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ORIGINAL ARTICLE

Hypofractionated Preoperative Chemoradiotherapy In Locally Advanced Rectal Cancer: Preliminary Results

Sedenay OSKEROĞLU KAPLAN,[1] Halil AKBÖRÜ,[2] Selvi DİNÇER TABAK,[2] Serap BAŞKAYA YÜCEL,[5] İbrahim MERAL,[3] Yunus SARALI,[3] Selma ŞENGİZ ERHAN,[4] Süleyman ALTIN[2]

[1]Department of Radiation Oncology, Mehmet Akif İnan Training and Research Hospital, Şanlıurfa-*Turkey*
[2]Department of Radiation Oncology, Okmeydanı Training and Research Hospital, İstanbul-*Turkey*
[3]Department of Medical Physics, Okmeydanı Training and Research Hospital, İstanbul-*Turkey*
[4]Department of Pathology, Okmeydanı Training and Research Hospital, İstanbul-*Turkey*
[5]Department of Radiation Oncology, Acıbadem Mehmet Ali Aydınlar University Atakent Hospital, İstanbul-*Turkey*

OBJECTIVE

The aim of the present study was to evaluate the efficacy and safety of preoperative hypofractionated chemoradiotherapy in our patients with locally advanced rectum cancer, which was previously observed in the Far East (KROG 11-02).

METHODS

Twenty-seven patients with locally advanced rectal cancer (cT3-4N0-2M0) between November 2014 and August 2016 were included in the study. A 2-week schedule of hypofractionated radiotherapy, 33 Gy/10 fractions, with concurrent 1 cycle of oral capecitabine (1650 mg/m2/day) was applied. Patients were planned to undergo surgery 6–8 weeks after the completion of chemoradiotherapy. End points were tumor responses and toxicity.

RESULTS

All patients underwent total mesorectal excision except for only 1 patient, and statistical analysis was performed on 26 patients. Of the 27 patients, 10 (38.4%) were downstaged, and 3 (11.5%) had a pathologically complete response. No grade 3–4 toxicity was observed in the patient group. Grade 1–2 hematologic toxicity developed in 2 (8%) patients, and no biochemical abnormality was observed. Gastrointestinal toxicity was observed in 17 (65%), genitourinary toxicity in 8 (30%), and radiodermatitis in 3 (11%) patients. One patient had permanent anastomosis and wound dehiscence, and presacral abscess was also seen in one patient. Enterocutaneous fistula developed in only one patient.

CONCLUSION

A 2-week schedule of radiotherapy with oral capecitabine in patients with locally advanced rectal cancer resulted in similar toxicity levels and tumor response rate in comparison with previous results.

Keywords: Capecitabine; hypofractioned radiotherapy; preoperative chemoradiotherapy; rectal cancer.

Introduction

Currently, neoadjuvant chemoradiotherapy/radiotherapy has become the standard treatment in locally advanced rectal cancer compared with postoperative modality due to both decreased side effect profile and increased local control and sphincter protection.[1] Long-course chemoradiotherapy (LCCRT, 45–50.4 Gy/25–28 fractions) is the preferred treatment for rectal tumors with extramural spread and/or regional

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Dr. Sedenay OSKEROĞLU KAPLAN
Radyasyon Onkolojisi Anabilim Dalı,
Mehmet Akif İnan Eğitim ve Araştırma Hastanesi,
Şanlıurfa-Turkey
E-mail: oskarum@gmail.com

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lymph node involvement, especially in the majority of Eastern European countries and in the United States. Short-course radiotherapy (SCRT, 25 Gy/5 fractions), which is more economical and comfortable than long-term treatment, is preferred, especially in middle and upper rectum patients without the involvement of mesorectal fascia, peripheral organ, or regional lymph node, in Northern Europe.

Although the most remarkable advantage of LCCRT over SCRT is the increased tumor response, two randomized phase III trials comparing neoadjuvant SCRT and LCCRT indicated no significant difference with regard to local control, disease-free survival, overall survival, organ preservation, and late toxicity rates.[2,3] Additionally, SCRT provides better patient compliance, shorter treatment time, and lower costs than standard fractionation with chemotherapy. In addition, according to recently published studies, short-term radiotherapy with delayed surgery for >4 weeks provides better pathological outcomes and fewer postoperative complications.[4]

To create a better treatment scheme with regard to patient comfort and quality of life, as well as to establish an equivalent treatment plan with regard to treatment efficacy and safety, we used a new protocol that is biologically similar to standard radiotherapy dose and previously observed by Lee et al.[5] for toxicity profile and reliability. We aimed to prospectively monitor the use of a 2-week schedule of hypofractionated radiotherapy regimen delivered as a total dose of 33 Gy/10 fractions, with 1 cycle of oral capecitabine in rectal cancer in our patient group in the presence of radiological and pathological data.

Materials and Methods

Patient eligibility

Eligibility criteria were histologically confirmed adenocarcinoma, distal margin of the tumor located <12 cm from the anal verge, cT3-4N0-2 classification as determined by magnetic resonance imaging (MRI) and/or endorectal ultrasonography (EUS), no evidence of distant metastasis, Karnofsky Performance Score ≥70, and adequate bone marrow, liver, and renal functions. Exclusion criteria were history of radiotherapy or chemotherapy, the existence of serious comorbidity, and fluoropyrimidine sensitivities.

Evaluation

In this prospective observational study, all patients with resectable locally advanced rectal adenocarcinoma received preoperative radiotherapy (33 Gy/10 fractions) with 1 cycle of oral capecitabine (1650 mg/m^2/day) from November 2014 to August 2016.

For clinical staging, we used clinical history, physical examination, digital rectal examination, carcinoembryonic antigen determination, blood profile, and staging examinations, including colonoscopy with biopsy, chest and abdomen computed tomography (CT) scans, endoscopic ultrasound, pelvic MRI, and positron emission tomography/CT. A lymph node size of >1 cm in MRI and/or EUS is considered to be clinically positive.

All patients were clinically staged to determine the pretreatment and posttreatment stages according to the American Joint Committee on Cancer criteria, 7th edition. Circumferential radial margin is defined as involvement within tumor margin ≤2 mm. The tumor regression grade (TRG) was assessed according to the classification recommended by Ryan TRG system.[6] Pathologic complete response (pCR) was defined as no visible microscopic disease in the primary tumor.

Patients were seen in the polyclinic two times during chemoradiotherapy to evaluate acute toxicity and compliance. Patients were also monitored 4 weeks after the completion of radiotherapy and time to surgery.

Treatment

All patients received pelvic RT with concurrent oral capecitabine. Pelvic RT was planned by the Eclipse 10.0 treatment planning system on the Rapid Arc Millennium 120 MLC system using intensity-modulated radiation therapy (IMRT) or volumetric arc therapy (VMAT) with a total dose of 33 Gy/10 fractions. All patients were simulated in the supine position. Fullness or empty bladder was not implemented. RT was delivered to the clinical target volume (CTV), including the entire mesorectum and obturator, presacral, and internal iliac lymph nodes (plus external iliac lymph nodes in cT4 patients and patients with positive obturator lymph nodes). The planning target volume was symmetrically generated with a 7 mm margin around the CTV. Peritoneal cavity, bladder, and femur heads were the organs at risk. Oral capecitabine was prescribed at a dose of 1650 mg/m^2/day only during radiotherapy with drug holidays on weekends, as used in the routine. Patients underwent total mesorectal excision 6–8 weeks after the completion of chemoradiation. Postoperative chemotherapy was at the discretion of the medical oncologist. The treatment scheme is shown in Figure 1.

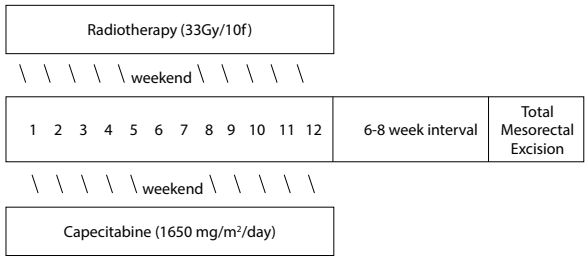

Fig. 1. Treatment scheme.

Statistical analysis

All statistical data were analyzed using SPSS version 17.0 (SPSS Inc., Chicago, IL, USA). All results were presented as the rate for categorical values or mean and median for continuous variables. A clinically and statistically significant correlation between continuous variables was calculated by Spearman's rank correlation test, rs (Spearman's correlation coefficient), and p value (two-tailed). A p value <0.05 was considered statistically significant.

Results

A total of 27 patients with locally advanced rectal cancer who received preoperative radiotherapy concurrently with oral capecitabine at Okmeydanı Research and Training Hospital were observed. One patient was excluded from the analysis due to surgery rejection. Among the 26 patients, 12 (46.1%) were male, and 14 (53.9%) were female. The mean age of the patients was 58 (51–77) years. The average follow-up time was 22 (7–37) months. According to pretreatment staging, 23 (88.4%) patients had cT3 lesions, and 3 (11.6%) patients had cT4 lesions. In addition, at the time of diagnosis, 20 patients had clinically node-positive disease. The clinical and pathological characteristics of all patients are shown in Table 1. Although all patients received the prescribed doses of oral capecitabine and radiotherapy, the treatment of 5 patients was extended by 1–2 days due to the malfunction of the Rapid Arc.

The median interval between the completion of chemoradiotherapy and surgery was 56 (36–88) days. Of the 26 patients, 24 (92.3%) underwent low anterior resection including 2 patients who had tumor within ≤2 cm to the anal verge. There were 3 patients in the sphincter-saving R1 resection group and 1 patient in the abdominoperineal resection R1 group. Among the 26 patients, 10 (38.4%) were downstaged, 3 (12%) had pCR, 6 (23.1%) were TRG1 with total tumor regression and single cells or small groups of cancer cells, 14 (53.8%) were TRG2 with residual cancer outgrown by fibrosis, and 6 (23.1%) were TRG3 with significant fibrosis outgrown by cancer and no fibrosis with extensive residual cancer. Three patients did not receive adjuvant chemotherapy due to comorbidity, treatment rejection, and surgical morbidity.

Early and late side effects that occurred during and within 1 month after chemoradiotherapy are listed in Table 2. No grade 3–4 toxicity was observed in the pa-

Table 1 Patients characteristics

Characteristic	n=26 (%)
Gender	
Female	14 (53.8)
Male	12 (46.2)
Differentiation	
Well	7 (26.9)
Moderate	15 (61.5)
Poor	3 (11.5)
Tumor distance from the anal verge (cm)	
0-2cm	4 (15.3)
2-5cm	8 (30.7)
>5cm	14 (53.8)
Median age (year)	Median (range): 58 (51-77)
Pre-CRT CEA (ng/ml)	Median (range): 4.5 (0.9-29)
cT stage	
T3	23 (88.4)
T4	3 (11.6)
cN stage	
N0	5 (19.2)
N1	4 (15.3)
N2	17 (65.3)
CRM	
Positive	6 (23)
Negative	21 (77)

CEA: carcinoembryonic antigen; CRT: chemoradiotherapy; CRM: circumferential margin

Table 2 Acute toxicity of preoperative treatment

Adverse events	n=26 (%)	
	Grade 1-2	Grade 3-4
Hematologic toxicity		
Leukopenia	2 (7.6)	-
Anemia	2 (7.6)	-
Thrombocytopenia	-	-
Non-hematologic toxicity		
Diarrhea	14 (53.8)	-
Dysuria	8 (30.7)	-
Radiodermatitis	3 (11.5)	-
Nausea and vomiting	5 (19.2)	-

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tient group. Grade 1–2 hematologic toxicity (leukopenia, anemia, and thrombocytopenia) developed in 2 (8%) patients, and no biochemical abnormality was observed. Grade 1–2 gastrointestinal toxicity (diarrhea, nausea, vomiting, and abdominal pain) was observed in 17 (65%), genitourinary toxicity in 8 (30%), and radiodermatitis in 3 (11%) patients, respectively. One patient had permanent anastomosis and wound dehiscence, and presacral abscess was also seen in one patient. Enterocutaneous fistula developed in only one patient.

Discussion

The most common regimens are SCRT with 5 fractions of 5 Gy over 1 week and LCCRT with a conventional dose of 1.8–2 Gy/fraction for a total dose of 45–50.4 Gy combined with 5-Fu-based chemotherapy; however, in different geographies, such as Japan and China, there are different hypofractionated regimens that had been tested in previous studies applied except for conventional dose of neoadjuvant radiotherapy in rectal cancer.[5,7,8] The aim of this trial was to evaluate the efficacy and safety of hypofractionated chemoradiotherapy, which was previously observed by Lee et al.,[5] in our patient group. While downstaging of the TNM stage and pCR was evaluated as efficacy, tolerability and toxicity profile were assessed as safety.

In this trial, downstaging was observed in 10 (38%) patients. In addition, 3 (12%) patients had pCR, and 6 (23.1%) patients had pCR with minimal tumor cells in fibrosis at the final pathology. As a result, we achieved to obtain comparable results with Lee et al.[4] who had 13.8% pCR and 33.8% downstaging.[5] In comparison with the results of previous studies, this regimen appears to be equal to preoperative chemoradiotherapy protocols that further increased the pCR rate to approximately 11% to 18%.[9-12] In addition, there are various studies in which SCRT with delay surgery had been tested to increase the pCR rates.[4,13] Two randomized studies that compared SCRT with immediate surgery and SCRT with delayed surgery reported a higher rate of pCR in the delayed surgery group.[14,15] In another randomized trial, the comparison of SCRT and delayed surgery with LCCRT showed a higher rate of pCR in the chemoradiation groups (3% vs. 13%).[16] Additionally, in the literature, there are some publications that had tested SCRT, followed by consolidation chemotherapy before surgery. Bujko et al.[17] stated that SCRT, followed by 3 cycles of 5-fluorouracil, oxaliplatin, and leucovorin (FOLFOX) chemotherapy in comparison with long-course oxaliplatin-based preoperative chemoradiation, reveals a higher pCR rate in the SCRT group (21% vs. 8%). Similarly, Myerson et al.[18] used a regimen of 5 fractions of pelvic radiation therapy, followed by 4 cycles of FOLFOX evaluated as a preoperative regimen for cT3-4 rectal cancer. There were a total of 21 (28%) ypT0 including 19 (25%) ypT0N0 complete response.[18]

Acute toxicity during SCRT is most often of grade 1–2. However, most of the post-radiation toxicity in the immediate surgery group occurred before the occurrence of acute post-radiation toxicity, and more side effects were seen when surgery was delayed. In the interim analysis of the Stockholm III randomized trial, severe acute toxicity in 4.2% of patients in the SCRT and delayed surgery group and in none of the patients in the immediate surgery group was reported.[4] Nevertheless, SCRT with delayed surgery showed a significantly lower incidence of postoperative complications than PSRT with immediate surgery (39.4% vs. 52.5%), and LCCRT caused prolonged treatment time with similar results.[14] In only one study, Yeo et al.[19] (KROG 10-01) reported short-course radiation concurrently combined with 5-Fu and leucovorin, followed by surgery 4–8 weeks later. The pCR rate was only 1.4%, and the acute grade 3–4 toxicity was 38%.[19] In this study, the most common side effect was grade 1–2 gastrointestinal toxicity as observed in 17 (65%) patients. Although this toxicity was slightly higher than the literature, there were no grade 3–4 toxicity and no toxicity-related treatment break.

In this study, a 2-week scheduled chemoradiotherapy with oral capecitabine showed very low toxicity profiles as Lee et al.[5] A shortened duration of treatment with 1 cycle of capecitabine probably prevented to observe more acute toxicity. Compared with the main study, toxicity profiles were similar, but any grade 3 toxicity was not observed in our study. That can be caused by a small number of patients or using highly conformal radiotherapy technologies, such as IMRT and VMAT in comparison with the standard three or four field box technique. Nowadays, especially developing technologies provide the opportunity for more reliable implementation of more intensive treatment modalities. Radiotherapy applied with technologies, such as IMRT and VMAT, compared with previous series, can reduce acute bowel toxicities by decreasing the radiation exposure of the small bowel.[20] Although there is a distinct advantage of IMRT in intestinal doses as shown in dosimetric studies, additional research is needed to determine whether IMRT is able to reduce the side effects during and after pelvic RT with hypofractionated radiotherapy.[21,22]

It has been reported that short-term radiation can lead to late intestinal obstruction and sexual dysfunction.[23] Hereby, instead of acute toxicity for hypofractionated radiotherapy, the risk of long-term complications raises doubt on reliability.[24-26] Therefore, concern regarding late toxicity due to hypofractionated schedule can be a significant deterrent for physicians. A 2-week course of preoperative chemoradiotherapy achieved a satisfying downstaging rate and low incidence in toxicity profiles, considering that the late effects of 33 Gy/10 fractions are similar with 25 Gy/5 fractions. According to the linear-quadratic model, assuming that a/b is 3 Gy at the late effect, biologically effective doses were 69.3 Gy3 and 66.7 Gy3, respectively.

Conclusion

Hypofractionated chemoradiation regimen with 33 Gy/10 fractions with oral capecitabine, followed by delayed surgery for preoperative treatment of rectal cancer, provided a favorable downstaging rate and tolerable toxicity profiles. Naturally, we need to perform long-term oncological outcomes and phase III trials with larger patient groups.

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Conflict of Interest: None declared.

Ethics Committee Approval: This study was conducted in accordance with local ethical rules.

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References

1. Sauer R, Becker H, Hohenberger W, Rödel C, Wittekind C, Fietkau R, et al; German Rectal Cancer Study Group. Preoperative versus postoperative chemoradiotherapy for rectal cancer. N Engl J Med 2004;351(17):1731–40.
2. Bujko K, Nowacki MP, Nasierowska-Guttmejer A, Michalski W, Bebenek M, Kryj M. Long-term results of a randomized trial comparing preoperative short-course radiotherapy with preoperative conventionally fractionated chemoradiation for rectal cancer. Br J Surg 2006;93(10):1215–23.
3. Ngan SY, Burmeister B, Fisher RJ, Solomon M, Goldstein D, Joseph D, et al. Randomized trial of short-course radiotherapy versus long-course chemoradiation comparing rates of local recurrence in patients with T3 rectal cancer: Trans-Tasman RadiationOncology Group trial 01.04. J Clin Oncol 2012;30(31):3827–33.
4. Pettersson D, Cedermark B, Holm T, Radu C, Påhlman L, Glimelius B, et al. Interim analysis of the Stockholm III trial of preoperativeradiotherapy regimens for rectal cancer. Br J Surg 2010;97(4):580–7.
5. Lee JH, Kim JG, Oh ST, Lee MA, Chun HG, Kim DY, et al. Two week course of preoperative chemoradiotherapy followedby delayed surgery for rectal cancer: a phase II multi-institutionalclinical trial (KROG 11-02). Radiother Oncol 2014;110(1):150–4.
6. Ryan R, Gibbons D, Hyland JM, Treanor D, White A, Mulcahy HE, et al. Pathological response following long-course neoadjuvant chemoradiotherapy for locally advanced rectal cancer. Histopathology 2005;47(2):141–6.
7. Zhan T, Gu J, Li M, Du C. Intermediate-fraction neoadjuvant radiotherapy for rectal cancer. Dis Colon Rectum 2013;56(4):422–32.
8. Francois Y, Nemoz CJ, Baulieux J, Vignal J, Grandjean JP, Partensky C, et al. Influence of the interval between preoperative radiation therapy and surgery on downstaging and on the rate of sphincter-sparing surgery for rectal cancer: the Lyon R90-01 randomized trial. J Clin Oncol 1999;17(8):2396.
9. Gérard JP, Conroy T, Bonnetain F, Bouché O, Chapet O, Closon-Dejardin MT, et al. Preoperative radiotherapy with or without concurrent fluorouracil and leucovorin in T3-4 rectal cancers: results of FFCD 9203. J Clin Oncol 2006;24(28):4620–5.
10. Bosset JF, Collette L, Calais G, Mineur L, Maingon P, Radosevic-Jelic L, et al; EORTC Radiotherapy Group Trial 22921. Chemotherapy with preoperative radiotherapy in rectal cancer. N Engl J Med 2006;355(11):1114–23.
11. Theodoropoulos G, Wise WE, Padmanabhan A, Kerner BA, Taylor CW, Aguilar PS, et al. T-level downstaging and complete pathologic response after preoperative chemoradiation for advanced rectal cancer result in decreased recurrence and improved disease-free survival. Dis Colon Rectum 2002;45(7):895–903.
12. Kim NK, Baik SH, Min BS, Pyo HR, Choi YJ, Kim H, et al. A comparative study of volumetric analysis, histopathologic downstaging, and tumor regression grade in evaluating tumor response in locally advanced rectal cancer following preoperative chemoradiation. Int J Radiat Oncol Biol Phys 2007;67(1):204–10.
13. Bujko K, Richter P, Smith FM, Polkowski W, Szczepkowski M, Rutkowski A, et al. Preoperative radiotherapy and local excision of rectal cancer with immediate radical re-operation for poor responders: a prospective

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doi: 10.5505/tjo.2018.1869

multicentre study. Radiother Oncol 2013;106(2):198–205.

14. Pettersson D, Holm T, Iversen H, Blomqvist L, Glimelius B, Martling A. Preoperative short-course radiotherapy with delayed surgery in primary rectal cancer. Br J Surg 2012;99(4):577–83.
15. Pach R, Kulig J, Richter P, Gach T, Szura M, Kowalska T. Randomized clinical trial on preoperative radiotherapy 25 Gy in rectal cancer--treatment results at 5-year follow-up. Langenbecks Arch Surg 2012;397(5):801–7.
16. Latkauskas T, Pauzas H, Gineikiene I, Janciauskiene R, Juozaityte E, Saladzinskas Z, et al. Initial results of a randomized controlled trial comparing clinical and pathological downstaging of rectal cancer after preoperative short-course radiotherapy or long-term chemoradiotherapy, both with delayed surgery. Colorectal Dis 2012;14(3):294–8.
17. Bujko K, Wyrwicz L, Rutkowski A, Malinowska M, Pietrzak L, Kryński J, et al; Polish Colorectal Study Group. Long-course oxaliplatin-based preoperative chemoradiation versus 5 × 5 Gy and consolidation chemotherapy for cT4 or fixed cT3 rectal cancer: results of a randomized phase III study. Ann Oncol 2016;27(5):834–42.
18. Myerson RJ, Tan B, Hunt S, Olsen J, Birnbaum E, Fleshman J, et al. Five fractions of radiation therapy followed by 4 cycles of FOLFOX chemotherapy as preoperative treatment for rectal cancer. Int J Radiat Oncol Biol Phys 2014;88(4):829–36.
19. Yeo SG, Oh JH, Kim DY, Baek JY, Kim SY, Park JW, et al. Preoperative short-course concurrent chemoradiation therapy followed by delayed surgery for locally advanced rectal cancer: a phase 2 multicenter study (KROG 10-01). Int J Radiat Oncol Biol Phys 2013;86(1):34–9.
20. Lawrie TA, Green JT, Beresford M, Wedlake L, Burden S, Davidson SE, et al. Interventions to reduce acute and late adverse gastrointestinal effects of pelvic radiotherapy for primary pelvic cancers. Cochrane Database Syst Rev 2018;1:CD012529.
21. Mok H, Crane CH, Palmer MB, Briere TM, Beddar S, Delclos ME, et al. Intensity modulated radiation therapy (IMRT): differences in target volumes and improvement in clinically relevant doses to small bowel in rectal carcinoma. Radiat Oncol 2011;6:63.
22. Arbea L, Ramos LI, Martínez-Monge R, Moreno M, Aristu J. Intensity-modulated radiation therapy (IMRT) vs. 3D conformalradiotherapy (3DCRT) in locally advanced rectal cancer (LARC): dosimetric comparison and clinical implications. Radiat Oncol 2010;5:17.
23. Birgisson H, Påhlman L, Gunnarsson U, Glimelius B. Late gastrointestinal disorders after rectal cancer surgery with and without preoperative radiation therapy. Br J Surg 2008;95(2):206–13.
24. Kapiteijn E, Marijnen CA, Nagtegaal ID, Putter H, Steup WH, Wiggers T, et al; Dutch Colorectal Cancer Group. Preoperative radiotherapy combined with total mesorectal excision for resectable rectal cancer. N Engl J Med 2001;345(9):638–46.
25. Peeters KC, Marijnen CA, Nagtegaal ID, Kranenbarg EK, Putter H, Wiggers T, et al; Dutch Colorectal Cancer Group. The TME trial after a median follow-up of 6 years: increased local control but no survival benefit in irradiated patients with resectable rectal carcinoma. Ann Surg 2007;246(5):693–701.
26. Marijnen CA, van de Velde CJ, Putter H, van den Brink M, Maas CP, Martijn H, et al. Impact of short-term preoperative radiotherapy on health-related quality of life and sexual functioning in primary rectal cancer: report of a multicenter randomized trial. J Clin Oncol 2005;23(9):1847–58.