의학 석사학위 논문

Preoperative Chemoradiotherapy of Locally Advanced Rectal Cancer: Preliminary Results of BID Fractionation

아 주 대 학 교 대 학 원

의 학 과

이 선 영

이선영의 의학 석사학위 논문을 인준함.

심사위원장 전 미 선 인

심 사 위 원 오 영 택 인

심 사 위 원 강 승 희 인

아 주 대 학 교 대 학 원

2008년 6월 23일

Preoperative Chemoradiotherapy of Locally Advanced Rectal Cancer: Preliminary Results of BID Fractionation

by

Lee Sun Young

A Dissertation Submitted to The Graduate School of Ajou University
in Partial Fulfillment of the Requirements for the Degree of

MASTER OF MEDICAL SCIENCES

Supervised by
Mison Chun, M.D., Ph.D.

Department of Medical Sciences
The Graduate School, Ajou University
August, 2008

- ABSTRACT -

Preoperative Chemoradiotherapy of Locally Advanced Rectal Cancer: Preliminary Results of BID Fractionation

Introduction: Preoperative chemoradiotherapy is an effective modality for patients with locally advanced rectal cancer. This study was designed to evaluate the efficacy, tolerance, and toxicity of preoperative chemoradiotherapy (CRT) in patients with locally advanced rectal cancer, using BID fractionation.

Patients and methods: Between January 2001 and November 2007, 35 patients were treated with preoperative CRT and then received operation for locally advanced rectal cancer. Three cycles of chemotherapy were delivered with 5-FU based regimen, mainly FOLFIRI (n=25), every 3 weeks. Radiation treatment scheme was 1.5 Gy (n=31) or 1.6 Gy (n=4) of radiation twice a day, and 1st course of radiotherapy of 21-24 Gy was delivered concurrently with 1st cycle of chemotherapy followed by 10-12 days rest period and 2nd course of radiotherapy of 21-24Gy was delivered concurrently with 2nd cycle of chemotherapy.

Results: The median follow up period was 19 months (5-36 months). All were T3 (n=24) or T4 (n=11) and the largest diameter of tumor mass was median 5cm (2.5-14cm). Overall downstaging rate was 71%. Pathologic complete response (pCR) rate was 11% (n=4), near CR rate (microscopically focal residual tumor, and less than 10% of viable cells) was 23% (n=8), and partial response rate was 60% (n=21). Upon operation, two patients were found to have unresectable tumor. Sphincter-preserving procedure was performed in 43% of 30 patients with lower rectal cancer.

Only 8 patients (23%) showed severe acute toxicity (grade 3 neutropenia in 4 patients, grade 3 and 4 perineal skin reaction in each one patient, and grade 3 diarrhea in 1 patient). Seven patients (20%) had treatment interrupted (1-8 days) because of following reasons; 3 for perineal skin reaction, 3 for chemotherapy-related problems, and 1 for anal abscess control problems. Late toxicity was observed in 2 patients; perineal open wound in one patients and rectovaginal fistula in the one patient.

Conclusion: Preoperative BID-fractionation CRT for locally advanced rectal cancer achieved 34% of pCR or near CR rate. And this treatment protocol was feasible as a preoperative treatment without compromising tumor response and with better tolerance in locally advanced rectal cancer.

Key words: rectal cancer, neoadjuvant, concurrent chemoradiotherapy, BID-fractionation

차 례

LIST OF FIGURES

LIST OF TABLES

I. INTRODUCTION

The therapeutic choice of rectal cancer remains to be surgery. The outcome of surgery is excellent in patients with early stage rectal cancer, however, the outcome of surgery alone is poor with longer survival rate of only 40-50%, and local failure rate of 25% in high-risk group. In high risk group, postoperative adjuvant radiotherapy with or without chemotherapy could reduce local failure rates by 10-15% (Rosen et al, 2007). Moreover, the introduction of total mesorectal excision (TME) in the management of rectal cancer has yielded the local failure rate of less than 10% (Kapiteijn et al, 2001).

Recently, preoperative radiotherapy with chemotherapy has been preferred for the management of locally advanced rectal cancer to preserve sphincter function and improve local control and recurrence-free survival. And many studies on the preoperative chemoradiotherapy (CRT) have been going on with novel agents. Various schemes of preoperative radiotherapy have been used. Most common scheme consists of conventional fractionation of five times per week, daily radiation. In addition, short course or twice daily fractionated radiotherapy has been used in some. (Coucke et al, 1995; Mohiuddin et al, 2006; Tsujinaka et al, 2008)

The therapeutic goal is to improve local control and reduce acute and

late toxicities. We used BID-fractionation protocol concurrently with each cycle of chemotherapy and enhanced the radiation dose while on chemotherapy.

Preliminary results were analyzed with regards to pathologic response, tolerance, and toxicity in locally advanced rectal cancer patients who were treated with preoperative CRT using BID-fractionation protocol.

II. MATERIALS AND METHODS

A. Patients

We analyzed patients have histologically confirmed adenocarcinoma of the rectum, without evidence of distant metastasis.

Between 2001 and 2007, 258 patients with primary rectal cancer received radiation therapy with/without concurrent chemotherapy. Fourty-one patients were treated for recurrent rectal cancer after surgery and the remaining 217 patients for newly diagnosed rectal cancer. Among 217 patients, 63 patients underwent preoperative radiotherapy.

Of 63 patients treated with preoperative radiotherapy, 20 patients were excluded: 5 patients were referred to another hospitals during or after completion of chemoradiotherapy (CRT), 8 patients were lost to follow-up or refused surgery after completion of CRT, 2 patients had incomplete treatment with poor general condition (pneumonia in one and COPD in the other), 2 patients had simultaneous liver metastasis, 1 patient was technically inoperable because of hip joint replacement surgery for tuberculoses arthritis, 1 patient died from neutropenia related with chemotherapy after 24 Gy, and 1 patient developed distant failure immediately after CRT. Total 43 patients with locally advanced rectal cancer (pretreatment clinical stage T3-4NanyM0), including clinically fixed or unresectable tumor, completed the planned preoperative CRT

with subsequent curative surgery. Of 43 patients, 35 patients received radiotherapy with twice-daily (BID) regimen and 8 patients with once a day (QD) regimen. We analyzed the 35 patients who were treated with BID regimen.

Although not the same for all patients, the pretreatment evaluation included complete blood count, chemical test with renal and liver function, carcinoembryonic antigen (CEA) level, digital rectal examination, colonoscopy with/without barium enema, chest radiography, and computed tomography (CT) scan of abdomen and pelvis with/without endoscopic ultrasound. Pretreatment clinical stage was carried out according to TNM stage (AJCC/UICC, 2002)

B. Treatment

1. Preoperative Chemoradiotherapy

The treatment schema is shown in Fig. 1.

Radiation volume encompassed the rectal mass the involved pelvic lymph-node(s) with a margin of 2-3cm in all direction. The inferior border excluded the perineal skin when feasible, on the exceptional cases where the tumor extended close to the anal verge. The posterior border of lateral fields included the sacrum and coccyx.

Radiation therapy of BID-fractionation regimen with split course is following; beginning with twice a day, fraction size 1.5 Gy (n=31) or 1.6

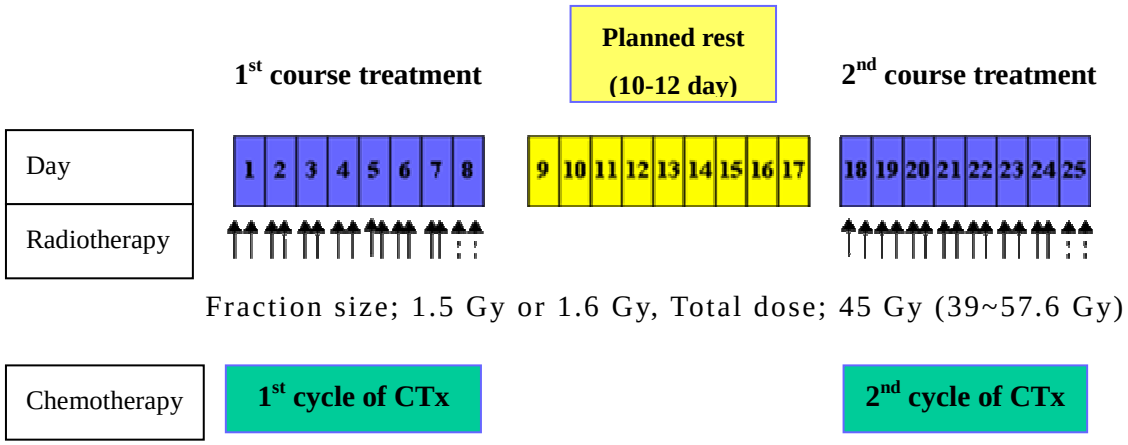

Fig. 1. The schedule of concurrent chemoradiation therapy. Radiation therapy was planned to start concurrently with 1st cycle of chemotherapy and delivered as BID-fractionation regimen with split course. The fraction size of radiation therapy was 1.5 Gy (n=31) or 1.6 Gy (n=4). After the radiotherapy of 7 or 8 days (1st course treatment, 21 Gy ~ 24 Gy), the planned rest period was median 11 days (range, 6-18 days). After then, another 7-8 days of radiotherapy (2nd course treatment) was started with 2nd cycle of chemotherapy and total dose was median 45 Gy. After the completion of radiotherapy, additional cycle of chemotherapy was delivered according to surgeons' judgment, based on tumor respectability by examination.

Gy (n=4), 5 days per week for 7-8 days (1st course treatment), followed by another 7-8 days (2^{nd} course treatment) with the same scheme. Most commonly used total dose was 45 Gy in 14 patients (less than 45 Gy in 11, between 40 Gy and 50 Gy in 10, and more than 50 Gy in 7). Between 1^{st} and 2^{nd} courses treatment, the planned rest period was median 11 days (6-18 days). Overall treatment time, including weekend and rest period, was median 32 days (27-41 days).

Radiation therapy was delivered with 10-MV or 15-MV photons and through three-field (PA/bilateral) or four-field (AP/PA/bilateral) technique. Patients were treated in the prone position using belly board device to exclude the small bowel out of radiation therapy field, whenever possible. Before 2^{nd} course treatment, all patients were evaluated with the CT scan of abdomen and pelvis, and treated with reduced field depending on the reduction of tumor size. At this time, three-dimensional conformal radiotherapy planning was utilized, whenever possible.

All patients received 5-FU based chemotherapy. The 1^{st} cycle of chemotherapy was started with the 1^{st} course of radiotherapy and 2^{nd} cycle of chemotherapy with 2^{nd} course of radiotherapy. The majority of patients received 3 cycles of chemotherapy before surgery, and some received additional chemotherapy according to clinician's judgment (total 3-4 cycles). The most common regimen was FOLFIRI (n=25), and

other regimens included FPL (n=3), FL (n=2), and oral chemotherapeutic agent (capecitabine in 3 and doxifluridine in 1).

The FOLFIRI regimen was administered as follows; irrinotecan 180 mg/m^2 as a 90 minutes infusion on day 1, leucovorin (LV) 200 mg/m^2 during irrinotecan followed by 5-FU bolus 400 mg/m^2 and 22 hours continuous infusion of 600mg/m^2 on day 1 and 2 every 2 weeks. The FL regimen consisted of 5-FU 400 mg/m^2 i.v. bolus and LV 20 mg/m^2 i.v. bolus for 4 days.

2. Surgery

Surgery was planned 3-4 weeks after the completion of chemo-radiotherapy. Total mesorectal excision (TME) was recommended.

3. Postoperative chemotherapy

All patients received 5-FU based postoperative chemotherapy, irrespective of pathologic response. The majority of patients received 3 cycles of FOLFIRI regimen (n=28) and others received FPL (n=1), FP (n=1), and oral chemotherapeutic agent (doxifluridine in 3 and tegafur in 1).

C. Response classification and toxicity criteria

Pathologic complete response (pCR) was defined as no residual

carcinoma on pathologic specimen. It was defined as near complete response (near pCR) when there was only microscopically residual disease with less than 10% of viable cancer (Roof et al, 2006).

Downstaging was documented by a decrease of post-CRT pathologic stage compared with pretreatment clinical stage. T-downstaging and N-downstaging were respectively evaluated and overall downstaging was documented by more than one of T or N-downstaging.

Acute toxicity was graded in accordance with Acute Radiation Morbidity Scoring Criteria proposed by Radiation Therapy Oncology Group (RTOG) and late toxicity with Late Radiation Morbidity Scoring Schema proposed by RTOG/EORTC.

D. Pathologic evaluation

The pathologic stage for each tumor was recorded according to 6th edition of AJCC/UICC TNM classification (Sobin et al, 2002). The R stage was recorded as follows: microscopically free margin was recorded as R0, microscopically involved margin as R1, and macroscopic residual disease or no resection as R2. Pathologic specimens were grossly reviewed in terms of general appearance of specimen, the gross shape (e.i. ulceration or fungating) and size of primary tumor, and the distance between resection margins and primary tumor. In detail, histopathologic type, the depth of invasion, the clearance of resection margin, the

presence or absence of lymphatic and perineural invasion, the number of lymph node examined, the number of lymph node involved, and other abnormalities were evaluated by pathologist.

E. Follow-up

Patients were clinically weekly assessed during treatment for the compliance, general condition, and toxicity. Complete blood count and body weight were also checked. After the completion of treatment, patients were assessed every 3 months for the first 2 years, every 6 years for the next 2 years and annually thereafter, with CT scan of abdomen and pelvis, chest radiography, colonoscopy, and lab study (CEA serum level, complete blood count, electrolyte, and chemistries).

III. RESULTS

Characteristics of patients and tumors are shown in Table 1. Median age was 56 years (range, 38-77 years). The pretreatment clinical stage was T3 in 24 patients, T4 in 11 patients (31%), and positive lymph-node in 23 patients (66%). The majority of tumors were located in distal rectum. The lower margin of primary tumor was within median 3cm from anal verge (25 patients within 5 cm and all within 8 cm). The largest diameter of primary tumor was median 5cm (range, 2.5-14 cm).

The follow up period was median 19 months (range, 5-39 months).

A. Surgery

The median period from the completion of radiotherapy to surgery was 41 days and from the completion of chemotherapy was 32 days.

Surgery was performed in all patients. Two patients were considered unresectable at the time of surgery after CRT and underwent open and closure (O&C) with palliative ileostomy because of lateral extension to the pelvic sidewall and bladder invasion. Thirty-three patients underwent curative surgery with abdominoperineal resection (APR) in 16 patients, low anterior resection (LAR) in 10 patients, and Hartmann's operation in 7 patients. The sphincter preservation was possible in 17 of all 35 patients (49%) and 13 of 30 patients (43%) who could undergo APR

Table 1. Characteristics of patient and tumor.

	No. of patients
Median age	56 years (range, 38-77)
Gender (M:F)	30:5
CEA level	Median 3.9 (0.98-97.7)
WNL	14
abnormal	18
Tumor size (cm)	Median 5 (range, 2.5-14)
<5cm	12
≥5cm	23
Pretreatment TNM stage	
T3N0	10
T3N1	14
T4N0-1	11
Distance of primary tumor from AV	Median 3.5 (range, 0-8)
≤ 5cm	25
6-10cm	10

without preoperative CRT.

B. Pathologic response

There were 4 patients who achieved pCR, accounting for pCR rate of 11% for all 35 patients. The pCR rate was 25% (6 of 24 patients) in T3 disease and 0% in T4 disease. Near pCR was observed in 8 patients (23%): 25% (6 of 24 patients) in T3 disease and 18% (2 of 11 patients) in T4 disease.

Overall downstaging occurred in 25 patients (71%). No change between clinical and pathological stage was observed in 8 patients (23%) and the progression of stage in 2 patients. T-downstaging was seen in 17 patients (49%) and N-downstaging in 15 patients (65%). Final pathology demonstrated T0 in 4 patients (11%), T1 in 1, T2 in 7 (20%), T3 in 18 (51%), and T4 in 5 patients (15%).

Twenty-five patients were node negative with the received specimen. Sixteen patients with clinically positive node before treatment were confirmed with pathologically negative node, pN0 and 16 patients showed no change. One patient had progressive node stage, and node stage in 1 patient was nonassessable although pelvic lymph-node dissection, TME and transabdominal hysterectomy with bilateral salphingoophorectomy (TAH c BSO) were performed due to vaginal invasion of primary tumor.

Table 2. The pathologic response.

	No.of patients	(%)
Complete remission (pCR)	**4**	**11**
Near complete remission (near pCR)	**8**	**23**
Pathologic T-stage		
ypT0	**4**	**11**
ypT1	**1**	**3**
ypT2	**7**	**20**
ypT3	**18**	**51**
ypT4	**5**	**15**
Pathologic N-stage		
ypN0	**25**	**71**
ypN1	**3**	**9**
ypN2	**3**	**18**
ypN3	**1**	**3**
ypNx	**1**	**3**
Resection margin status		
R0	**29**	**83**
R1	**4**	**11**
R2	**2**	**6**

In 33 patients who underwent tumor resection, no patient had no R2 resection and 4 patients (11%) had an R1 resection with closed resection margin at final pathology. Of the 4 patients, 2 had positive deep resection margin and 2 with circumferential resection margin. Two patients each in T3 and T4 disease had an R1 resection, respectively.

C. Toxicity and treatment interruption

Acute toxicities during CRT are summarized in Table 3. Overall severe (grade 3 or higher) toxicity were 20%. Neutropenia was the most common severe toxicity; 4 patients (11%) experienced grade 3 neutropenia. No grade 4 hematologic toxicity occurred. Grade 2 perineal skin reaction occurred in 5 patients (14%) and grade 3 and 4 in each one. Grade 2 acute diarrhea occurred in 6 patients and grade 3 in 1 patients. Grade 2 cystitis occurred in 2 patients, and no grade 3 or 4 cystitis occurred.

The causes and durations of interruption are shown in Table 4. Seven patients required the interruption of radiation therapy due to severe acute toxicity: perineal skin reaction with/without persistent proctitis (3 patients), chemotherapy-related problems (3 patients), and uncontrolled anal abscess (1 patient).

Table 3. Acute toxicities by RTOG criteria.

	Grade			
	2	3	4	5
Hematologic				no death
neutropenia		4		
thrombocytopenia	1	0		
Lower gastrointestinal				
diarrhea	6	1		
Genitourinary				
cystitis	2			
Skin	5	1	1	

Table 4. Causes and durations of treatment interruption

Cause	n	Days
Perineal skin reaction	2	6/1
Perineal skin reaction + persistent proctitis	1	3
Chemotherapy-related problems	3	8/1/3
Anal abscess control problem	1	7

No postoperative complication that required surgical intervention

occurred within 30 days after the initial operation and also until last follow up.

Late toxicities were developed in 2 patients: open perineal wound and fistula in one each patient. No patients developed soft tissue necrosis, ulceration, or bony fracture.

Postoperative mortality was 3 % (1 patient). One died from acute myocardiac infarction on the next day after curative surgery: he had primary tumor within 4 cm from the anal verge and was treated with radiotherapy (45 Gy/30 fractions) and chemotherapy (FOlFIRI regimen, 3cycle), followed by low anterior resection.

IV. DISCUSSION

During the past three decades, the remarkable advance has been made in the management of rectal cancer. Based on the results of large prospective randomized studies (Gastrointestinal Tumor Study Group; 1985, Fisher et al, 1988; Krook et al, 1991; Wolmark et al, 2000; Colorectal Cancer Collaborative Group, 2001), the combined use of radiotherapy and chemotherapy has been recommended as an adjuvant treatment because it is more effective in the reduction of local recurrence and a greater potential for improved survival than postoperative radiotherapy alone (NIH consensus conference, 1990).

In addition, recently, preoperative radiation therapy with chemotherapy has recently been a preferred approach for locally advanced rectal cancer in many institutes and trials. Several potential advantages of preoperative radiotherapy have been identified: 1) downsizing and downstaging effects, consequently resulting in the improvement of pCR, clear resection margin (R0), and local control, 2) the possibility of sphincter preserving surgery in distal rectal cancer, 3) more radiosensitive, probably due to higher oxygen tension prior to surgical compromise of the regional blood vessels, 4) less acute and late toxicity rates due to more mobile of small bowel and less likely inclusion of small bowel within the radiation field prior to surgery, and 5) the reduction of tumor cell spillage during surgery by the sterilization

of tumor cells before surgery. Above mentioned, ideal rationales make preoperative approach more popular, and clinical results also support and accelerate the use of preoperative approach for locally advanced rectal cancer.

Swedish rectal cancer trial made good first step forward for preoperative radiotherapy of resectable rectal cancer (Minsky, 1997). Swedish rectal cancer trial compared short-term preoperative radiation therapy (25 Gy delivered in five fractions in one week) followed by surgery within 1 week (n=553) with surgery alone (n=557) in resectable rectal cancer patients (Swedish rectal cancer trial, 1997). After five years of follow-up, the rate of local recurrence was 11 % in combined radiotherapy group and 27% in surgery alone group ($P<0.001$) and overall five-year survival rate was 58 % and 48% ($P<0.004$), respectively. Because of short overall treatment time and the option of immediate surgery, this concept has now been used frequently in patients with operable carcinoma of the rectum throughout Europe. Nevertheless, major radio- and tumor biological shortcomings among others are short interval between radiation therapy and surgery, which does not allow for significant tumor shrinkage and sphincter preservation in low lying tumors, and the high single dose which may induce more acute and late toxicity has also prompted criticism (Minsky, 1997).

The results of randomized German study (protocol CAO/ARO/AIO-94)

showed improved local control and sphincter-preservation and reduced toxicity in preoperative CRT group, compared with postoperative CRT group (Sauer et al, 2004). After this encouraging result, preoperative CRT has been established as the standard treatment in resectable, locally advanced rectal cancer. And many investigations on preoperative CRT have been done and are still ongoing with novel agents. There has been used various schemes of preoperative radiotherapy with chemotherapy have been used in each institutes and polities. Generally, there are short course scheme (25Gy in 5 fractions) and conventional scheme in radiation therapy. Preoperative clinical trials based on TME have recently been reported.

Among short course schemes, one is the above mentioned Swedish rectal cancer trial and the other is Dutch trial (Kapiteijn et al, 2001). Differing from the Swedish trial, TME in Dutch trial was standardized and all underwent TME. Patients with resectable rectal cancer were randomly assigned either to preoperative radiotherapy with TME (n=924) or TME alone (n=937). The overall survival rate at two years was similar in two groups (82% vs 81.8%, p=0.84), whereas the rate of local recurrence at two years was 2.4% in combined group and 8.2% in TME alone (P<0.001). Patients in combined group lost slightly more blood during operation (p<0.001) and had more perineal complication (p=0.05) than in TME alone.

The European Organization for Research and Treatment of Cancer (EORCT) 22921 trial (Bosset et al, 2006) compared preoperative RT (45 Gy in 25 fractions with 5.4 Gy boost) with preoperative CRT (45 Gy in 25 fractions). With median 5.4 years of follow up period, the rate of local recurrence at 5 years were 8% in preoperative CRT group (n=506), whereas 13% in preoperative RT group (n=505). There was no significant difference between two groups on 5 years overall survival rate with 64.8% in preoperative RT group and 65.8 % in preoperative CRT group (p=0.84). In EORTC 22921 trial using limited radiation field, pCR rate was 13.7% (Bosset et al, 2005). This rate is not different compared with CRT with standard field.

The application of limited field in preoperative treatment seems to be reasonable since the 5 years local failure rate was reduced from 30% to 4% after TME was done (Bosset et al, 2005). Preoperative radiation therapy using limited volume showed comparable response rate and lesser toxicities. Although longer follow-up is needed to confirm the impact on the local control and survival, many institutes including ours have used limited volume since favorable results of TME have been reported. It is quite possible that high dose could be delivered to limited volume by technique with intensity modulated radiotherapy (IMRT).

Because locoregional failures commonly occurred in the low pelvic and presacral region, high dose radiation should be considered to be

given to that lesion, especially in patients at high risk of locoregional failure (Yu et al, 2008). Recently, molecular imaging using tracer (e.i., ^{18}F-fluoromisonidazole (^{18}F-FMISO)) has been used in assessment of hypoxic or radioresistant regions. ^{18}F-FMISO PET scanning may help localize the boost field, where probably benefit from more intense or higher doses of radiation in high risk patients. With combination of hypoxic image, IMRT could possibly give higher dose to the boost field and improve the local control without increment of side effects.

High radiation dose is an independent factor to affect pCR. Sanghera et al. updated factors affecting pathologic response, based on 4732 patients treated with preoperative CRT in prospective phase II and phase III trials (Sanghera et al, 2008). Significant factors associated with pCR were the use of two drugs, infusional administration of 5-flurouracil, and radiotherapy dose of 45 Gy and above. The adjusted mean pCR rate in lesser than 45Gy was 0.09 compared with 0.20 (95% confidence interval, 0.10-0.31) in more than 55 Gy (P=0.02). Mohiuddin et al. reported the correlation between higher dose of radiation and the likelihood of achieving pCR. pCR rate was observed in 44% of patients who received radiation dose ≥55 Gy as compared to 13% of patients treated with a dose ≤50 Gy (p=0.05) (Mohiuddin et al, 2000)

Several studies reported significant correlations between downstaging after preoperative CRT and the improvement of local control and overall

survival. Mohiuddin et al reported that 5 year overall survival was 100% for ypT0–2N0 compared with 80% for ypT3–4N0 and 73% for pTxN1–2 (Mohiuddin et al, 2000). Tsujinaka et al showed that there were benefits of 5 year survival rate (79.5%, p=0.015) and 5 year local recurrence-free rate (100%, p=0.034) in responders after preoperative radiotherapy for locally advanced low rectal cancer (Tsujinaka et al, 2008). Longer follow up is needed to demonstrate whether patient with pathologic complete response had favorable outcome.

In addition to short course and conventional schemes as modality of preoperative radiotherapy in locally advanced rectal cancer, preoperative hyperfractionated accelerated radiotherapy (HART) has been proposed to improve the local control by avoidance of delaying between two modalities, based on the feasibility of trial 89-01 (post-op HART; 48 Gy in 3 weeks) (Coucke et al, 1993). In 91-01 trial (Coucke et al, 1995), preoperative HART (41.6 Gy in 2.5 weeks) followed by immediate surgery was feasible with lower acute toxicity, compared to postoperative HART.

Accelerated repopulation reduces local control, especially in rapid proliferating tumors, and the prolongation of overall treatment time (OT) is related with poor outcome. Therefore, accelerated hyperfractionation scheme could improve local control by the compensation of repopulating tumor cells and the shortening of OT. To enhance the tolerance,

radiotherapy in this study was delivered in split course with planned rest period of about 10-12 days. Fowler suggested that treatment outcome is better when larger numbers of smaller fractions are used with a selected OT **(**Fowler, 1990). In this study, we suggest that because larger numbers of smaller fractions were delivered without the prolongation of OT compared with conventional scheme, local control in this scheme may be not bad than conventional scheme.

In this study, there were 4 patients (11.4%) who achieved pCR. pCR rate in this study is smaller than 10-30% in other studies. This may be due to tumor volume. Studies on pretreatment T4 tumor in less than 20% showed over 20% of pCR rates. In Radiation Therapy Oncology Group (RTOG) Trial 0012 (Mohiuddin et al, 2006), pCR rate after preoperative CRT was 33% in pretreatment T3 tumor, whereas 18% in pretreatment T4 tumor. If concerning that in this study some had fixed or tethered rectal mass, pretreatment T4 tumor were 31%, or oral chemotherapeutic agent occupied high proportion (20%), our results may be considered to comparable.

In spite of acute toxicity, BID protocol with split course in our present study had a few interruptions of RT, no reduction of radiation dose, and no discontinuation. Furthermore severe late toxicities were found in only two patients; delayed perineal wound healing and fistula, respectively.

For preoperative treatment, there is the risk of overtreatment of early

stage tumors. Therefore, accurate pretreatment staging is not only indispensable to avoid unnecessary preoperative multimodal treatment in early stage rectal cancer, but also to identify locally advanced disease. Although judicious application of technologies, including CT/MRI and EUS, and the advance of innovative techniques, including 3D-endosonoscophy, may further improve accuracy of staging, cautions are needed to decide whether patients should be treated with preoperative modality.

V. CONCLUSION

BID radiation therapy with concurrent 5-FU based chemotherapy had comparable treatment outcome and less acute toxicities and tolerable. Therefore, this treatment protocol could be considered to be a tolerable alternative in patients with locally advanced rectal cancer.

Studies with large number of patients are warranted to confirm the increasing of tolerability without the interruption of radiotherapy, and possibly to enhance the tumor shrinkage in advanced rectal cancer.

REFERENCES

1. Bosset JF, Calais G, Mineur L, Maingon P, Radosevic-Jelic L, Daban A, Bardet E, Beny A, Briffaux A, Collette L: Enhanced tumorocidal effect of chemotherapy with preoperative radiotherapy for rectal cancer: preliminary results--EORTC 22921. *J Clin Oncol* 23:5620-5627, 2005

2. Bosset JF, Related Articles, LinksBosset JF, Collette L, Calais G, Mineur L, Maingon P, Radosevic-Jelic L, Daban A, Bardet E, Beny A, Ollier JC: Chemotherapy with preoperative radiotherapy in rectal cancer. *N Engl J Med* 355:1114-1123, 2006

3. Colorectal Cancer Collaborative Group: Adjuvant radiotherapy for rectal cancer: a systematic overview of 8,507 patients from 22 randomised trials. *Lancet* 358:1291-1304, 2001

4. Coucke PA, Cuttat JF, Mirimanoff RO: Adjuvant postoperative accelerated hyperfractionated radiotherapy in rectal cancer: a feasibility study. *Int J Radiat Oncol Biol Phys* 15:885-9, 1993

5. Coucke PA, Sartorelli B, Cuttat JF, Jeanneret W, Gillet M, Mirimanoff RO: The rationale to switch from postoperative hyperfractionated accelerated radiotherapy to preoperative hyperfractionated accelerated radiotherapy in rectal cancer. *Int J Radiat Oncol Biol Phys* 30:181-8, 1995

6. Fisher B, Wolmark N, Rockette H, Redmond C, Deutsch M, Wickerham DL, Fisher ER, Caplan R, Jones J, Lerner H, et al.: Postoperative adjuvant chemotherapy or radiation therapy for rectal cancer: results from NSABP protocol R-01. *J Natl Cancer Inst* 80:21-29, 1988

7. Fowler JF: How worthwhile are short schedules in radiotherapy? A series of exploratory calculations. *Radiother Oncol* 18:165-81, 1990

8. Gastrointestinal Tumor Study Group: Prolongation of the disease-free interval in surgically treated rectal carcinoma. *N Engl J Med* 312:1465-1472, 1985

9. Kapiteijn E, Marijnen CA, Nagtegaal ID, Putter H, Steup WH, Wiggers T, Rutten HJ, Pahlman L, Glimelius B, van Krieken JH, Leer JW, van de Velde CJ: Preoperative radiotherapy combined with total mesorectal excision for resectable rectal cancer. *N Engl J Med* 345:638-646, 2001

10. Krook JE, Moertel CG, Gunderson LL, Wieand HS, Collins RT, Beart RW, Kubista TP, Poon MA, Meyers WC, Mailliard JA: Effective surgical adjuvant therapy for high-risk rectal carcinoma. *N Engl J Med* 324:709-715, 1991

11. Minsky BD: Adjuvant therapy for rectal cancer--a good first step. *N Engl J Med* 336:1016-1017, 1997

12. Mohiuddin M, Hayne M, Regine WF, Hanna N, Hagihara PF, McGrath P, Marks GM: Prognostic significance of postchemoradiation stage following preoperative chemotherapy and radiation for advanced/recurrent rectal cancers. *Int J Radiat Oncol Biol Phys* 48:1075-1080, 2000

13. Mohiuddin M, Regine WF, John WJ, Hagihara PF, McGrath PC, Kenady DE, Marks G: Preoperative chemoradiation in fixed distal rectal cancer: dose time factors for pathological complete response. *Int J Radiat Oncol Biol Phys* 46:883-888, 2000

14. Mohiuddin M, Winter K, Mitchell E, Hanna N, Yuen A, Nichols C, Shane R, Hayostek C, Willett C: Randomized phase II study of neoadjuvant combined-modality chemoradiation for distal rectal cancer: Radiation Therapy Oncology Group Trial 0012. *J Clin Oncol* 24:650-655, 2006

15. NIH consensus conference. Adjuvant therapy for patients with colon and rectal cancer. *Jama* 264:1444-1450, 1990

16. Roof KS, Coen J, Lynch TJ, Wright C, Fidias P, Willett CG, Choi NC: Concurrent cisplatin, 5-FU, paclitaxel, and radiation therapy in patients with locally advanced esophageal cancer. *Int J Radiat Oncol Biol Phys* 65:1120-1128, 2006

17. Rosen LS, Bilchik AJ, Beart RW Jr, Benson AB 3rd, Chang KJ, Compton CC,Grothey A, Haller DG, Ko CY, Lynch PM, Nelson H, Stamos MJ, Turner RR, Willett CG: New approaches to assessing and treating early-stage colon and rectal cancer: summary statement from 2007 Santa Monica Conference. *Clin Cancer Res* 13:6853s-6856s, 2007

18. Sanghera P, Wong DW, McConkey CC, Geh JI, Hartley A: Chemoradiotherapy for rectal cancer: an updated analysis of factors affecting pathological response. *Clin Oncol (R Coll Radiol)* 20:176-183, 2008

19. Sauer R, Becker H, Hohenberger W, Rödel C, Wittekind C, Fietkau R, Martus P, Tschmelitsch J, Hager E, Hess CF, Karstens JH, Liersch T, Schmidberger H, Raab R: Preoperative versus postoperative chemoradiotherapy for rectal cancer. *N Engl J Med* 351:1731-1740, 2004

20. Sobin LH, Wittenkind CH: International Union Against Cancer. TNM calssification of malignant tumors. 6th ed. New York: Wiley-Liss, 2002

21. Swedish Rectal Cancer Trial: Improved survival with preoperative radiotherapy in resectable rectal cancer. *N Engl J Med* 336:980-987, 1997

22. Tsujinaka S, Kawamura YJ, Konishi F, Aihara H, Maeda T, Mizokami K: Long-term efficacy of preoperative radiotherapy for locally advanced low rectal cancer. *Int J Colorectal Dis* 23:67-76, 2008

23. Willett CG, Czito BG, Bendell JC: Radiation therapy in stage II and III rectal cancer. *Clin Cancer Res* 13:6903s-6908s, 2007

24. Wolmark N, Wieand HS, Hyams DM, Colangelo L, Dimitrov NV, Romond EH, Wexler M, Prager D, Cruz AB Jr, Gordon PH, Petrelli NJ, Deutsch M, Mamounas E, Wickerham DL, Fisher ER, Rockette H, Fisher B: Randomized trial of postoperative adjuvant chemotherapy with or without radiotherapy for carcinoma of the rectum: National Surgical Adjuvant Breast and Bowel Project Protocol R-02. *J Natl Cancer Inst* 92:388-396, 2000

25. Yu TK, Bhosale PR, Crane CH, Iyer RB, Skibber JM, Rodriguez-Bigas MA, Feig BW, Chang GJ, Eng C, Wolff RA, Janjan NA, Delclos ME, Krishnan S, Das P: Patterns of locoregional recurrence after surgery and radiotherapy or chemoradiation for rectal cancer. *Int J Radiat Oncol Biol Phys* 15 :1175-1180, 2008.

- 국문요약-

국소진행성 직장암 환자의 술 전 병용 항암 : BID 방사선요법

아주대학교 대학원의학과

이선영

(지도교수: 전미선)

연구목적: 국소진행성 직장암 환자의 병용 항암요법의 치료효과, 순응도 및 부작용을 알아보고자 한다.

재료 및 방법: 2001 년 1 월부터 2007 년 12 월까지 국소진행성 직장암으로 술전 방사선치료를 시행한 환자 35 명을 대상으로 분석하였다. 모든 환자는 5-FU 를 기본으로 하는 항암치료를 받았으며, 주로 사용된 항암제는 FOLFIRI (n=25)이였고, 대부분의 환자에서 방사선치료 중 총 3 차례가 시행되었다. 방사선치료는 다음과 같이 시행되었다: 일회에 1.5 Gy 씩 하루에 두 차례 첫 항암치료와 함께 21-24 Gy 시행되었고, 10-12 일간의 쉬는 기간 후에, 같은 방식으로 2 번째 항암치료와 함께 21-24 Gy 의 방사선이 조사되었다.

결과: 중앙추적관찰 기간은 19 개월 (5-36)이었다. 모두가 T3 (n=25) 혹은 T4 (n=10)이였고 가장 큰 종양의 지름은 중앙값 5cm (2.5-14cm)이었다. 총 병기감소는 71%이였고, 병리적 완전 관해율은 11% (n=4), 거의 완전 관해율 23% (10% 미만의 세포가 살아있는 현미경적 국소잔류종양) (n=8),

부분관해 60% (n=21)이였다. 2 명은 수술이 불가능하였다. 괄약근 보전 술식은 하부직장암인 30 명중 43%에서 가능하였다.

7 명 (20%)이 1~7 일간 다음과 같은 이유로 방사선치료를 쉬었다: 회음부 피부 부작용 3 명, 항암치료 부작용 3 명, 항문농양 1 명. 7 명만 (20%) 심한급성 부작용을 경험하였다 (4 명에서 등급 3 중성구 감소, 2 명에서 각각 등급 3, 등급 4 회음부 피부 부작용, 1 명에서 등급 3 직장염). 두 명은 각각 개방성 회음부 상처 지연과 직장 질 누공로 지연 부작용을 경험하였다

결론: 본 논문에서 국소진행성 직장암에서 술 전 BID 방사선치료와 동시에 항암 화학 요법 시 34%의 완전 및 거의 완전 관해율을 얻었다. 이 치료방법은 비슷한 치료효과를 갖고 더 좋은 순응도로 국소진행성 직장암 환자에서 술 전 요법으로 시행 될 수 있을 것으로 생각된다.

핵심어: 직장암, 술 전, 동시 항암 화학 방사선치료