 years. This is the same as the report of many authors<sup>1,3,8,26</sup>.

Some authors reported that grade 3 complication rates are higher in stage IIb and III than in stage I and IIa<sup>27</sup>. But in this study, the overall crude incidence ranges from 10 to 20% and the five year actuarial frequency 17.5% to 38.6%. Although the complication rate was a little higher in stage III, this was not statistically significant, and we could not find any correlation of complication with stage.

The radiation dose and the volume treated are important factors that can affect the complication. Pourquier et al reviewed the dosimetry of external and intracavitary irradiation in their study and concluded that complications increased sharply with cumulative doses above 7,000~7,500 cGy<sup>31</sup>. The relationship of radiation dose and complication was also observed in our study. The mean bladder doses in cGy for the group with complications were higher than those of without complication (Table 4). Estimating the total bladder dose, TDF and CRE was used in addition to cGy and all of these estimates showed similar correlation. But the bladder dose and the severity of complication was not well correlated, possibly because of small number of cases with complication. And there exists a tendency of positive correlation of radiation dose and 5 year actuarial incidence of complication.

Powell-Smith observed a higher incidence of complication in patients with large pelvic field<sup>28</sup>. Kottmeier and Gray reported that the grade 2 and

3 bladder injuries were about 6% to 7% in patients receiving less than 8,000 cGy, 9.5% in those receiving upto 9,000 cGy and 29% in patients treated with higher doses<sup>29</sup>. And many other authors reported significant increase in complications in the bladder or rectum with higher doses of intracavitary radium and increasing whole pelvis external irradiation doses<sup>6,30</sup>. In our previous report of rectal complications, dose delivered to whole pelvis did not correlate with the incidence of late rectal complication, but total rectal dose did<sup>25</sup>. And many authors reported 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<sup>1,29</sup>. But in the present study, we found no statistical significance of total bladder dose.

Pourquier et al reported that the critical dose and threshold region varied as a proportion of the external and intracavitary contributions to the total dose and they emphasized the whole pelvis dose, demonstrating that the highest risk of complication occurred above 45Gy external dose to whole pelvis<sup>31</sup>. Hamberger et al also reported significant increase in complication of bladder and rectum with increasing whole pelvis dose<sup>6</sup>. They observed 3.1% incidence of severe complication with 4,000 cGy whole pelvis dose, 10% incidence with 5,000 cGy and 20% incidence with 6,000 cGy whole pelvis dose. We could also observe that the whole pelvis dose approached the statistical significance, especially in CRE units.

Cunningham et al and Kagan 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<sup>32,33</sup>. These methods were applied to our patients, resulting in a comparable outcome to other reports. And it must be emphasized that the vaginal gauze packing and vaginal flexibility are important because optimal source geometry could be obtained through the careful gauze packing in competent vagina.

It is generally said that the classic factors of poor tolerance to radiotherapy such as marked overweight, hypertension and previous abdominopelvic surgery are not correlated with control rates but clearly influence the incidence of complication<sup>34</sup>. But this study did not show such

results, and the age of patients was the only factor that influenced the complication rate significantly. Some authors have reported a higher probability of developing complications in elderly patients, and Perez et al found no difference in complication rate because they reduced the intracavitary and external radiation doses by 5%~10% in patients older than 65 years<sup>11</sup>. But we could not observe such finding and on the contrary, elderly patients developed less complication. At present, the reason for such finding is not certain.

In this analysis, the incidence of complication decreased as the distance between two ovoids increased, and the ovoid distance appeared as a statistically significant factors. But we could not find any statistical significance in ovoid size which was significant in previous study about rectal complication.

Fletcher reported that fractionating the intracavitary insertion over several weeks improves the tolerance of the normal tissues and allows for regression of central tumor<sup>35</sup>, and Perez et al also noted that in patients receiving a total dose of 6,000 cGy to bladder or rectum, higher complication rates was noted when only one intracavitary insertion was performed, compared with two or three insertions<sup>11</sup>. That was consistent with our rectal complication study results, but we could not find such finding in this study. And there was no correlation between bladder injuries and retroflexion of the uterus.

It is difficult to explain these negative results which were proven to be statistically significant in the analysis of rectal complications. But we can derive a conclusion that the optimal source geometry is determined by careful vaginal gauz packing as well as by anatomical relationship of cervix and adjacent organs and the flexibility of vagina.

### 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 bladder.

Cumulative incidence of radiation complication of grade 2 or 3 were 2.5% in bladder at five years. The mean bladder 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

significant statistically. The incidence of complication was affected by the factors such as the age of patient and the distance between ovoids. Although statistical significance was not found, whole pelvis dose was an important factor that can influence the rate of complication.

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국문초록 =

## 자궁경부암에서 방사선량과 방광합병증의 관계

서울대학교 의과대학 치료방사선과학교실

하성환 · 정웅기 · 김종훈

1979년부터 1986년까지 자궁경부암으로 진단되어 외부방사선 및 강내 방사선 치료를 받은 550명의 환자를 대상으로 방광합병증과 방사선량에 대한 후향적 분석을 시행하였다. 전체 환자 550명중 468명은 근치적 목적으로 방사선 치료를 받았으며, 82명은 수술후에 추가적인 방사선 치료를 받았다. 이들 82명중 43명은 수술절제연 양성으로, 31명은 원발질환의 재발로, 8명은 stump cancer로 방사선 치료를 받았다. Grade 2와 3를 포함하는 방광합병증의 발생률은 5년에 2.5%였다. 합병증이 생긴 환자군의 방광에 조사된 방사선량은  $7487 \pm 768$  cGy이었으며, 이는 합병증이 발생하지 않은 환자군의  $7150 \pm 808$  cGy보다 많았고 통계학적 유의성이 있었다( $p < 0.01$ ). 방광합병증의 정도에 따른 방사선량의 차이는 통계학적 유의성이 없었다( $p > 0.05$ ). 전체 합병증의 발생률은 방광에 조사된 방사선량에 따라 증가하였는데, 6,500 cGy 이하에서는 5년 합병증 발생률이 5.0%이었으며 8,000 cGy 이상 조사된 환자군에서는 27.7%이었다. 방광합병증에 영향을 줄수 있는 요인들을 Cox의 방법에 의해 다변량 분석한 결과 환자의 연령이 증가할수록, ovoid 사이의 거리가 멀수록 합병증 발생률이 적었다( $p < 0.05$ ). 골반 전체에 조사된 방사선량도 통계적 유의성에 근접하는 중요한 요소로서 방사선량이 많아질수록 합병증 발생률은 증가하였다. TDF와 CRE 단위로 분석하였으며 선량과 합병증의 관계는 cGy 단위의 결과와 같았다.