Pre-operative Radiochemotherapy with Raltitrexed for Resectable Locally-advanced Rectal Cancer: A Phase II Study*

MARIA CRISTINA LEONARDI[1], MARIA GIULIA ZAMPINO[2], FABRIZIO LUCA[3], BARBARA ALICJA JERECZEK-FOSSA[1], ELENA PETAZZI[1], BRUNILDA TATANI[3], ROBERTA LAZZARI[1], ROBERTO BIFFI[3], KATIA LORIZZO[2], ELENA MAGNI[2], DIEGO SCANNIFFIO[2], FRANCO ORSI[4], GUIDO BONOMO[4], GIUSEPPE PETRALIA[4], CRISTINA TROVATO[5], CRISTIANO CROSTA[5], BRUNO ANDREONI[3,6] and ROBERTO ORECCHIA[1,6]

Divisions of [1]Radiation Oncology, [2]Medical Oncology, [3]General Surgery, [4]Radiology and [5]Endoscopy, European Institute of Oncology, Milan; [6]University of Milan, Milan, Italy

Abstract. *Background: The aim of the study was to evaluate the response to and toxicity of pre-operative radiochemotherapy containing raltitrexed (Tomudex) for resectable rectal adenocarcinoma. Patients and Methods: From November 2000 to June 2002, 18 consecutive patients staged T3 N0/N+ were treated with pre-operative chemotherapy (3 mg/m^2 of raltitrexed on days 1, 19, 38) and concurrent radiotherapy (RT) (50.4 Gy) in 6 weeks, followed by radical surgery within 8 weeks. Results: The treatment compliance was high. No major acute toxicity was reported. Concerning late toxicity, genitourinary adverse effects were prevalent. A complete response was observed in one patient (6%), partial response in eight (47%), stable disease in seven (41%) and progression in one case. Three-year actuarial disease-free and overall survival rates were 37% and 87.5%, respectively. Conclusion: Raltitrexed did not increase the pathological response rate compared with the rates obtained with use of preoperative RT alone and reported in the literature. Acute morbidity was low and acceptable, while late toxicity was considerable, prevalently concerning sexual dysfunction and urinary complications.*

Rectal carcinoma is one of the most common cancers in the United States and in Western Europe (1, 2). Local recurrence after radical surgery is the major threat, occurring in 15% to 30% of patients and resulting in therapeutic failure and death (3). Randomized trials have shown better results in terms of local control and survival in patients treated with postoperative radiochemotherapy when compared to surgery alone. However, such an approach is correlated to significant acute and chronic morbidity and may reduce the overall compliance to treatment (4-7). In randomized studies of pre-operative radiotherapy (RT) alone, promising results with manageable toxicity were reported (8, 9). The addition of chemotherapy in a neo-adjuvant setting should bring some further advantages, based on the ability to act as an enhancer of the RT response. Currently, new chemotherapeutic agents are under investigation. In the present study, raltitrexed, a quinazoline folate analog that acts as a specific thymidylate synthase inhibitor and as a radiation sensitizer, was administered for three cycles concomitantly with pre-operative RT. This drug does not require the positioning of a central catheter and has a long terminal half-life (260 hours) (10). The aim of this phase II trial was to evaluate the toxicity and response to treatment in patients with clinically resectable locally-advanced rectal cancer.

Patients and Methods

Patients with resectable histologically-proven locally advanced rectal adenocarcinoma were eligible for this study. The clinical staging work-up consisted of computed tomography (CT) of abdomen and pelvis, chest X-ray or CT, routine blood tests, complete colonoscopy, endoscopic ultrasonography (EUS) and rectal examination. Hematological, renal and liver toxicities were graded by the National Cancer Institute Common Toxicity Criteria (NCI-CTC) (11). Toxicity of the gastrointestinal tract, genitourinary tract and skin were graded on the base of the Radiation Therapy Oncology Group (RTOG) scale (12). Late toxicity, registered 6 months after the completion of the neo-adjuvant radiotherapy and on every follow-up visit, was evaluated based on the Subjective Objective Management Analytic Late Effect of Normal Tissue (SOMA/LENT) criteria (13). Tumor

* The authors are members of the Digestive Tumors Task Force of the European Institute of Oncology and participated in the design, execution and data analysis of this trial.

Correspondence to: Maria Cristina Leonardi, Division of Radiation Oncology, European Institute of Oncology, Via Ripamonti 435, 20141, Milan, Italy. Tel: 0039 02 57489037, Fax: 0039 02 57489036, e-mail: cristina.leonardi@ieo.it

Key Words: Raltitrexed, neoadjuvant chemoradiotherapy, rectal carcinoma.

response was assessed according to the World Health Organization (WHO) criteria (14). Down-staging was defined as any reduction of stage between the clinical and pathological stage.

Pre-operative treatment protocol. Pre-operative radiotherapy was delivered using a high-energy linear accelerator (15 MV). All patients received 45 Gy in 25 fractions over 5 weeks to the whole pelvis followed by a boost dose of 5.4 Gy in three fractions to the tumor mass with a 2-3 cm margin, at 1.8 Gy per fraction (up to the total dose of 50.4 Gy). The whole pelvis was treated with four-field technique, while the boost area was irradiated in the majority of patients with posterior-anterior and two lateral fields (three-field technique). Customized blocking, an immobilization system and hypogastric compressor were used in all cases. Concurrent chemotherapy using raltitrexed at 3 mg/m^2 was administered as a short *i.v.* infusion for about 15 min on days 1, 19 and 38 (3 cycles). Six weeks after the end of RT, clinical and radiological assessments (chest X-ray/CT, abdomen and pelvis CT and EUS) were performed. Surgical resection was undertaken within 8 weeks from completion of the pre-operative RT to allow patient recovery and maximum tumor shrinkage.

Statistical analysis. This phase II trial was planned as two-stage trial taking into account treatment response. The initial sample size comprised 35 patients and an interim analysis was fixed for the first 18 cases. The aim was to achieve at least a 10% pathological complete response rate.

Disease-free and overall survival were calculated from the date of surgery and assessed with the Kaplan-Meier methodology. The response rate and toxicity were calculated as a simple ratio.

Results

From November 2000 to June 2002, 18 consecutive patients entered the present clinical trial. The sociodemographic and clinical patient characteristics are shown in Table I.

Table I. *Patient characteristics.*

Characteristic	No. of patients
Median age, years (range)	62.5 (40-72)
Gender	
Male	13
Female	5
Performance status (ECOG)	
0	5
1	13
TNM staging at diagnosis	
cT3N0	11
cT3N+	7
Grading	
2	8
3	1
unknown	9

Treatment compliance. All but three out of the 18 patients completed the planned three cycles of chemotherapy: one patient refused the third cycle, two patients received only two cycles due to transaminitis. The raltitrexed dose was reduced by 25% in four patients and in one patient in the second and third cycles, respectively. A 50% reduction was made in one patient in the second and third cycles and in one patient in the third cycle, due mainly to transaminitis. None of the patients experienced grade 4 toxicity. There was no delay of cycles. All patients received the prescribed radiation dose and in four cases a short interruption of less than a week was necessary. Post-operatively, all patients but three (one refusal, one anasthomotic leakage, one complete pathological response) received chemotherapy with adjuvant intent of fluorouracil modulated by folinic acid.

Surgery. After a median of 58 days from radiotherapy, 17 patients underwent surgery, while one patient refused. Twelve patients underwent anterior resection of the rectum (RAR) and the remaining five had abdomino-perineal rectum resection (Miles'procedure). Distal and radial margins were negative in all patients. In two cases, one liver localization was detected intra-operatively and was radically resected. Total mesorectal excision was routinely performed. The median number of the examined lymph nodes was eleven (range 3-23), while the number of metastatic lymph nodes varied from zero to five (median of 0.75). The median length of the surgery and of the hospital stay was 215 min (range 95-360) and 13 days (range 11-30), respectively. Out of the 17 operated patients, six (35%) developed complications related to the surgery but were treated conservatively: two anasthomotic leakages, four wound infections managed with drainage and antibiotics. No post-operative deaths occurred.

Toxicity. Acute toxicity was monitored weekly during treatment. There was no severe toxicity and no patient required hospital admission because of acute reactions. The incidence of acute and chronic toxicities is shown in Tables II and III, respectively.

Response evaluation. Upon pathological examination, one patient (6%) showed a complete pathological response (ypT0). A partial pathological response was achieved in eight patients (47%) (two ypT1 and six ypT2). Seven additional patients (41%) had stable disease. One patient (6%) developed disease progression (ypT4). Overall, tumor down-staging occurred in 53% of the patients (9/17). With regard to lymph node down-staging, out of the seven patients with ultrasound-staged nodal positive disease, three had no pathological evidence of nodal involvement after radiochemotherapy.

Local control and survival. The median follow-up was 37 months (range 28-49). Overall, twelve (71%) out of the 17

Table II. *Acute toxicity.*

Acute toxicity (n=18)	G1/G2 n (%)	G3 n (%)	G4 n (%)
Transaminitis	8 (44%)	6 (33%)	-
Leukopenia	2 (11%)	1 (5.5%)	-
Anemia	3 (17%)	-	-
Asthenia	2 (11%)	-	-
Increased creatinine level	1 (5.5%)	-	-
Diarrhea	9 (50%)	1 (5.5%)	-
Tenesmus	7 (39%)	-	-
Rectal mucosal loss	1 (5.5%)	-	-
Abdominal pain	3 (17%)	-	-
Nausea/vomiting	2 (11%)	-	-
Dysuria	4 (22%)	-	-
Urinary frequency	3 (17%)	-	-
Urinary urgency	1 (5.5%)	-	-
Dermatitis	9 (50%)	3 (17%)	-

Table III. *Chronic toxicity.*

Chronic toxicity (n=17)	G1/G2 n (%)	G3 n (%)	G4 n (%)
Urinary frequency	-	1 (6%)	2 (12%)
Urinary incontinence	1 (6%)	-	2 (12%)
Decreased urinary stream	3 (18%)	-	-
Rectal mucosal loss*	1 (8%)	1 (8%)	-
Stool frequency*	7 (58%)	1(8%)	-
Sphincter control*	2 (17%)	-	-
Erectile dysfunction**	2 (17%)	1 (8%)	5 (42%)
Ejaculation dryness**	-	-	1 (8%)
Skin hypersensibility	3 (18%)	-	-
Perineal pain	2 (12%)	1 (6%)	-

*Toxicity rate evaluated in patients who underwent anterior resection of the rectum (12/17).
**Toxicity rate calculated in male patients (12/17).

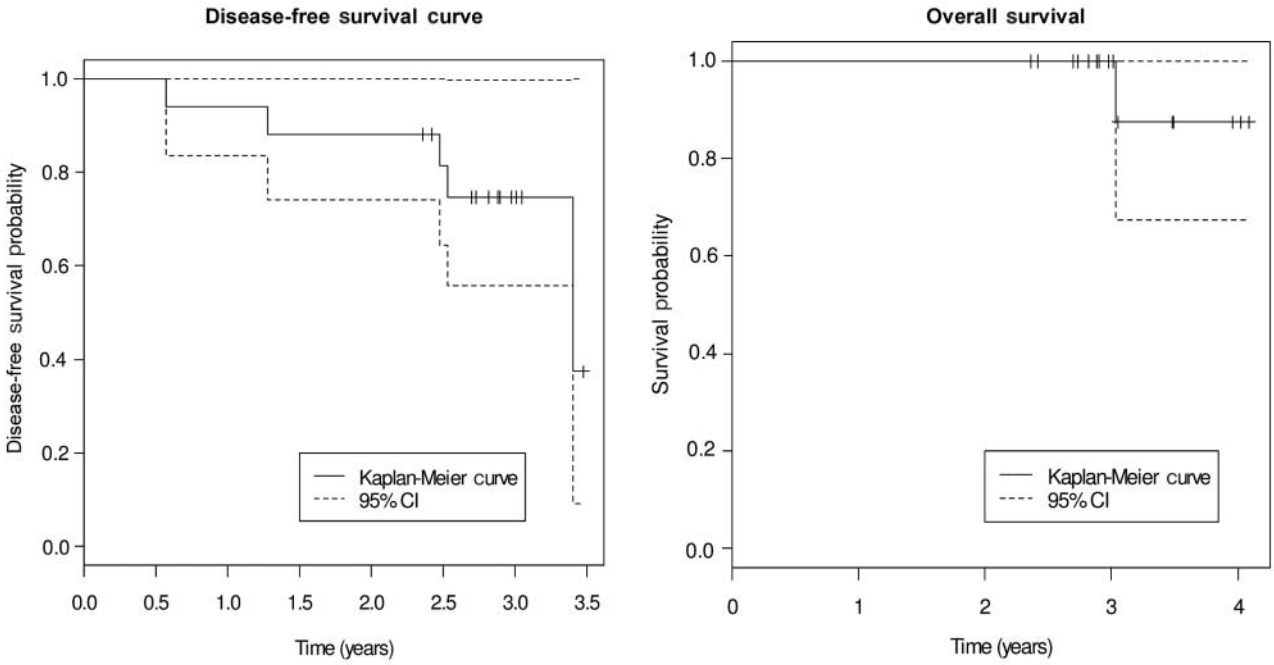

Figure 1. *Three-year actuarial disease-free survival (left) and overall survival (right) among all patients.*

patients who completed the whole treatment were alive and disease-free at last contact. Five patients developed recurrent disease (in one case pelvic lymph nodes and in four distant failure) and one of them died due to lung metastasis. For all patients, the actuarial disease-free survival rate at 3.4 years from surgery was 37% (95% CI, 0.09-1.0), while the actuarial overall survival rate was 87.5% (95% CI, 0.673-1.0) (Figure 1).

Discussion

For rectal cancer, the primary end-points of chemoradiotherapy are local control and survival (15-17). Taking into account the quality of life of the patients, down-staging, tumor resectability and sphincter preservation are not less important objectives. The rationale of pre-operative chemoradiotherapy is based on the assumption that it

should be as effective as in the post-operative setting but less toxic (18, 19). For rectal cancer, the most common drug used in combination with RT is fluorouracil, either in the adjuvant or neo-adjuvant setting but, due to its short half-life (8 min), a continuous infusion became necessary in order to obtain response and to report good tolerance (20, 21). With the aim of reducing the disadvantages of the venous central catheter, new chemotherapeutic agents, such as capecitabine, oxaliplatin, tegafur and raltitrexed, are currently under investigation (22-25). Previous phase I and II trials supporting the use of raltitrexed not exceeding 3 mg/m^2 in association with RT have been conducted in several institutions with promising results in terms of down-staging and toxicity (26-28).

In our phase II trial, only one complete pathological response, corresponding to 6%, was observed. This compares unfavorably with the published rates in chemoradiotherapy series that range from 10 to 35% (29-31). Globally, tumor down-staging was observed in nine out of 17 evaluable patients, corresponding to 53%. This value is low compared to the other series (32). Moreover, the incidence of partial response is very similar to the stable disease rate (47% *vs.* 41%). Overall compliance to the combined treatment was high. Fifteen out of 18 patients completed the planned chemotherapy: the major dose-limiting toxicity was benign transaminitis. The radiotherapy compliance was very high; all 18 patients completed the entire treatment without significant interruptions. Acute toxicity can be considered acceptable: less than 20% of patients developed grade 3 skin toxicity due to irradiation of the perineal plane and the incidence of the grade 3 gastrointestinal toxicity was about 5%.

As far as late toxicity is concerned, the incidence of grade 3 toxicity was limited, while grade 4 toxicity was significantly high, especially for the genitourinary tract and sexual function. Such high rates are impressive and can have both surgery- and radiochemotherapy-related etiology. Most patients suffered from urinary dysfunctions, but only males complained about sexual problems (five patients had grade 4 impotence). The data on the long-term morbidity show that short-course pre-operative radiotherapy has an adverse effect on sexual activity and function for both male and female patients (33, 34). The median duration of the surgery (215 min) was not influenced by the neo-adjuvant treatment, but the surgeons encountered more difficulties in dissecting the mesorectum because of the initial fibrosis. In our series, the post-operative complication rate compared favorably with those observed in other institutions. The clinical management was easy and did not require prolonged hospitalization. There was no post-operative mortality.

In conclusion, the feasibility and low acute toxicity of pre-operative radiochemotherapy containing ratiltrexed were indicated. However, the low response rate and relatively high incidence of late toxicity call for new studies that focus on the integration of novel agents expressing radio-sensitizing or anti-angiogenic properties with altered fractionation and/or dose-escalation radiotherapy schedules.

References

1 Fernandez E, Bosetti C, La Vecchia C, Levi F, Fioretti F and Negri E: Sex differences in colorectal cancer mortality in Europe, 1955-1996. Eur J Cancer Prev *10(3)*: 299-300, 2001.

2 Negri E, La Vecchia C and Recarli A: Cancer mortality in Italy, 1998. Tumori *88*: 89-94, 2002.

3 Minsky BD: The role of radiation therapy in rectal cancer. Semin Oncol *24*: S18-25, S18-29, 1997.

4 Bosset JF and Horiot JC: Adjuvant treatment in the curative management of rectal cancer: a critical review of the results of clinical randomised trials. Eur Cancer *29A*: 770-774, 1993.

5 Sauer R: Adjuvant and neoadjuvant radiotherapy and concurrent radiochemotherapy for rectal cancer. Pathol Oncol Res *8*: 7-17, 2002.

6 Thomas PR and Lindblad AS: Adjuvant postoperative radiotherapy and chemotherapy in rectal carcinoma: a review of the Gastrointestinal Tumor Study Group experience. Radiother Oncol *13(4)*: 245-252, 1988.

7 Fietkau R and Rodel C: Postoperative radiochemotherapy of rectal carcinoma reduces the incidence of locoregional recurrences but does not improve the prognosis of patients – the results of a randomised study of the NSABP-R02. National Surgical Adjuvant Breast and Bowel Project Protocol. Strahlenther Onkol *176*: 381-382, 2000.

8 Swedish Rectal Cancer Trial: Improved survival with preoperative radiotherapy in resectable rectal cancer. N Engl J Med *336*: 970-977, 1997.

9 Dahlberg M, Glimelius B, Graf W and Pahlman L: Preoperative irradiation affects functional results after surgery for rectal cancer (results from a randomised study). Dis Colon Rectum *41*: 543-551, 1998.

10 Clarke SJ, Beale PJ and Rivory LP: Clinical and preclinical pharmacokinetics of raltitrexed. Clin Pharmacokinet *39(6)*: 429-443, 2000.

11 Arbuck SG, Ivy SP and Setser A: The revised Common Toxicity Criteria: version 2.0. Cancer Therapy Evaluation Program (CTEP website), 1999.

12 Cox JD, Stetz J and Pajak TF: Toxicity criteria of the Radiation Therapy Oncology Group (RTOG) and the European Organization for Research and Treatment of Cancer (EORTC). Int J Radiat Oncol Biol Phys *31*: 1341-1346, 1995.

13 Pavj J-J, Denekamp J, Letschert J, Littbrand B, Mornex F, Bernier J, Gonzales-Gonzales D, Horiot J-C, Bolla M and Bartelink H: Late effects toxicity scoring: the SOMA scale. EORTC Late Effects Working Group. Radiother Oncol *35*: 11-15, 1995.

14 WHO Handbook for Reporting Results for Cancer Treatment: Tumor response criteria World Health Organization (WHO). World Health Organization offset publication no. 48, Geneva, Switzerland, 1979.

15 Stryker S, Kiel K, Rademaker A, Shaw J, Ujiki G and Poticha S: Preoperative "chemoradiation" for stages II and III rectal carcinoma. Arch Surg *131*: 514-519, 1996.

16 Rullier E, Goffre B, Bonnel C, Zerbib F, Caudry M and Saric J: Preoperative radiochemotherapy and sphincter-saving resection for T3 carcinomas of the lower third of the rectum. Ann Surg *234*: 633-640, 2001.
17 Brown CL, Ternent CH, Thorson AG, Christensen MA, Blatchford GJ, Shashidharan M and Haynatzki GR: Response to preoperative chemoradiation in stage II and III rectal cancer. Dis Colon Rectum *46*: 1189-1193, 2003.
18 Sauer R, Fietkau R, Wittekind C, Rodel C, Martus P, Hohenberger W, Tschmelitsch J, Sabitzer H, Karstens JH, Becker H, Hess C and Raab R: Adjuvant *vs.* neoadjuvant radiochemotherapy for locally advanced rectal cancer: the German trial CAO/ARO/AIO-94. Colorectal Dis *5(5)*: 406-415, 2003.
19 Bosset JF, Calais G, Daban A, Berger C, Radosevic-Jelic L, Maingon P, Bardet E, Pierart M and Briffaux A: Preoperative chemoradiotherapy *versus* preoperative radiotherapy in rectal cancer patients: assessment of acute toxicity and treatment compliance. Report of the 22921 randomised trial conducted by the EORTC Radiotherapy Group. Eur J Cancer *40(2)*: 219-224, 2004.
20 Crane CH, Skibber JM, Birnbaum EH, Feig BW, Singh AK, Delclos ME, Lin EH, Fleshman JW, Thames HD, Kodner IJ, Lockett MA, Picus J, Phan T, Chandra A, Janjan NA, Read TE and Myerson RJ: The addition of continuous infusion 5-FU to preoperative radiation therapy increases tumor response, leading to increased sphincter preservation in locally advanced rectal cancer. Int J Radiat Oncol Biol Phys *57*: 84-89, 2003.
21 Rich TA: Irradiation plus 5-Fluorouracil: cellular mechanisms of action and treatment schedules. Semin Radiat Oncol *7(4)*: 267-273, 1997.
22 Corvò R, Pastrone I, Scolaro T, Marcenaro M, Berretta L and Chiara S: Radiotherapy and oral Capecitabine in the preoperative treatment of patients with rectal cancer: rationale, preliminary results and perspectives. Tumori *89*: 361-367, 2003.
23 Dunst J, Reese T, Sutter T, Zuhlke H, Hinke A, Kolling-Schlebusch K and Frings S: Phase I trial evaluating the concurrent combination of radiotherapy and Capecitabine in rectal cancer. J Clin Oncol *20*: 3983-3991, 2002.
24 Gambacorta MA, Valentini V, Coco C, Morganti AG, Smaniotto D, Miccichè F, Mantini G, Barbaro B, Garcia Vargas JE, Magistrelli P, Picciocchi A and Cellini N: Chemoradiation with Raltitrexed and Oxaliplatin in preoperative treatment of stage II-III resectable rectal cancer: phase I and II studies. Int J Radiat Oncol Biol Phys *60*: 139-148, 2004.
25 Gerard JP, Chapet O, Nemoz C, Romestaing P, Mornex F, Coquard R, Barbet N, Atlan D, Adeleine P and Freyer G: Preoperative concurrent chemoradiotherapy in locally advanced rectal cancer with high-dose radiation and Oxaliplatin-containing regimen: the Lyon R0-04 phase II trial. J Clin Oncol *21(6)*: 1119-1124, 2003.
26 James RD, Botwood N, Vernon CC and Price P: Raltitrexed plus radiotherapy for the treatment of unresectable/recurrent rectal cancer: a phase I study. Ann Oncol *14*: 570-573, 2003.
27 Gambacorta MA, Valentini V, Moranti AG, Smaniotto D, Mantini G, Miccichè F, Ratto C, Doglietto GB, De Paoli A, Rossi C, Cellini N and Garcia Vargas JE: Preoperative chemoradiation with Raltitrexed (Tomudex) in T3-4 rectal carcinoma: a phase I-II study. Int J Radiat Oncol Biol Phys *54*: 248-252, 2002.
28 Gambacorta MA, Valentini V, Morganti AG, Mantini G, Miccichè F, Ratto C, Di Miceli D, Rotondi F, Alfieri S, Doglietto GB, Garcia Vargas JE, De Paoli A, Rossi C and Cellini N: Chemoradiation with Raltitrexed (Tomudex) in preoperative treatment of stage II-III rectal cancer: a phase II study. Int J Radiat Oncol Biol Phys *60*: 130-113, 2004.
29 Moore HG, Gittleman A, Minsky BD, Wong D, Paty PB, Weiser M, Temple L, Saltz L, Shia J and Guillem JG: Rate of pathologic complete response with increased interval between preoperative combined modality therapy and rectal cancer resection. Dis Colon Rectum *47(3)*: 279-286, 2004.
30 Mohiuddin M, Hayne M, Regine WF, Hanna N, Hagihara PF, McGrath P and Marks GM: Prognostic significance of postchemoradiation stage following preoperative chemotherapy and radiation for advanced/recurrent rectal cancers. Int J Radiat Oncol Biol Phys *48(4)*: 1075-1080, 2000.
31 Garcia-Aguilar J, Hernandez de Anda E, Sirivongs P, Suk-Hwan Lee, Madoff RD and Rothemberger D: A pathologic complete response to preoperative chemoradiation is associated with lower local recurrence and improved survival in rectal cancer patients treated by mesorectal excision. Dis Colon Rectum *46*: 298-304, 2003.
32 Brown CL, Ternent CH, Thorson AG, Christensen MA, Blatchford GJ, Shashidharan M and Haynatzki GR: Response to preoperative chemoradiation in stage II and III rectal cancer. Dis Colon Rectum *46*: 1189-1193, 2003.
33 Marjnen CAM, van de Velde CJH, Putter H, van den Brink M, Maas CP, Martijn H, Rutten HJ, Wiggers T, Kranenbarg EK, Leer J-W H and Stiggelbout AM: Impact of short-term preoperative radiotherapy on health-related quality of life and sexual functioning in primary rectal cancer: report of a multicenter randomized trials. J Clin Oncol *23(9)*: 1847-1858, 2005.
34 Bonnel C, Parc YR, Pocard M, Dehni N, Caplin S, Parc R and Tiret E: Effects of preoperative radiotherapy for primary resectable rectal adenocarcinoma on male sexual and urinary function. Dis Colon Rectum *45*: 934-938, 2002.

Received January 9, 2006
Accepted March 16, 2006