

Analysis of Radiotherapy Associated Factors in Stage IIb Carcinoma of Uterine Cervix

Chang Woo Moon, M.D., Tae Sig Jeung, M.D. and Ha Yong Yum, M.D.*

Department of Therapeutic Radiology, Kosin Medical College and Medical Center, Pusan, Korea

331 patients of stage IIb uterine cervix cancer treated by radiation alone at Kosin Medical Center between June 1980 and Dec. 1985 were analysed to determine parameters of radiotherapy associated to disease states. Survival rate was highest among the reported (82.8% for crude and 82.4% for disease free survival). Pelvic control rate in 6 weeks after the end of radiotherapy was 93.6% in the patients treated with ICR following total pelvic radiation and 71.6% with small field additional external irradiation. 5 year survival rate in those who achieved pelvic control was 98.9% and 12.9% in those who had pelvic failure and/or metastasis after radiation. The survival rate figured maximal 88.5% with dosage of 7500~8500 cGy to point A with acceptable incidence of complications (4.9%) but without increasing survival above it and minimal 74.1% with dosage of less than 6500 cGy. The treatment failure was counted 18.7% (62 of 331 patients): Local failure 72.6% (45 of 62 patients), locoregional failure 3.2% (2 of 62 patients) and distant failure 24% (15 of 62 patients). Late complications were found in 50 patients (15.1%) and 42% of them was rectal bleeding and stenosis. The dose of 8500 cGy to point A was found to be critical for complication and 70% of complications occurred above it and was more serious one such as fistula.

Rectal complications were developed above rectal dose 6500 cGy and bladder complication above bladder dose 7500 cGy. Major cause of death was cachexia due to locoregional failure (73.7% of death), next was due to metastasis to lung, liver and bone, and only 3 patients died of complication of intestinal perforations and obstruction. In conclusion higher external radiation dose for a bulky uterine cervix and barrel shaped uterus was essential for local control.

Key Words: Radiotherapy cancer of uterine cervix, analysis of radiotherapy factors

INTRODUCTION

Carcinoma of uterine cervix has been the most frequent cancer in female malignancies in this country and it is known to be curable disease by progressive increase of cure rate achieved by early detection with successful screening of pap-smear and multidisciplinary approach of therapy and improvement of therapeutic technique^{2,5,24}.

Radiotherapy has established to have full therapeutic role in all staged cancers of uterine cervix though surgery is preferred in youngwomen who have early staged cancer (stage I and IIa) for preservation of vaginal and ovarian function^{5,23}. There has been general acceptance to irradiate staged IIb or more cancer of uterine cervix that is most frequent in this country^{2,18,21}.

The purpose of this report is to determine parameters of radiotherapy associated to disease

states, survival, patterns of failure and complications in retrospective review of our technique of radiotherapy.

MATERIAL AND METHOD

1. Clinical Features

331 patients of stage IIb cancer of uterine cervix who were treated between 1980 and 1985 in the departement of radiation therapy at Kosin Medical college and medical center in Pusan, Korea and were successfully followed with periodic examination for 5 to 10 years, were included for this study. The age distribution was as in Table 1 with 39.5% of patients ranged between 50 and 60 years, all patient had routine work ups including CBC, liver function profiles, urinalysis, electrolytes, chest X-ray, pelvic examination. X-ray CT and punch biopsy. IVP, barium enema, cystoscopic examination, pelvic sonography and radionuclide scanning including liver, renal and gallium scan were performed but not as routine procedures. Staging was determined by FIGO staging system. Pathologic classification was as seen on Table 2. 98% (325 out

*reprints request to: Ha Yong Yum, Kosin medical college and medical center #34, Am Nam Dong, Suh-Ku, Pusan, Korea

Table 1. Age Distribution

Age	No. of patients
– 40	42 (12.7)
– 50	119 (36)
– 60	131 (39.5)
61 –	39 (11.8)
Total	331

* () : %

Table 2. Histology (Cell Type) Distribution

Cell type	No. of patients
Well diff. sq. cell ca. *	241 (72.8)
Poorly diff. sq. cell ca. #	84 (25.4)
Adenocarcinoma	5 (1.5)
Adenosquamous cell ca.	1 (0.3)
Total	331

* Keratinizing

Nonkeratinizing

; No differentiated histologic type with small and large cell type.

; () ; %

of 331 patients) was squamous cell carcinoma:72.8% (241 patients) was well differentiated subtype and 25.4% (84 patients) poorly differentiated one. Mean duration between development of initial symptoms and diagnosis was 5, 6 months.

All but seven had vaginal bleeding and/or leukorrhea and others had abdominal or low back pains. 11.2% (37 of 331 patients) was found to have enlarged pelvic nodes greater than 2 cm in greatest diameter on X-ray CT. Table 3 displays distributions of enlarged pelvic nodes. All but 2 was on more than 50 in Karnofsky performance status. For response to radiation all patients were determined by clinical findings of pelvic and rectal examination, CT of pelvis and some of those by biopsy. Complete response (CR) was complete regression of cancer mass with no clinical cancer effect in 6 weeks after completion of radiotherapy. Partial response (PR) was defined as clinical regression of cancer mass more than 50% and no response (NR) was less than 50%. Local recurrence was determined by clinically visible or palpable new mass or cancer tissue in vagina and/or uterine cervix after 6 months follow up. Regional recurrence was defined

Table 3. Locoregional Lymph Node Metastases Distribution Before Radiotherapy

LN.	No. of patients
Obturator node	6 (16.2)
External iliac node	2 (5.4)
Internal iliac node	3 (8.1)
Common iliac node	–
Obturator & external iliac nodes	1 (2.7)
Obturator & internal iliac nodes	4 (10.8)
Obturator, external & internal iliac nodes	13 (35.2)
Obturator, external, internal & common iliac nodes	8 (21.6)
Total	37 (11.2)

; Suspected enlarged lymph nodes with more than cm in size in CT of pelvis. (metastasis)

; () ; %

by new palpable mass in pelvic wall and some of them was confirmed by biopsy.

If regrowing mass was evident clinically within 6 months after completion of radiotherapy, the patient was classified to persistent disease. Diagnosis of complications was determined clinically by symptoms, clinical, and laboratory findings as well as radiographic procedure and occasionally confirmed by surgical procedure. Crude survival rate were calculated by the Kaplan-Meier Method²²⁾ according to response of radiations, radiation dose to cancer mass and point A. Complications were measured according to doses to point A and to rectum and bladder. Pattern of failures were also analyzed.

2. Radiotherapy Technique

All patients was irradiated by 4 MeV X-ray linear accelerator. 270 patients were treated to deliver 4000 cGy to total pelvis via 4 field box technique with 200 cGy fractional daily dose, 5 fractions weekly: followed by intracavitary irradiation (ICR) in 202 patients of these and in 68 of these followed by external small field additional dose. ICR(s) were performed using Fletcher's applicator loaded with 45, 30, 30 mCi of Cs-137 sources in tandem and 2 colpostat loaded by 45 mCi each with ovoid caps for 48-72 hours. Cs-137 loadings were modified to reduce radiation to adjacent small bowel and by calculation of dose to point A and B and rectum and bladder. Small field booster irradiations were performed to deliver 2000~3000 cGy, but oc-

asionally upto 3600~4000 cGy with daily 200 or 230 or 250 cGy tumor dose depending upon residual mass in thorough dosimetry with 90% of isodose curve encompassing just residual cancer mass in uterine cervix and paracervical regions via 4 field box technique or bilateral arc technique with 2 different isocenters using usual field size 4 to 5×6 cms.

Higher external total pelvic radiations were given for pelvic node positive on X-ray CT and large mass in uterine cervix such as barrel shaped uterus or uterine cervix or more than 6×6 cm sized bulky exophytic mass. Higher external radiations were given to deliver 4600 cGy to 5000 cGys to total pelvis in 20 to 25 fractions, for 4 to 5 weeks before ICR or small field additional radiations. In cases of no opening of endocervical canal due to cancer involvement at the end of 4000 cGy to total pelvis, additional 1000 cGy in 5 fractions in 5 days in small field was added, followed by ICR, when endocervical canal was usually opened. Otherwise small field booster irradiation was added with 2000 cGy or more. These patients were included in group of upto 5000 cGy to total pelvis. 61 patients were treated with upto 5000 cGy to total pelvis: followed by ICR in 48 of them and by small field booster in 13 of them. The field size of total pelvic irradiation modified to encompass pelvic side wall laterally, common iliac nodes superiorly, upper 1/2 of vagina inferiorly by lower margin at inferior border of obturator foramen, posterior 1/3 bladder anteriorly and anterior half of rectum posteriorly.

Cs-137 ICR dosimetry was performed to reference points of expected maximal dose in bladder and rectal wall, vaginal wall and point A and B by hand calculation utilized tables of dose distribution about Cs-137 sources in tissue calculated by V. Krishnaswamy⁷⁾.

RESULTS

Among 331 patients, 292 patients (88.2%) showed complete response (CR) 35 patients (10.5%) partial response (PR) and 4(1.3%) no response (NR). CR was achieved in 93.6% of the patients treated by external total pelvic irradiation and subsequent ICR and in 71.6% of the patients treated by small field additional radiation following total pelvic irradiation(Table 4).

Among 331 patients, 274 patients were alive longer than 5 years and 266 of them lived without disease. Crude 5 year survival was 82.8% and disease free 5 year survival was 82.4%(Fig. 1). 5

Table 4. Comparison Between RT. Tech. and Response

Res.	Tech. (no. of patients)		Total
	External RT with reduced field RT	External RT with ICR	
CR	58 (71.6)	234 (93.6)	292
PR/NR	23 (28.4)	16 (6.4)	39
Total	81	250	331

. () ; %

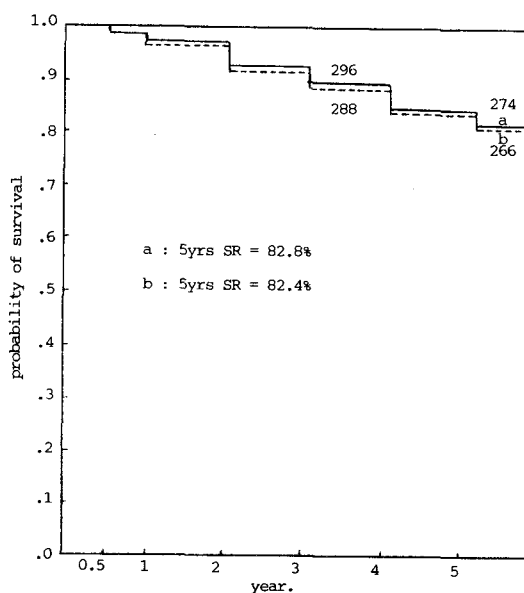


Fig. 1. Overall and disease free SR by radiotherapy alone of stage IIb uterine cervix cancer 8 pts : lives with recurrent/metastatic cancer during follow up a: overall SR (total pts; 331) b: disease free SR (total pts; 323)

year crude survival rate was 92.9% (272 patients) among 292 patients who had achieved CR vs only 5.1% (2 patient) among 39 patients who failed to achieve CR lived longer than 5 years ($p < 0.001$) as seen in Fig. 2.

266 (91.4%) of 291 patient who did not have recurrence or metastasis lived longer than 5 year vs only 8(12.9%) of 40 patients who had recurrence or metastasis lived longer than 5 years ($p < 0.001$) as seen in Fig. 3. Crude survival rate was 84% (247 patients) in 294 patients of negative pelvic nodes vs 73% (27 patients) in 37 patients of positive nodes(Fig. 4).

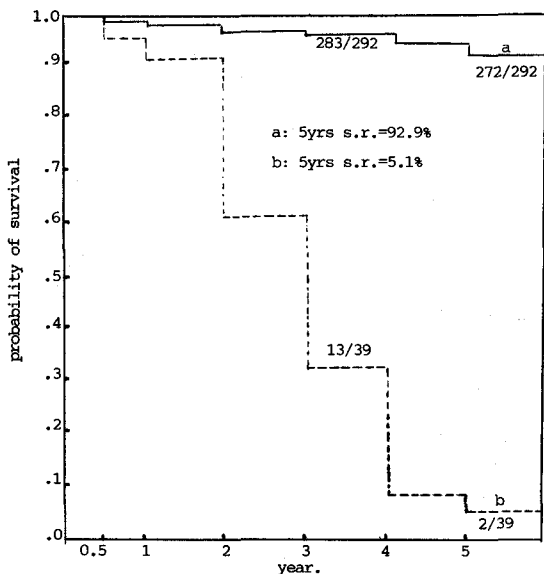


Fig. 2. Overall survival rate by complete response group and incomplete response group with radiotherapy alone. a; complete response group (CR). b; incomplete response group (PR or NR); highly significant ($p < 0.001$).

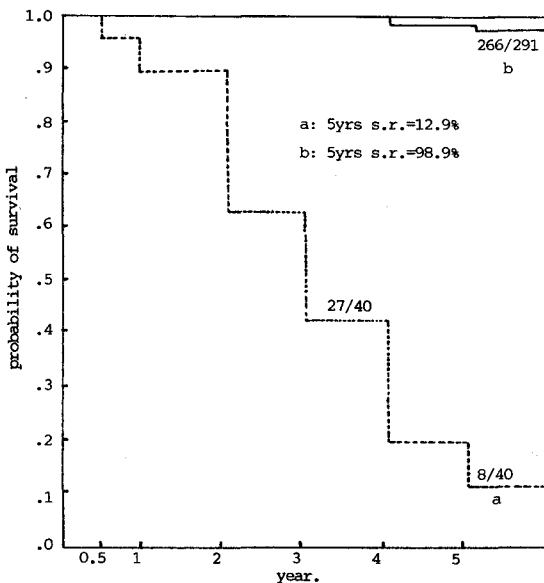


Fig. 3. Overall survival rate by recurrent/metastatic and persistent group and no recurrent/metastatic and persistent group after radiotherapy alone in uterine cervical carcinoma. a; recurrent/metastatic and persistent group after RT. b; control group; highly significant ($p < 0.001$).

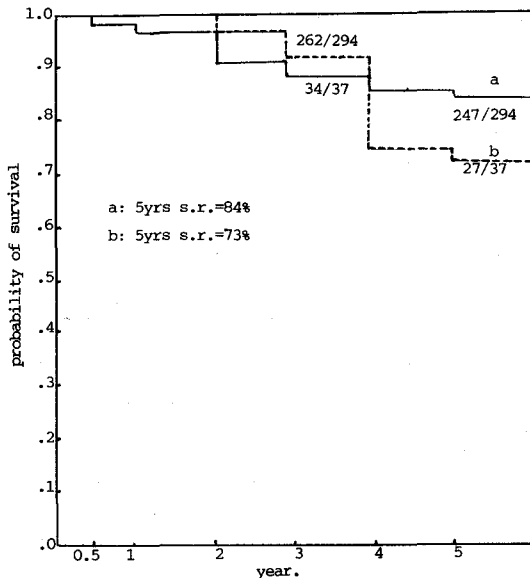


Fig. 4. Overall survival rate by preradiotherapy locoregional pelvic lymph node metastasis group and no pelvic lymph node metastasis group in stage IIb uterine cervical ca. a; no pelvic lymph node metastasis group b; preradiotherapy pelvic lymph node metastasis group; no significant

Table 5. Overall and Disease-free Survival Rates by Total Dose of Radiotherapy Alone in Uterine Cervical Carcinoma Point A/Parametrium)

Total dose	No. of patients	5 year overall survival rate (%)	5 year disease-free survival rate (%)
- 6500cGy	57	74.1	72
- 7500cGy	112	75	70.1
- 8500cGy	144	88.5	87.5
- 9500cGy	24	87.5	87.5
9501cGy -	24	87.5	87
Total	331	82.8	82.4

; No significant.

5 year crude survival was maximal 88.5% by the dosage of 7500~8500 cGy to point A without increasing survival above it and minimal 74.1% by less than 6500 cGy (Table 5).

Patients of receiving ICR showed better 5 year survival rate than the patients received small field radiation (88% vs 66.7%, $P = 0.2$) as seen on Fig. 5.

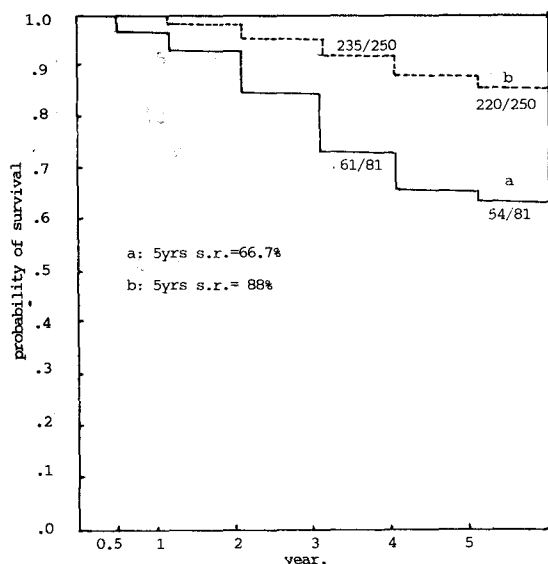


Fig. 5. overall survival rate by radiotherapy technique. a; 4 field external RT with reduced field ARC therapy in uterine cervical mass only. b; 4 field external RT with intracavitary brachytherapy with CS137 radio active source. ; borderline significant ($p < 0.06$)

The survival rate was not affected by age and pathologic type.

As seen on table 6, treatment failure was 18.7% (62 of 331 patients): local failure 72.6% (45 of 62 patients), locoregional failure 3.2% (2 of 62 patients) and distant failure 24.2% (15 of 62 patients), and only 8 of 62 patients who had recurrences in locoregional region lived longer than 5 year with diseases. 62.9% of treatment failure (39 of 62 patients) was found within 12 months after radiotherapy (Table 7).

Table 8 exhibits radiation complications.

Acute radiation reactions were found in 139 patients (42%) that were subsided by conservative treatment and 3-7 days resting. 50 patients (15.1%) were developed late complications as a nuisance. Almost half of them was serious rectal bleeding and stenosis with edema in 21 patients (42%). Complications were found to be higher in patients of receiving higher external irradiation: 27.2% in external small field irradiation vs 11.2% ICR as seen on Table 9. Complications were developed 7.4% (2 of 27 patients) at receiving upto 6500 cGy to point A, 3.6% (4 of 112 patients) at receiving upto 7500 cGy, 4.9% (7 of 144 patients) at receiving upto 8500

Table 6. Patterns of Treatment Failure (Persistent and Recurrent Metastases) After RT

Pattern	No. of patients	Period (month)
Local failure (uterine cervix)	# 45 (4) (72.6%)	(24, 35, 38, 41.) \$
Locoregional failure (uterine cervix and pelvic node)	2 (1) (3.2%)	24, (47).
Paraaortic nodes	4 (1) (6.5%)	23, 25, 35, (48).
Supraclavicular nodes	3 (1) (4.8%)	19, 32, (52).
Lung	5 (1) (8.1%)	15, 39, 45, 50, (52).
Liver	2 (3.2%)	4, 6.
Bone / multiple	1 (1.6%)	14.
Total	62 (8)* (18.7%)	

Local failure ; 45pts

. 37pts = persistent ca. (all regrowth within 12 months)

. 21pts = regrowth after 6 months.

. 16pts = regrowth within 6 months.

. 8pts = recurrent ca.

Total ; locoregional failure ; 47/62 = 75.8%

distant metastases ; 15/62 = 24.2%

* 8pts (8/62) ; recurrence but lives with disease.

\$ () ; treatment failure period in patients (8pts) living with disease.

\$ others treatment failure period ; 1, 2, 2, 3, 3, 3, 4, 4, 4, 4, 4, 5, 5, 5, 5, 6, 6, 7, 7, 7, 7, 8, 8, 8, 8, 8, 8, 9, 9, 9, 9, 10, 10, 10, 10, 11, 11, 12, 38, 19, 37, 39.

Pattern of treatment	No. of patients			Total
	Local failure	Locoregional failure	Distant meta.	
	45 (72.6%)	2 (3.2%)	15 (24.2%)	62

cGy but jumped up 58.3%(14 of 24 patients) in those who received upto 9500 cGy and 87.5% (21 of 24 patients) in those received above 9500 cGy as seen on Table 10. The dose of 8500 cGy to point A was found to be critical for complication and complication occurred 70% of those (35 of 50 patients) who received radiation above it and it was found to be more serious one such as fistula.

Table 11 shows relationship between the tumor dose calculated at the surface of exocervix and complication. Tumor dose upto 10500 cGy showed 3.7% of complications, however complications was found to be increased 38.1% if the tumor received

10500 cGy more dose.

Rectal complications (rectovaginal fistula:4 patients and severe rectal stenosis: 21 patients) were developed above rectal dose of 6500 cGy but bladder complication (hemorrhagic cystitis) was found in one patients above 7500 cGy at bladder (Table 12). Acute proctitis was found in 17.5% (58 patients) during radiotherapy and acute cystitis 9.7% (32 patients) and combined acute reaction 10.4% (23 patients).

Table 7. Duration Between End of RT and Treatment Failure (persistent and recurrent metastasis)

Duration	No. of patients
- 6 months	16 (25.8)*
- 12 months	23 (37.1)*
- 24 months	6 (9.7)
- 36 months	5 (8.1)
36 months -	12 (19.4)
Total	62 (18.7)

* 16 + 21 (21/23) = persistent ca. () ; %

Table 8. Late (Chronic) Complication

Complication	No. of patients
Severe rectal bleeding/stenosis	21 (42)
Fistula (rectovaginal/sigmoidovaginal)#	4 (8)
Intestinal obstruction (distal ileum)	1 (2)
Severe leg edema/lymphedema	4 (8)
Subcutaneous abdominal fibrosis	3 (6)
Severe cervical necrosis	16 (32)
Others (hemorrhagic cystitis)	1 (2)
Total	50 (15.1)

; Acute complications ; 139 (42%) ; () ; %

1pt=sigmoidovaginal fistula with perforation and peritonitis.

Table 9. Comparison Between External Dose and Complication

Compli.	External dose (no. of patients)				Total
	External (4portal) with reduced field RT		External (4portal) with ICR		
	4000cGy	5000cGy	4000cGy	5000cGy	
Severe rectal stenosis	6	2	8	5	21
Fistula #	1		1	2	4
Intest. obst.	1				1
Severe leg edema	2	1	1		4
Severe cervical necrosis	5	1	7	3	16
Subcuta. abdo. fibrosis	3				3
Other (hemorrhagic cystitis)				1	1
Total	18	4	17	11	50

* Acturial percentage of complication by various radiation technique

. External (4portal) with reduced field RT - . 4000cGy = 18/68 (26.5%) (27.2% = all) . 5000cGy = 4/13 (30.8%)

. External (4portal) with ICR - . 4000cGy = 17/202 (8.4%) (11.2% = all) . 5000cGy = 11/ 48 (22.9%)

Rectovaginal (3pts) and sigmoidovaginal (1pt) fistulas.

Table 10. Relationship Between Radiotherapy Technique & Total Dose (Point A) and Complication

Compli.	Total dose (no. of patients)										Total	
	-6500cGy		-7500cGy		-8500cGy		-9500cGy		9501cGy-			
	#	*	#	*	#	*	#	*	#	*	#	*
Severe rectal stenosis			1		1	3	3	4	3	6	8	13
Fistula			1					1		2	1	3
Intest. obst.					1						1	1
Severe leg edema					1		1		1	1	3	1
Severe cx. necrosis	1	1	1	1	1	2	2	2	1	4	6	10
Severe abdo. fibrosis							1		2		3	3
Others										1		1
Total	1/5	1/22	3/46	1/66	4/14	5/130	7/9	7/15	7/7	14/17	22/81	27/250
Total	2/27 (7.4%)		4/112 (3.6%)		7/144 (4.9%)		14/24 (58.3%)		21/24 (87.5%)		50/331 (15.1%)	

Reduced field RT, * ICR

Table 11. Relationship Between Total Dose in Uterine Cervical Mass by External (4 portal) with ICR and Complication

Complication	Total dose (no. of patients)					Total
	-8500cGy	-9500cGy	-10500cGy	-11500cGy	12500cGy	
Severe rectal stenosis	1	1	2	3	6	13 (46.4)
Fistula #				1	2	3 (10.7)
Severe leg edema					1	1 (3.6)
Severe cervical necrosis	1	1	2	3	3	10 (35.7)
Others (h. cystitis)				1		1 (3.6)
Total	2/22 (9)	2/63 (3.2)	4/130 (3.1)	8/21 (38.1)	12/14 (85.7)	28 (11.2)

* () : % # : Rectovaginal (2pts) and sigmoidovaginal (1pt) fistulas.

Table 12. Relationship Between Rectal/Bladder Total Doses and Complication

Complication	Total dose (no. of patients)				Total
	-5500cGy	-6500cGy	-7500cGy	7501cGy-	
Rectal compl.					
fistula (rectovaginal)		1	1	2	4
severe rectal stenosis	1	6	9	5	21
Bladder compl.					
hemorrhagic cystitis				1 (1/12)	1
Total % of rectal complication	1/59 (1.7%)	7/188 (3.7%)	10/72 (13.9%)	7/12 (58.3%)	25/331 (7.6%)

* Acute proctitis = 58/331 (17.5%) Acute cystitis = 32/331 (9.7%)
Both acute proctitis and cystitis = 23/331 (10.4%)

Table 13. Analysis Between Complications and Treatment Failure

Complication	Total	No. of patients			Failure period (month)	Death period
		Local failure	Regional failure	DM		
Severe rectal stenosis	21	2			19, 37	37, 43
Fistula	4			1*	25	31
Severe leg edema	4	2	1		11, 39, 10	27, 44
Severe cervical necrosis	16	5			10, 10, 11	25, 28
Others	5				37	39
Total	50	9	1	1		

* Paraaortic node metastasis with sigmoidovaginal fistula / perforation and peritonitis.

* DM : distant metastasis

* Combined complication with treatment failure

. 11/50 = 22%

. locoregional failure : 10/11 = 90.0%

Table 14. Causes of Death and Period (month)

Cause	No. of patients	Period
Cachexia (poor general condition) due to locoregional failure	42 (73.7)*	1, 12, 12, 14, 17, 17, 18, 18, 18, 18, 22, 22, 23, 24, 24, 24, 24, 25, 25, 26, 27, 28, 29, 29, 30, 31, 42, 43, 49.
Pulmonary failure due to lung meta.	8 (13.9)	17, 22, 31, 36, 40, 48, 49, 55.
Hepatic failure due to liver meta.	2 (3.5)	5, 7.
RT complication (fistula with perforation, intest. obst.)	3 (5.3)#	24, 48, 56.
Sudden death due to multiple spine meta.	1 (1.8)	14.
Intercurrent disease (car accident)	1 (1.8)	58.
Total	57 (17.2)	

* 42 pts = . 37pts ; due to persistent ca.

. 4pts ; due to local (recurrent) failure.

. 1pt ; due to locoregional (recurrent) failure.

1pt ; combined paraaortic node meta. with sigmoid colon perforation, and then died at 24mo. (with sigmoidovaginal fistula / period)

. carcinoma induced deaths ; 54 (54/57 = 94.7%) pts.

. treatment failure pts ; 62pts—. 54pts = died. but 8pts lives during 5year follow-up.

As seen in Table 13, only 22% (11 of 50 patients) of complications was combined with locoregional failure, therefore locoregional failure was found not to be a major factor to contribute complications, and 11 patients of them were dead: 9 of them died by locoregional failure and one died of fistula. Main cause of death was cachexia due to locoregional failure 73.7% (42 of 57 patients) and next orders: pulmonary failure 13.9% (8 of 57 patients) radiation complication 5.3% (3 of 57 patients), hepatic failure 2 patients, sudden death with multiple spine metas-

tasis in one and car accident in one (Table 14). Table 15 displays relationship between radiation technique and causes of death.

30 out of 250 patients (12%) who received ICR and 27 out of 81 patients (33.3%) who received small field external beam booster following total pelvic irradiation were dead. Death by radiation complication was only 1 (1.2%) in patient received small field external booster radiation and 2 (0.8%) in those of ICR.

Table 15. Analysis of Death Causes RT Technique

Cause	RT tech. (no. of patients)		Total
	External (4portal) with reduced field RT (%)	External (4portal) with ICR (%)	
Cachexia due to locoregional failure	22*	20#	42
Pulmonary failure	3	5	8
Hepatic failure	1	1	2
RT compli.	1\$	2@	3
Sudden death due to multiple spine meta.		1	1
Intercurrent disease (car accident)		1	1
Total	27 (33.3)	30 (12)	57

* 21 pts = due to persistent ca.

1 pt = due to recurrent ca (local failure)

16 pts = due to persistent ca.

4 pts = due to recurrent ca. (locoregional failure)

\$ Intest. obstruction in ileum.

@ Sigmoidovaginal fistula with perforation and peritonitis (1pt) and rectovaginal fistula (1 pt.)

Table 16. Comparison of 5 Year Survival Rate of Stage II Cancer of Uterine Cervix Reported by Others

Stage	% of 5 years survival	Authors
Stage IIa-b	68	Combes P. F et al ¹⁹⁾
Stage IIb	76	Horiot JC et al ²⁴⁾
Stage IIa-b	76.8	Okawa T. et al ²²⁾
Stage IIa-b	68.9	Masubuchi K. et al ²³⁾
Stage IIb	67	Kim CY et al ²⁵⁾
Stage IIb	56.7	Lee MZ et al ¹⁷⁾
Stage IIb	68	Perez CA et al ²¹⁾
Stage IIb	82.8	Our study

DISCUSSION

The goal of radiotherapy for cancer patients is achievement of highest tumor control and survival with lowest incidence of complication rate. It has been generally accepted that higher dose of irradiation delivered to the medial and lateral parametrium with external beam and subsequent intracavitary radiation lowered pelvic failure rate with increasing control of tumors and survival however with associated increase of incident rate of complication³⁾. The tumor control is correlated with function of the extent of the tumor and radia-

tion dose given. 4500~5000 cGy is essential for control of subclinical disease^{8,28)}. Jampolis et al²⁹⁾ reported, in analysis of 916 patients treated with radiotherapy alone for invasive carcinoma of the uterine cervix, that 60% of the patients of stage Ib and IIa-b and 25% of those of stage III who had pelvic failure received insufficient radiation below 5000~6000 cGy. Chism SE et al³⁰⁾ and Perez CA et al²⁰⁾ in analysis of dose to point A, noted that in stage II the pelvic recurrence rate was 42~44%, with dose below 6000 cGy, 22% with 6000~7500 cGy and 15~18% with 7500~9000 cGy. In stage III the recurrent rate was 58% with dose below 6000 cGy, 43% with 6000~7500 cGy and 32% with 7500~9000 cGy by Perez et al²⁰⁾ and it was 80% with dose below 6000 cGy, 63% with 6000~7000 cGy and 50% with higher dose by Chism et al³⁰⁾. Pelvic recurrence in analysis of dose to lateral pelvic wall (point B) was reported by Perez et al, 36.4% with dose upto 4500 cGy, 6.5% with 4501~5000 cGy, and 23% with 5000~6000 cGy in stage IIb and in stage III 65.5% with dose upto 4500 cGy, 32.8% with 4500~5000 cGy and 36% with 5000~6000 cGy.

Castro JR et al³¹⁾ reported there was not tumor control by less than 5000 cGy to pelvis for various staged disease whereas 12 of 18 patients achieved pelvic tumor control in his 108 patients treated solely by external radiation because of technical inability to perform ICR. We had much superior

results on analysis 331 patients of stage IIb treated by higher pelvic radiation with low treatment failure. Treatment failure rate was 18.7%: Pelvic failure 14.2% and distant failure 4.5% whereas Perez CA et al¹⁹⁾ reported treatment failure was 14~16% in pelvic failure and 22~23.8% of metastasis. Total pelvis was irradiated routinely with 4000 cGy fractional dose whereas for 6×6 cm sized exophytic tumor mass or barrel shaped uterine cervix total pelvis was irradiated with slightly higher dose 4600 cGy/4 weeks to 5000 cGy/5weeks with 200~230 cGy, daily fractional dose^{11,14,19,24,25)}. In analysis of dose to medial parametrium (point A), 5 year survival rate was 74% with dose below 6500 cGy, 75% with 6500~7500 cGy, 88.5% with 7500~8500 cGy, 87.5% with 8500~9500 cGy and 87.5% with the dose above it. Radiation dose to point A with 7500~8500 cGy was optimal to maximize survival with acceptable incidence (4.9%) of complication without increasing survival by increase of dose above it.

Radiation to point A above 8500 cGy upto 9000 cGy, however could be attempted to achieve the control of pelvic cancer for specific state of disease with barrel shaped uterine cervix or a bulky exophytic mass greater than 6 cm in diameter or poor response to 4000 cGy total pelvic radiation, however cautious dosimetry to small bowel, rectum and urinary bladder should be performed. Overall 5 year survival rate 82.8% and disease free 5 year survival rate 82.4% was surprisingly higher in comparison with others as seen in Table 16. We found survival was positively correlated to initial achievement of CR in 6 weeks after radiotherapy. Better survival figure in patients treated with ICR and low incidence of complication was due to unfavorable state of disease in patients of having small field additional external radiation^{9,12,16)}. The patients who had inability to be performed ICR was treated solely external radiation in shrinking field technique.

Akine Y et al²⁷⁾ reported low 5 year survival rate 36% when patient with stage II carcinoma of uterine cervix was treated by external radiation alone. Ulmer HU. et al²⁹⁾ reported 75% of 5 year survival rate for stage II carcinoma of uterine cervix treated solely by external irradiations that seemed to be superior to ours 66.7%, however Ulmer's series included stage IIa with only vaginal involvement in 1/2 of the patients. Much superior 5 year survival figure, 88% in the patients treated by ICR was found to be due to higher achievement of CR (98.6% vs 71.6% by external small field RT) because ICR was usually performed at more than 80% regression of

tumor of external pelvic radiation. Pelvic lymph node metastases was noted to be one of important prognostic factors.^{1,5,13,25)}

The crude survival rate was noted to be inferior 73% in the patients of having positive pelvic nodes to the survival rate 84% of the patients who had negative pelvic nodes on X-ray CT finding though it was statistically not significantly different. However the X-ray CT finding of pelvic node positive greater than 2 cm in diameter must have false positive due to reactive hyperplasia and negative finding must also have false negative. Llusia JB et al¹⁾ reported that pelvic node metastases was found 33.3% in patients of uterine cervical cancer regardless of staging and 4000 cGy was insufficient to control pelvic lymph nodes, however higher radiation with 5000~7000 cGy sufficiently controlled metastatic pelvic nodes but did not completely sterilize. Bladder complication occurred between 6 and 42 months after radiotherapy and most of the rectal complication occurred within 12 months following therapy. Mean delays in the expression of symptoms of injury were 10 months for the rectum and 22 months for the bladder^{32,33)}.

This long latent period was suggested by Orton CG³²⁾, that a significant proportion of patients who might be expected to develop bladder complications will be in fact not survive long enough for the symptoms to be observed. He reported also a correlation between incidence and severity of complications and TDF. More than 2 grade of late complications of our study was slightly higher, 15.1% than others 7% to 12.2%^{8,21,23)}. The patients received 4000 cGy to total pelvis and ICR, showed complication rate 8.4% as reported by others^{3,4,6,10,18,23)} but those who received upto 5000 cGy total pelvic irradiation with additional small field external radiation due to inability to perform ICR revealed highest complication rate 30.8%. The complication rate increased from 11.2% with ICR in booster to 27.2% with external small field additional dose in booster as seen on Table 9, it displayed also 14.5% increment by 4000 cGy increasing to 5000 cGy of total pelvic irradiation. In view of incidence of complication correlated to total radiation dose given to point A, with 7500~8500 cGy complications rate was 4.9%. If radiation dose to point A increase upto 9500 cGy, complication rate will jump up 58.3%. Perez et al described doses to point A over 7000 cGy, grade 2 sequelae were observed in 10% of all staged patients and grade 3 complication in 8% of those with stage IIa and beyond but doses over 8000 cGy grade 2 and 3

complication increased from less than 5% to 10~15%. In our series we observed the rectum was more vulnerable to radiation than bladder.

By radiation dose below 6500 cGy to the rectum incidence of complication was only 3.7% but it jumped up 58.2% with increasing rectal dose over 7500 cGy. There was however no correlation between complication and treatment failure, therefore there was no expectation of dosage inhomogeneity in our treatment system^{17,34}). During radiotherapy the development of acute radiation reactions was high due to high total pelvic radiation with high fractional dose particularly for a barrel shaped uterus and a bulky uterine cervix mass. It was usually subsided however by several days resting with conservative medical treatment. Most of our patient's death was by pelvic failure particularly regional failure due to initially bulky necrotic mass or barrel shaped uterus in 73.7% of death with resulting later cachexia and 19.2% of them was died of metastases in lung, liver and spines. Only 3 patients was counted for death by complications (fistula with intestinal perforation and intestinal obstruction). Among 62 patients with pelvic failure 8 patients lived in 5 year follow up. Therefore from result of this study further more increment of pelvic control for centrally anoxic bulky mass in uterine cervix might be achieved by imperative defining of optimal dose schedule of irradiation with combining of hyperthermia³⁵).

CONCLUSION

1. High external pelvic radiation with 4000 cGy to total pelvis followed by ICR to deliver 6500 cGy to point A was proper dosage schedule for stage IIb cancer of uterine cervix as cancer infiltration in paracervical regions is minimal.

2. Further higher pelvic irradiation with 4600~5000 cGy in higher fractional dose, for a bulky uterine mass and barrel shaped uterus followed by ICR to deliver 7500~8500 cGy to point A was found to be optimal with expected maximal 5 year survival rate 88.5%, with no further increment of survival by dosage above it, however with acceptable complication 4.5%.

3. Further more imperative optimization of dosage schedule is sine quanon for individualizing patient by proper examination at the end of pelvic external irradiation.

4. Further increment of pelvic control and survival rate of the cancer of uterine cervix is expected to be achieved by combination of optimization of

radiation dose schedule and hyperthermia for the bulky uterine cervix and barrel shaped uterus.

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== 국문초록 ==

자궁 경부암 처지

고신대학교 의과대학 치료방사선학교실

문 창 우 · 정 태 식 · 염 하 영

1980. 6.부터 1985. 12.까지 고신의료원 치료방사선과에서 방사선 단독 치료한 병기 IIb 자궁경부암 환자 331명에 대하여 후향적으로 생존율 치료 실패 및 합병증 등에 영향을 미칠 수 있는 방사선 치료 요소들을 분석조사 하였다. 5년 생존율과 무병생존율은 각각 82.8%와 82.4%였다. 방사선 치료 6주 경과에 분석한 골반내 관해율은 전골반 외부 조사후 강내조사한 예에서는 98.6%였고 축소조사한 추가 치료한 예에서는 71.6%였다. 전골반 방사선 조사후 완전관해를 보였던 예에서의 5년 생존율은 98.9%였지만 국소치료실패 및 원격전이한 예에서는 12.9%였다. Point A에 7500~8500 cGy를 조사한 예에서는 88.5%의 5년 생존율을 보였고 합병증은 4.9%였지만 그 이상의 조사량에서는 생존율은 증가하지 않았고 합병증만 증가하였다. 18.7%(62예)에서 치료실패를 보였는데, 이중 국소치료 실패가 72.6%(45예), 국소 및 골반외부 치료실패가 3.2%(2예)였으며 원격전이 실패는 24%(15)였다. 합병증은 15.1%(50예)였는데 이중 42%가 직장 출혈 및 협착이었다. Point A의 조사량은 8500 cGy가 합병증 유발의한계 조사량이었으며 합병증의 70%가 그 이상의 조사량에서 발생하였다.

직장 합병증은 6500 cGy 이상에서 발생하였고 방광합병증은 7500 cGy이상에서 발생하였다. 사망의 원인으로는 국소치료실패로 인한 전신쇠약이 대다수였으며 전체 사망원인으로는 국소치료 실패로 인한 전신쇠약이 대다수였으며 전체 사망원인의 73.7%였고 그외 폐, 간, 뼈 전이순이었으며 방사선합병증으로 인한 사망은 3예에 지나지 않았다. 상기와 같은 결과에 대한 결론으로 크기가 아주 큰 종양이나 Barrel형태의 종양의 방사선 치료에는 지금 많이 사용되고 있는 4000 cGy이상의 외부 조사량이 강내조사전에 골반관해를 성취하기 위해 필요한 것을 알 수 있었다