

- 3 -

* . * . * . * . * . † . † . †

가

1996 1 1999 3 AJCC 2 3

3 B (am I) (am II)

5-FU 375 mg/m²/day leucovorin 20 mg/m²/day 3

5 8 45 Gy/25

fractions/5 weeks 1998 6 228 228

Arm I 1

am II 2 3 23

am I 11 (9.7%), am II 9 (8%)

am I 22 (19.5%), am II 35 (31%) am I (p=0.046)

3 (70.2% vs 59.2%, p=0.2) 3 (89.4% vs 88.0%, p=0.47) 가

RTOG grade 1 78.3% 79.9%

, RTOG grade 3 2.1%, 6%

10 am I 71.2%, am II 42.6% am I

(p=0.02)

가

: , , , 3

가

1 4) North Central Cancer Treatment Group (NCCTG)

5 10%

5) National Surgical Adjuvant Bowel and Breast Project (NSABP) R-01 Dukes' stage B C

가

가

6) GITSG 7180 methyl-CCNU가

가 5-FU

8 12)

1999 12 20 2000 3 13

45 65% 15 35% 50%

Tel: (02)2224-4423, Fax: (02)486-7258

E-mail: kim@radonc.uck.edu

7 :

가 1) 3 8 28

5-FU 375 mg/m²/day leucovorin 20 mg/m²/day

3

1996 1 1999 3

AJCC 2

5

1 3 29 31

6

3 5 2 57 59

85 87

가

4

14

14 가 1,000 1,500/ul 가

50,000 75,000/ul 5-FU 75%

가 1,000/ul 가 50,000/ul

5-FU 50%

가

1996 1 1999 3

AJCC 2 313

1998 6 228

1987 AJCC

14

가 Radiation Therapy Oncology Group (RTOG)

15 , Eastern Cooperative Oncology

Group (ECOG) 가 2

(creatinine <1.5 mg/dL or creatinine clearance >50 mL/min,
serum bilirubin <1.5 mg/dL, SGOT/SGPT <3 folds of normal)
(WBC >4,000/ul, platelets >100,000/
ul, hemoglobin >10 gm/dL)

3 3

(2 vs 3)

(N0 vs N1 vs N2, 3)

Table 1

2 .

(Arm I, 113) ,

2

(Arm II, 113) .

Table 1. Patients Characteristics

	Total	Arm I	Arm II
Median follow-up	23 months	24 months	23 months
Number of Patients	226	113 (50.0%)	113 (50.0%)
Sex			
male	140 (61.9%)	73 (64.6%)	67 (59.3%)
female	86 (38.1%)	40 (35.4%)	46 (40.7%)
Age			
median	55	55	54
range	29 81	32 78	29 81
Stage			
II	74 (32.7%)	35 (31.0%)	39 (34.5%)
III	152 (67.3%)	78 (69.0%)	74 (65.5%)
Surgery			
APR [*]	81 (35.8%)	43 (38.1%)	38 (33.6%)
LAR [†]	141 (62.4%)	68 (60.2%)	73 (64.6%)
PE [‡]	4 (1.8%)	2 (1.8%)	2 (1.8%)

^{*} APR : abdominoperineal resection

[†] LAR : low anterior resection

[‡] PE : pelvic exenteration

1.5 cm (obturator foramen) , 가 30 (13.3%).
 4 , 3
 4 cm 30 가 25 (11.1%),
 1 cm 가 3 (1.3%),
 1 가 1 (0.4%),
 (absolute neutrophil count)가 1000 가 1 (0.4%) (Table 2).
 , 3 9 (8.0%),
 16 (14.2%)
 3 . 6 가 174
 2 3 , 6 (77.0%) , 1 5 가 30 (13.3%),
 , CEA, X- 가 22 (9.7%) . 5
 2 6 , 30 27 (11.9%) 가
 , 3 (1.3%)
 , 22 18 (8.0%)
 , 3 (1.3%)
 , 1 (0.4%) (Table 3).
 Kaplan-Meier , Log- 5.9
 Rank 6.3

Table 3. Compliance of Chemotherapy

Chemotherapy cycles	Total	Arm I	Arm II
0	22 (9.7%) [*]	12 (10.6%)	10 (8.8%)
1 5	30 (13.3%) [†]	15 (13.3%)	15 (13.3%)
6 8	174 (77.0%)	86 (76.1%)	88 (77.9%)
Total	226	113	113

^{*} Patient refusal (18)/ wound complication (3)/ death before treatment (1)

[†] Patient refusal (27)/ distant metastasis (3)

Table 2. Compliance of Radiation Therapy

Radiation therapy	Total	Arm I	Arm II
Complete	189 (83.6%)	97 (85.9%)	92 (81.4%)
Incomplete	7 (3.1%) [*]	4 (3.5%)	3 (2.7%)
No RT [†]	30 (13.3%) [†]	12 (10.6%)	18 (15.9%)
Total	226	113	113

^{*} Patient refusal (3)/ GI complication (4)

[†] Radiation therapy

[†] Patient refusal (25)/ wound complication (3)/ distant metastasis (1)/ death before treatment (1)

Table 4. Hematologic Toxicity during Radiation Therapy

Grade [*]	Total	Arm I	Arm II
0	41 (21.7%)	27 (27.6%)	14 (15.4%)
1	91 (48.2%)	47 (48.0%)	44 (48.4%)
2	53 (28.0%)	22 (22.4%)	31 (34.1%)
3	4 (2.1%)	2 (2.0%)	2 (2.2%)
Total [†]	189	98	91

^{*} by RTOG toxicity criteria

[†] 37 out of 226 patients : not received radiation therapy

7 :

2. RTOG 76.2% (144/189) (Table 4).
 2, 3, 4 (2.1%)
 가 RTOG 2 43.2% (86/199), 3 6.0% (12/199) (Table 5).
 2 (22.4% vs 34.1%, $p=0.16$).
 가
 120 10 가 68 (56.7%) ,
 95 (79.2%)
 10 가 71.2%
 42.6% ($p=0.02$),
 (78.0% vs 80.3%)
 (Table 6).

Table 5. Hematologic Toxicity during Maintenance Chemotherapy

Grade*	Total	Arm I	Arm II
0	40 (20.1%)	18 (18.6%)	22 (21.6%)
1	61 (30.7%)	31 (32.0%)	30 (29.4%)
2	86 (43.2%)	42 (43.2%)	44 (43.1%)
3	12 (6.0%)	6 (6.2%)	6 (5.9%)
Total†	199	97	102

* by RTOG toxicity criteria

† 22 out of 226 patients : not received Chemotherapy
 5 patients : received at other hospital

Table 6. GI Toxicity during Radiation Therapy

	Total	Arm I	Arm II
Diarrhea (times/ day)			
1-3	8 (6.7%)	4 (6.8%)	4 (6.6%)
4-6	20 (16.6%)	7 (11.8%)	13 (21.3%)
7-9	17 (14.2%)	5 (8.5%)	12 (19.7%)
10	68 (56.7%)	42 (71.2%)	26 (42.6%)
irregular	7 (5.8%)	1 (1.7%)	6 (9.8%)
Medication			
Yes	95 (79.2%)	46 (78.0%)	49 (80.3%)
No	25 (20.8%)	13 (22.0%)	12 (19.7%)
Total	120*	59	61

* Patients received low anterior resection

(5.8%) , 5 , 6 , 11
 가
 3 , 1 .
 3 .
 226 2 (0.8%),
 39 (17.3%), 가
 18 (8.0%)
 가 2 (1.7%),
 가 13 (11.5%), 가 가
 9 (8.0%) , 가
 가 가 26 (23.0%),
 가 9 (8.0%) (Table 7)
 ($p=0.046$). 7.5
 % 2.2% (Table 8), 8.0%
 가 11.1% 5.8% (Table 9).

Table 7. Patterns of Failure

	Local	DM*	Both
Arm I	2 (1.8%)	13 (11.5%)	9 (8.0%)
Arm II	0 (0%)	26 (23.0%)	9 (8.0%)
Total	2 (0.9%)	39 (17.3%)	18 (8.0%)

* Distant metastasis

Table 8. Patterns of Local Failure

Site	Total	Arm I†	Arm II†
Tumor bed	17 (7.5%)	10 (8.8%)	7 (6.2%)
Node†	5 (2.2%)	2 (1.8%)	3 (2.7%)
Total	20 (8.8%)	11 (9.7%)	9 (8.0%)

* 1 patient : recur at both site

† regional lymph node

Table 9. Pattern of Distant Metastasis

Site	Total	Arm I†	Arm II‡
Liver	18 (8.0%)	6 (5.3%)	12 (10.6%)
Lung	25 (11.1%)	10 (8.8%)	15 (13.3%)
PAN*	13 (5.8%)	5 (4.4%)	8 (7.1%)
Other	9 (4.0%)	6 (5.3%)	3 (2.7%)
Total	57 (25.2%)	22 (19.5%)	35 (31.0%)

* paraaortic lymph node

† three patients : multiple metastases

‡ three patients : multiple metastases

Table 10. Last Follow-Up Status of Patients

Arm	NED [*]	AWD [†]	DWD [‡]	DOD [§]
I (113)	88 (77.9%)	13 (11.5%)	1 (0.9%)	11 (9.7%)
II (113)	80 (70.8%)	25 (22.1%)	1 (0.9%)	7 (6.2%)
Total	168 (74.3%)	38 (16.8%)	2 (0.9%)	18 (8.0%)

^{*} no evidence of disease, [†] alive with disease
[‡] alive without disease, [§] death of disease

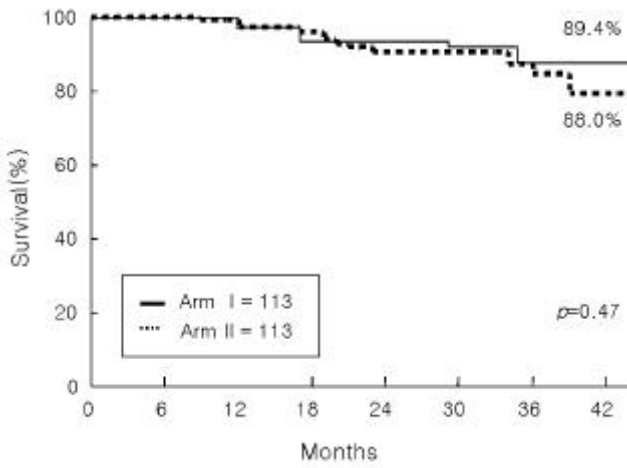


Fig. 1. Overall survival rate of 'early (arm I)' and 'late (arm II)' radiation therapy group.

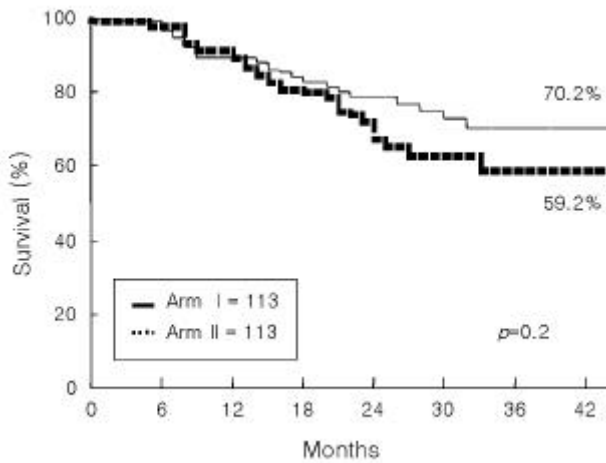


Fig. 2. Disease free survival rate of 'early (arm I)' and 'late (arm II)' radiation therapy group.

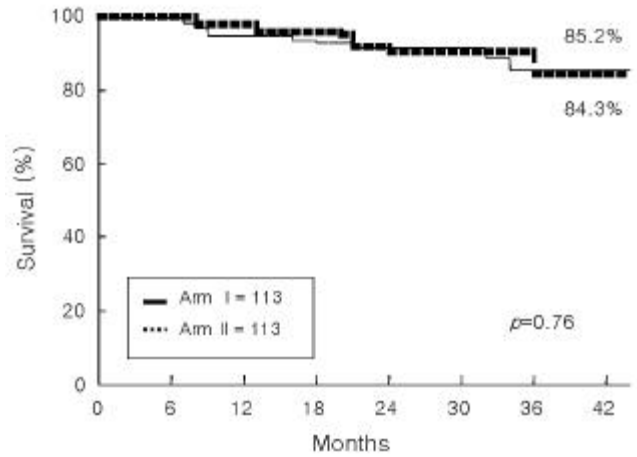


Fig. 3. Local recurrence free survival rate of 'early (arm I)' and 'late (arm II)' radiation therapy group.

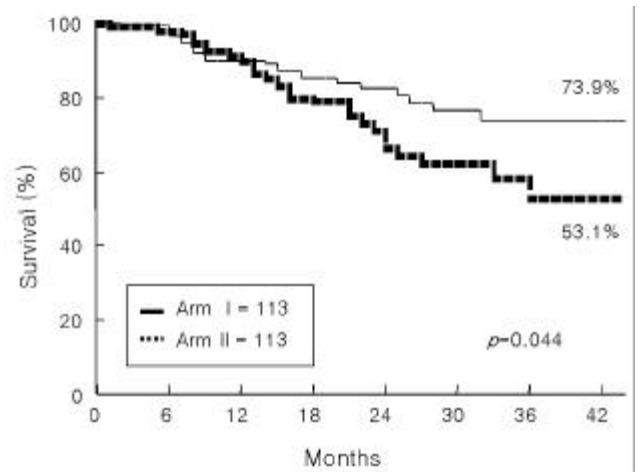


Fig. 4. Distant metastasis free survival rate of 'early (arm I)' and 'late (arm II)' radiation therapy group.

88 (77.9%), 13 (11.5%),
 11 (9.7%),
 1, 80
 (70.8%), 25 (22.1%),
 7 (6.2%), 1
 (Table 10). 3 86.3%
 64.9%, 89.4%, 70.2%
 88.0%, 59.2% 가
 (Fig. 1, 2). 3 85.0%
 85.2%, 84.3%
 (p=0.76)(Fig. 3),

4 .

가 168 (74.3%), 18 (8.0%)
 38 (16.8%), 1, 1

Table 11. Postoperative Adjuvant therapy of Rectal Cancer

Study group (median F/ U)	Patient number	Tx regimen [§]	RT start	LFR (%)	DM (%) [†]	DFS (%) [‡]	Overall Survival (%)
GITSG 7175 (80 M)	46	• RT+MF MF	Tx day 1	11	26	-	56
GITSG 7180 (5.8 Y)	95	• RT+MF MF	Tx day 1	17	40	54 [‡]	54
NCCTG 79-47-51 (>7 Y)	104	• RT+5FU 5FU		16	26	68 [‡]	55
NCCTG 79-47-51 (>7 Y)	104	• MF RT +5FU MF	Tx day 64	14	29	-	53
NCCTG 86-47-51 (46 M)	332	• MF/ 5FU RT +5FU (B [†]) MF/ 5FU	Tx day 64	-	40	53	60
	328	• MF/ 5FU RT +5FU (PVI [‡]) M/ F/ 5FU		-	31	63	70
INT-0114 [*] (48 M)	-	• 5FU RT +5FU 5FU	Tx day 57	12	31	62	78
	-	• FL RT+FL FL		9	28	68	80
	-	• 5FU +LM RT +5FU 5FU +LM		13	33	62	79
	-	• 5FU +LV +LM RT +FL 5FU +LV +LM		9	32	63	79
this study [*] (23 M)	113	• FL RT+FL FL	Tx day 1	10	20	70	89
	113	• RT+FL FL	Tx day 57	8	31	59	88

* 3 year data, † bolus infusion, ‡ protracted venous infusion, § MF :5FU +methyl-CCNU, FL :5FU +leucovorin, LV :leucovorin, LM :levamisole, local failure rate, † distant metastasis, ‡disease free survival

64.3% , 73.9%, 53.1% (p=0.044)(Fig. 4, Table 11).
 가
 NCCTG가 5-FU methyl-CCNU 가
 methyl-CCNU 가 가
 8, 9) 5-FU leucovorin 10 12)
 5-FU leucovorin
 가 INT 0114 levamisol
 , 5-FU, leucovorin,
 R-01 , NCCTG 5 7) GITSG
 20% 5-FU 5-FU leucovorin 13)
 가 , NSABP R-01 가
 가 ,
 NCCTG 5-FU leucovorin
 25% 13.5% 46%
 28.8% 가 38% 가
 53% , 3 8
 , NCCTG INT-0114
 가

64, 57 가 3, 1 가 3, .

RTOG 3 2.1%, 6% 가 23

(11.1%) 16 (14.2%) 9 (8.0%) 가 18 가 27 (11.9%) GITSG 7175 15%, 가 30%, 56%, GITSG (tolerance) 17%, 40%, 54% 가 64 NCCTG 79-47-51 14%, 가 29% INT 0114 8 가 139 53% (6, 7, 13, 14) 10% 20%, 3 89% , 가 18 2, 8, 31, 88% (Table 10). 가

가 14, 15) 20% 30% 가 Table 11 35% 16% NCCTG 4.4% (9/204) 가 가 71.2%, 10 42.6% (p=0.02), 78.0%, 80.3% 가 가 5 가 10% 가 6 11 (5.3%) , 가

3
가

가

가

가 12.4%

5 가 19.9%

가

가

가

가

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Abstract

A Prospective Randomized Trial Comparing the Sequence of
Adjuvant Chemotherapy and Radiotherapy following
Curative Resection of Stage II, III Rectal Cancer

Kyoung Ju Kim, M.D.^{*}, Jong Hoon Kim, M.D.^{*}, Eun Kyung Choi, M.D.^{*}, Hyesook Chang, M.D.^{*}
Seung Do Ahn, M.D.^{*}, Je Hwan Lee, M.D.[†], Jin Cheon Kim, M.D.[‡] and Chang Sik Yu, M.D.[‡]

^{*}Department of Radiation Oncology, [†]Medical Oncology, and [‡]General Surgery.
College of Medicine, University of Ulsan

Purpose : To evaluate the side effects, pattern of failure, and survival rate according to the sequence of postoperative adjuvant radiotherapy and chemotherapy, patients with stages II and III rectal cancer who had undergone curative resection were randomized to 'early radiotherapy group (arm I)' or 'late radiotherapy group (arm II)', then we intend to determine the most effective sequence of the radiotherapy and chemotherapy.

Materials and Methods : From January 1996 to March 1999, 313 patients with curatively resected stages II and III rectal cancer have been randomized to 'early' or 'late' radiation therapy group and received combined chemotherapy (5-FU 375 mg/m²/day, leucovorin 20 mg/m², IV bolus daily D1-5, 8 cycles) and radiation therapy (whole pelvis with 45 Gy/25 fractions/5 weeks). Arm I received radiation therapy from day 1 with first cycle of chemotherapy and arm II received radiation therapy from day 57 with third cycle of chemotherapy after completion of first two cycles. Preliminary analysis was performed with 228 patients registered up to Jun 1998. Two out of the 228 patients were excluded because of double primary cancer. Median follow-up period was 23 months.

Results : Local recurrence occurred in 11 patients (9.7%) for arm I and 9 patients (8%) for arm II. There was no significant difference between both groups ($p=0.64$). However, distant metastasis was found in 22 patients (19.5%) for arm I and 35 patients (31.0%) for arm II and which showed statistically significant difference between the two groups ($p=0.046$). And neither 3-year disease-free survival (70.2% vs 59.2%, $p=0.2$) nor overall survival (89.4% vs 88.0%, $p=0.47$) showed significant differences. The incidence of leukopenia during radiation therapy and chemotherapy was 78.3% and 79.9% respectively but leukopenia more than RTOG grade 3 was only 2.1% and 6.0% respectively. The incidence of diarrhea more than 10 times per day was significantly higher in the patients for arm I than for arm II (71.2% vs 41.6%, $p=0.02$) but this complication was controlled with supportive cares.

Conclusion : Regardless of the sequence of postoperative adjuvant radiation therapy and chemotherapy after curative resection for rectal cancer, local recurrence rate was low with combined chemoradiotherapy. But distant metastasis rate was lower in early radiation therapy group than in late radiation therapy group and the reason is unclear. Most patients completed these treatments without severe complication, so these were thought to be safe treatments but the treatment compliance should be improved.

Key Words : Rectal cancer, Radiation therapy, Chemotherapy, Phase III clinical trial