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Original Article

The outcome of 5-fluorouracil chemotherapy after the completion of neoadjuvant chemoradiotherapy, administered until 2 weeks before rectal cancer resection

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Abstract

Background: In most institutions, locally advanced rectal cancer is treated with neoadjuvant chemoradiotherapy followed by surgery 6–8 weeks later, allowing time for tumor response and recovery from chemoradiotherapy-related toxicities. In our hospital, we continuously administer chemotherapy after the completion of chemoradiotherapy, until 2 weeks before surgery for most patients.
Methods: This was a retrospective study. Patients received a diagnosis of adenocarcinoma of the rectum at our hospital between January 2003 and December 2008 and received neoadjuvant chemoradiotherapy and curative surgery. Chemoradiotherapy consisted of continuous infusion of 225 mg/m^2 5-fluorouracil, 5 days per week. Radiation therapy was delivered at 1.8 Gy per day, 5 days per week for 5–6 weeks (median radiation dose, 50.4 Gy). Chemotherapy was continued until 2 weeks before surgery, and surgery was performed 6–8 weeks after completion of chemoradiotherapy.
Results: The study included 119 patients (median age, 61 years; range, 24–84 years). Twenty-nine patients (24.4%) had a complete response and 65 (54.6%) had a partial response. Over a median follow-up duration of 52 months, 10 patients experienced local recurrence and 18 had distant metastasis. The 5-year overall and disease-free survival rates were 80.6% and 72.9%, respectively. Grade 3–4 toxicity only occurred in 14 patients (11.8%).
Conclusion: Continued chemotherapy with 5-fluorouracil after completing neoadjuvant chemoradiotherapy until 2 weeks before surgery for locally advanced rectal cancer results in a good pathological control rate, with low toxicity. Patients who achieved a complete pathological response had a better long-term oncological outcome than those who did not.

Keywords: chemotherapy; 5-fluorouracil; neoadjuvant chemoradiotherapy; rectal cancer

1. Introduction

Preoperative chemoradiotherapy (CRT) followed by total mesorectal excision (TME) is an important treatment strategy for locally advanced rectal cancer (defined as T3 or node-positive rectal cancer). Preoperative CRT is associated with a lower local recurrence rate and general toxicities than postoperative CRT.[1–3] Neoadjuvant CRT usually results in a reduced tumor size, increased tumor mobility, and histopathologic downstaging, with correspondingly improved long-term oncologic outcomes.[4] Approximately 15–20% of patients have a pathological complete response (pCR) at the time of surgery,[5–7] although the likelihood of a pCR may be related to

Conflicts of interest: The authors declare that there are no conflicts of interest related to the subject matter or materials discussed in this article.

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the timing of tumor resection, the chemotherapy regimen, and the radiotherapy dose.

In most institutions, locally advanced rectal cancer is generally treated with neoadjuvant CRT followed by surgery, ~6−8 weeks later, to allow for a tumor response to CRT and recovery from CRT-related toxicity. In our hospital, we continue to administer chemotherapy after the completion of CRT until 2 weeks before surgery for locally advanced rectal cancer. Here, we report the oncological outcome, pathological complete response rate, and toxicities associated with this strategy.

2. Methods

2.1. Data source

We retrospectively reviewed the medical records of patients in whom adenocarcinoma of the rectum was diagnosed (tumor located within 12 cm from the anal verge) who received neoadjuvant CRT in our hospital between January 2003 and December 2008. Patients with tumor metastasis or unresectable tumors, those who only underwent local excision, and those who achieved a clinical complete response under observation alone were excluded. The rectal adenocarcinoma diagnosis was based on sigmoidoscopy biopsy. T staging was scored by transrectal ultrasonography or magnetic resonance imaging (MRI), and N staging was scored by pelvic computed tomography (CT). Distant metastasis was evaluated using an abdominal CT scan and chest X-ray film for all patients. Clinical data including age, sex, Eastern Cooperative Oncology Group performance status, operative method, tumor recurrence, tumor distance from the anal verge, pretreatment clinical tumor stage and size, histologic grade, radiotherapy dose, chemotherapy toxicities, preoperative clinical stage, postoperative pathological stage, site of tumor recurrence, survival status, and duration of follow-up were analyzed.

The treatment program is shown in Fig. 1. All patients were treated with 5-fluorouracil (5-FU) continuous infusion at a dose of 225 mg/m^2, 5 days per week, concurrent with radiotherapy. Radiation therapy was delivered at 1.8 Gy per day, 5 days per week for 5−6 weeks, and the median radiation dose was 50.4 Gy (range, 43.2−65.5 Gy). Chemotherapy was continued until 2 weeks before surgery, and the patient underwent surgery within 6−8 weeks after finishing radiotherapy. The clinical response was evaluated by post-CRT CT, sigmoidoscopy, and digital rectal examination. After surgery, planned adjuvant treatment was a 5-FU based chemotherapy regimen.

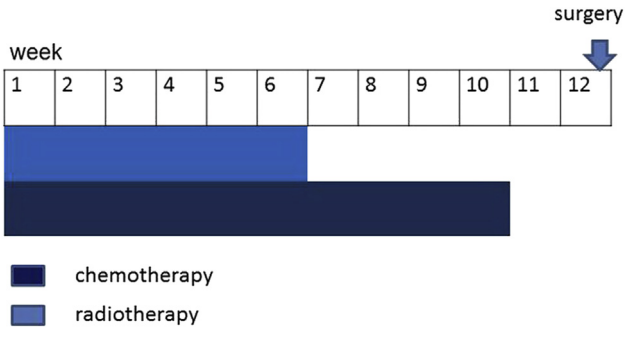

Fig. 1. Treatment schedule for patients included in this study.

2.2. Statistical analyses

We compared the general characteristics between groups with and without pCR. We analyzed differences with respect to specific clinical factors according to whether patients had a complete response using Student t test, Yates' correction and Fisher's exact test. We compared the recurrence rate between groups with and without pCR using Fisher's exact test.

Overall survival was defined as the time from the beginning of CRT to the date of the last follow-up visit or death. Disease-free survival was defined as the time from surgery to the date of death, last follow-up visit, or treatment failure (local or distant recurrence). Local recurrence was defined as tumor recurrence in the pelvis, perineum, or anastomosis site. Distant metastasis was defined as tumor recurrence outside the pelvis. The follow-up duration was defined as the time from surgery to the last follow-up visit or any type of event. We used the Kaplan−Meier survival method to compare disease-free and overall survival for patients with and without pCR, and log-rank test to identify significant differences. All analyses were performed using GraphPad Prism Version 5 (GraphPad Software, San Diego, CA, USA). A p value <0.05 was considered statistically significant.

3. Results

Between January 2003 and December 2008, 127 patients were included in our study; eight patients did not complete the full course of CRT (6 due to CRT intolerance and 2 due to disease progression during CRT). Finally, a total of 119 patients were included in the analysis. The characteristics of all 119 patients are summarized in Table 1. Seventy-four patients were men and 45 were women, with a median age of 61 years (range, 24−84 years). Thirty-six patients (30.3%) underwent transrectal ultrasonography for clinical T staging and 83 (69.7%) underwent MRI for clinical T staging. The preoperative clinical stage of the patients was stage II in 41 cases (34.5%) and stage III in 78 cases (65.5%), and the median tumor size was 2.8 cm (range, 0.8−12 cm). After neoadjuvant CRT, all patients underwent surgery, which involved lower anterior resection in 81 cases (31 cases with protective ileostomy), abdominoperineal resection in 37 cases, and Hartmann procedure in one case. Of 67 patients with a low rectal tumor (tumor located $\leq$ 5 cm from the anal verge), 30 patients (44.8%) had sphincter preservation. The final pathological stage revealed complete remission in 29 cases (24.4%), stage 0 (ypTisN0M0) disease in one case (0.8%), stage I disease in 31 (26.1%), stage II disease in 31 (26.1%), and stage III disease in 27 (22.7%). Total downstaging was observed in 94

Table 1
Patient characteristics.

Patient characteristics	*n* (%)
Age (y)	
Median (range)	61 (24−84)
Sex	
Male	74 (62.2)
Female	45 (37.8)
Performance status	
0	74 (62.2)
1	34 (28.6)
2	11 (9.2)
Tumor location	
Lower (≤5 cm)	67 (56.3)
Middle (>5−≤ 10 cm)	48 (40.3)
Upper (>10−≤ 12 cm)	4 (3.4)
Pre-CRT clinical stage	
II	41 (34.5)
III	78 (65.5)
Pre-CRT T stage	
T2	18 (15.1)
T3	95 (79.8)
T4	6 (5)
Pre-CRT N stage	
N0	41 (34.4)
N1	61 (51.3)
N2	17 (14.3)
Tumor size (cm)	
Median (range)	2.8 (0.8−12)

CRT = chemoradiotherapy.

Table 2
Comparison of the general characteristics of complete responders and non-complete responders to chemoradiotherapy.

	Complete responders (n = 29)	Noncomplete responders (n = 90)	p
Age (y)	63.6 ± 15.7	60.5 ± 15.8	0.353[a]
Sex			0.99[b]
Male	18 (62.1)	56 (62.2)	
Female	11 (37.9)	34 (37.8)	
Distance from the anal verge (cm)	5.6 ± 2.9	6.1 ± 2.8	0.403[a]
Tumor size (mm)	28.6 ± 18.4	34.6 ± 20.7	0.163[a]
Pre-CRT clinical stage			0.999[b]
Stage II	10 (34.5)	31 (34.4)	
Stage III	19 (65.5)	59 (65.6)	
Pre-CRT T stage			0.915[c]
T2	5 (17.2)	13 (14.4)	
T3	23 (79.3)	72 (80)	
T4	1 (3.4)	5 (5.6)	
Pre-CRT N stage			0.431[c]
N0	10 (34.5)	31 (34.4)	
N1	17 (58.6)	44 (48.9)	
N2	2 (6.9)	15 (16.7)	
Histologic differentiation			0.405[c]
Well	3 (10.3)	6 (6.7)	
Moderate	25 (86.2)	73 (81.1)	
Poor	1 (3.4)	11 (12.2)	
Curative surgery (R0 resection)	29 (100)	88 (97.8)	0.999[c]
Sphincter preservation	21 (72.4)	60 (66.7)	0.728[b]

Data are presented as n (%) or mean ± SD.
CRT = chemoradiotherapy.
[a] Student t test.
[b] Yates' correction.
[c] Fisher's exact test.

patients (79%). Twenty-nine patients (24.4%) had a complete response and 65 (54.6%) had a partial response. Upstaging occurred in five patients after surgery. Of the 29 patients with complete response, 21 (72.4%) received adjuvant chemotherapy. Of the 90 patients with no complete response, 80 (88.9%) received adjuvant chemotherapy. Of the 101 patients who received adjuvant chemotherapy, 94 (93.1%) completed the planned number of treatment cycles.

The median follow-up time was 52 months (range, 7−100 months), during which local recurrence occurred in 10 (8.4%) patients and distant metastasis occurred in 18 (15.1%). The 5-year overall and disease-free survival rates were 80.6% and 72.9%, respectively. Four patients had concomitant local recurrence and distant metastasis.

As shown in Table 2, neither age (p = 0.353), sex (p = 0.99), tumor location (p = 0.403), tumor size (p = 0.163), pre-CRT clinical staging (p = 0.999), pre-CRT T staging (p = 0.915), pre-CRT N staging (p = 0.431), sphincter preservation (p = 0.728), nor histologic type (p = 0.405) were significantly different between patients who did or did not achieve a complete response.

Fewer patients who achieved a complete response had local recurrence (0% vs. 11.1%, p = 0.116), distant metastasis (0% vs. 20%, p = 0.006) or any type of recurrence (0% vs. 26.7%, p = 0.001) compared to those who failed to achieve a complete response (Table 3). The 5-year disease-free survival rate was 96.6% for the pCR group and 65.6% for the non-pCR group [hazard ratio (HR): 5.306; 95% confidence interval (CI): 1.283−6.202; p = 0.009; Fig. 2]. The 5-year overall survival rate was 96.6% for the pCR group and 75.8% for the non-pCR group (HR: 2.379; 95%CI: 0.634−6.507; p = 0.069; Fig. 3).

3.1. Toxicity

The toxicity events are listed in Table 4. The most common adverse events related to CRT were leukopenia (30.3%) and diarrhea (25.2%). Overall, Grade 3−4 toxicities developed in 14 patients (11.8%), of whom Grade 4 leukopenia developed in one, Grade 4 diarrhea in one, Grade 3 leukopenia in six, Grade 3 diarrhea in one, Grade 3 anemia in two, a Grade 3 dermatologic complication in two, and Grade 3 vomiting in one.

Table 3
Comparison of the oncological outcomes in complete responders and non-complete responders to chemoradiotherapy with continued chemotherapy.

	Complete responders	Noncomplete responders	p[a]
Local recurrence	0	10 (11.1)	0.116
Distant metastasis	0	18 (20)	0.006
Overall recurrence	0	24 (26.7)	0.001

Data are presented as n (%).
[a] Fisher's exact test.

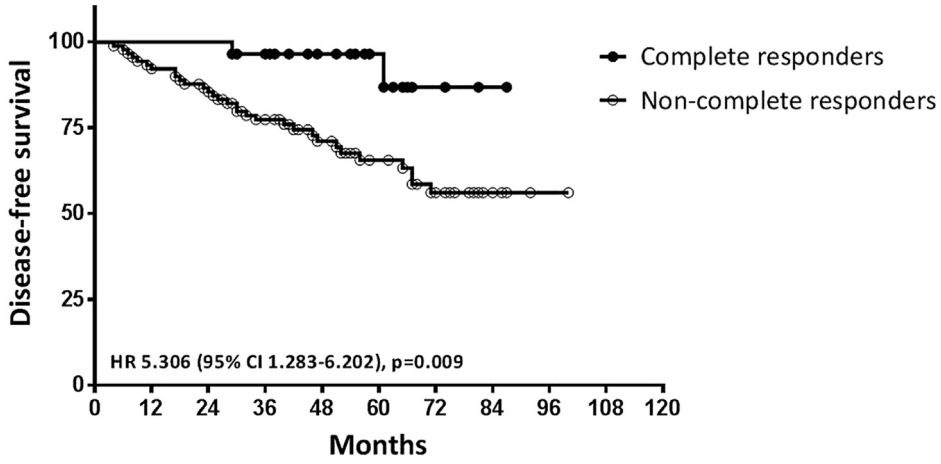

Fig. 2. Cumulative disease-free survival of patients who achieved a complete response ("Complete responders") and those who failed to achieve a complete response ("Noncomplete responders") after chemoradiotherapy. Cumulative proportion surviving at 5 years, Complete responders: 0.966. Noncomplete responders: 0.656. CI = confidence interval; HR = hazard ratio.

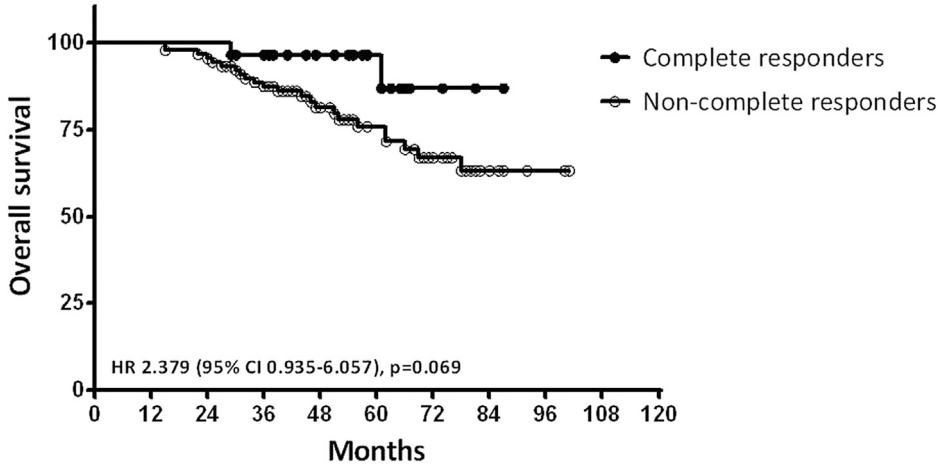

Fig. 3. Cumulative overall survival of patients who achieved a complete response ("Complete responders") and those who failed to achieve a complete response ("Noncomplete responders") after chemoradiotherapy. Cumulative proportion surviving at 5 years, Complete responders: 0.966. Noncomplete responders: 0.758. CI = confidence interval; HR = hazard ratio.

4. Discussion

Currently, neoadjuvant CRT with 5-FU is widely used for treating locally advanced rectal cancer in order to achieve tumor downstaging and shrinkage, thereby increasing the likelihood of curative surgical resection and reducing the risk of local recurrence.[8,9] Many studies have found that patients with pCR after CRT are less likely to have local or distant recurrence, and survive for longer than those with non-complete response.[10–12] Therefore, conventional CRT has been modified in a number of studies, for example, by including additional chemotherapeutic agents, extending the interval between CRT and surgery, and adding continued chemotherapy in the period between CRT and surgery. Additional chemotherapeutic agents that have been studied in this context include oxaliplatin[13,14] and cetuximab.[15,16] These resulted in a pCR rate of 8–19%, which is lower than the 24.4% observed in our study. Although adding irinotecan[17] resulted in a higher pCR rate of 26%, the incidence of acute Grade 3–4 toxicity was as high as 42%, and hence, this therapy cannot be well tolerated by most patients. None of these studies convincingly showed that adding these

Table 4
Toxicity events in patients.

Toxicity	Grades 1–2	Grades 3–4
Gastrointestinal		
Diarrhea	28 (23.5)	2 (1.7)
Nausea	22 (18.5)	0
Vomiting	12 (10)	1 (0.8)
Mucositis	8 (6.7)	0
Hematologic		
Anemia	16 (13.4)	2 (1.7)
Leukopenia	29 (24.4)	7 (5.9)
Thrombocytopenia	14 (11.8)	0
Dermatologic	15 (12.6)	2 (1.7)

Data are presented as *n* (%).

chemotherapy agents can improve the pCR, and the combination of two or more chemotherapy agents may result in higher toxicity rates and a higher cost.

The results of additional chemotherapy during the resting period after CRT have also been reported. Garcia-Aguilar et al[18] reported a nonrandomized prospective trial comparing one group of patients who underwent CRT consisting of 5-FU followed by surgery 6 weeks later, with another group treated with an additional two cycles of modified FOLFOX-6 in the 4 weeks following the completion of CRT and then surgery 3−5 weeks later. This study concluded that additional chemotherapy after CRT was well tolerated and may increase the pCR rate (18% vs. 25%), although this difference was not statistically significant. Furthermore, surgery was delayed for patients undergoing additional chemotherapy, and it is therefore possible that the increased pCR rate was actually attributable to a longer CRT-to-surgery interval. The oncological outcome was also not reported in this study.

Another additional chemotherapy regimen after CRT completion, investigated by Habr-Gama et al,[19] consisted of three extra cycles of bolus 5-FU. Their study included 29 patients, of whom 14 (48%) had a clinical complete response for at least 12 months and five (17%) had ypT0 after local excision. The overall complete response rate was 65%. However, none of the patients underwent TME, and occult cancer might not have been detected during the median follow-up period of 24 months. Another complication is that 17% of patients had stage I disease, which may have contributed to the high pCR rate.

In our study, continuously administered chemotherapy with 5-FU after the completion of radiotherapy until 2 weeks before surgery for locally advanced rectal cancer resulted in a pCR rate of 24.4%, which is higher than that obtained using conventional 5-FU-based CRT (15−20%).[5−7] The high pCR rate might be attributable to the prolonged exposure of irradiated tumor cells to chemotherapy. Furthermore, only 14 patients (11.8%) experienced Grade 3−4 toxicity and most tolerated the treatment well, with good treatment compliance. When compared to adding chemotherapeutic agents to CRT, such as oxaliplatin[14] or irinotecan,[17] which resulted in an incidence of Grade 3−4 toxicity >20%, the toxicity associated with our approach was more tolerable.

In the current study, the 5-year disease-free survival rate (96.6% vs. 65.6%, $p = 0.009$) and 5-year overall survival rate (96.6% vs. 75.8%, $p = 0.069$) were higher in the complete response group than in the noncomplete response group. Several previous studies reported that patients with a pCR after CRT had better long-term outcomes than those who did not achieve a pCR,[10−12] although another study found similar outcomes between these patient groups.[20] Our study also confirmed that patients with a pCR more often achieved 5-year disease free and overall survival. Overall survival did not differ significantly between pCR and non-pCR groups in our study, which might be due to the higher median age (61 years) and the relatively small size of the former group. The local recurrence rate, distant metastasis rate, and overall recurrence rate were lower in pCR group. These findings further support the importance of achieving a pCR in order to improve long-term oncological outcome.

There are a number of limitations to our study. First, although the pCR rate was higher in our study than in most studies reported in the literature, the benefit of the continued chemotherapy was difficult to interpret because of the absence of a control group. Second, owing to the retrospective design of the study, it is possible that some data were missing and that some cases of disease relapse had not been recorded because of poor communication. Furthermore, the radiation dose and chemotherapy dose cannot be well controlled in a retrospective study. Finally, the study had only a small sample size. A multicenter randomized prospective study is needed to validate our findings.

In conclusion, continued chemotherapy with 5-FU after the completion of neoadjuvant CRT until 2 weeks before curative surgery for locally advanced rectal cancer results in only a low level of toxicity and a good pCR rate. Patients who had a pCR after CRT had better long-term oncological outcomes.

References

1. Sauer R, Becker H, Hohenberger W, Rödel C, Wittekind C, Fietkau R, et al. Preoperative versus postoperative chemoradiotherapy for rectal cancer. *N Engl J Med* 2004;**351**:1731−40.
2. Frykholm GJ, Glimelius B, Pahlman L. Preoperative or postoperative irradiation in adenocarcinoma of the rectum: final treatment results of a randomized trial and an evaluation of late secondary effects. *Dis Colon Rectum* 1993;**36**:564−72.
3. Hyams DM, Mamounas EP, Petrelli N, Rockette H, Jones J, Wieand HS, et al. A clinical trial to evaluate the worth of preoperative multimodality therapy in patients with operable carcinoma of the rectum: a progress report of National Surgical Breast and Bowel Project Protocol R-03. *Dis Colon Rectum* 1997;**40**:131−9.
4. Biondo S, Navarro M, Marti-Rague J, Arriola E, Pares D, Del Rio C, et al. Response to neoadjuvant therapy for rectal cancer: influence on long-term results. *Colorectal Dis* 2005;**7**:472−9.
5. Lim SB, Yu CS, Hong YS, Kim TW, Kim JH, Kim JC, et al. Long-term outcomes in patients with locally advanced rectal cancer treated with preoperative chemoradiation followed by curative surgical resection. *J Surg Oncol* 2012;**106**:659−66.
6. Smith KD, Tan D, Das P, Chang GJ, Kattepogu K, Feig BW, et al. Clinical significance of acellular mucin in rectal adenocarcinoma patients with a pathologic complete response to preoperative chemoradiation. *Ann Surg* 2010;**251**:261−4.
7. An X, Lin X, Wang FH, Goodman K, Cai PQ, Kong LH, et al. Short term results of neoadjuvant chemoradiotherapy with fluoropyrimidine alone or in combination with oxaliplatin in locally advanced rectal cancer: a meta analysis. *Eur J Cancer* 2013;**49**:843−51.
8. Kapiteijin E, Marijnen CM, Nagtegaal ID, Putter H, Steup WH, Wiggers T, et al. Preoperative radiotherapy combined with total mesorectal excision for resectable rectal cancer. *N Engl J Med* 2001;**345**:638−46.
9. Bosset JF, Collette L, Calais G, Mineur L, Maingon P, Radosevic-Jelic L, et al. Chemotherapy with preoperative radiotherapy in rectal cancer. *N Engl J Med* 2006;**255**:1114−23.
10. Maas M, Nelemans PJ, Valentini V, Das P, Rödel C, Kuo LJ, et al. Long-term outcome in patients with a pathological complete response after chemoradiation for rectal cancer: a pooled analysis of individual patient data. *Lancet Oncol* 2010;**11**:835−44.
11. Kuo LJ, Liu MC, Jian JJ, Horng CF, Cheng TI, Chen CM, et al. Is final TNM staging a predictor for survival in locally advanced rectal cancer after preoperative chemoradiation therapy? *Ann Surg Oncol* 2007;**14**:2766−72.

12. Chari RS, Tyler DS, Anscher MS, Russell L, Clary BM, Hathorn J, et al. Preoperative radiation and chemotherapy in the treatment of adenocarcinoma of the rectum. *Ann Surg* 1995;**221**:778−86.
13. Gérard JP, Azria D, Gourgou-Bourgade S, Martel-Laffay I, Hennequin C, Etienne PL, et al. Comparison of two neoadjuvant chemoradiotherapy regimens for locally advanced rectal cancer: results of the Phase III trial ACCORD 12/0405-Prodige 2. *J Clin Oncol* 2010;**28**:1638−44.
14. Aschele C, Cionini L, Lonardi S, Pinto C, Cordio S, Rosati G, et al. Primary tumor response to preoperative chemoradiation with or without oxaliplatin in locally advanced rectal cancer: pathologic results of the STAR-01 randomized Phase III trial. *J Clin Oncol* 2011;**29**:2773−80.
15. Velenik V, Ocvirk J, Oblak I, Anderluh F. A Phase II study of cetuximab, capecitabine and radiotherapy in neoadjuvant treatment of patients with locally advanced resectable rectal cancer. *Eur J Surg Oncol* 2010;**36**:244−50.
16. Dewdney A, Cunningham D, Tabernero J, Capdevila J, Glimelius B, Cervantes A, et al. Multicenter randomized Phase II clinical trial comparing neoadjuvant oxaliplatin, capecitabine, and preoperative radiotherapy with or without cetuximab followed by total mesorectal excision in patients with high-risk rectal cancer (EXPERT-C). *J Clin Oncol* 2012;**30**:1620−7.
17. Mohiuddin M, Winter K, Mitchell E, Hanna N, Yuen A, Nichols C, et al., Radiation Therapy Oncology Group Trial 0012. Randomized Phase II study of neoadjuvant combined-modality chemoradiation for distal rectal cancer: Radiation Therapy Oncology Group Trial 0012. *J Clin Oncol* 2006;**24**:650−5.
18. Garcia-Aguilar J, Smith DD, Avila K, Bergsland EK, Chu P, Krieg RM, et al. Optimal timing of surgery after chemoradiation for advanced rectal cancer: preliminary results of a multicenter nonrandomized phase II prospective trial. *Ann Surg* 2011;**254**:97−102.
19. Habr-Gama A, Perez RO, Sabbaga J, Nadalin W, São Julião GP, Gama-Rodrigues J, et al. Increasing the rates of complete response to neoadjuvant chemoradiotherapy for distal rectal cancer: results of a prospective study using additional chemotherapy during the resting period. *Dis Colon Rectum* 2009;**52**:1927−34.
20. Onaitis MW, Noone RB, Fields R, Hurwitz H, Morse M, Jowell P, et al. Complete response to neoadjuvant chemoradiation for rectal cancer does not influence survival. *Ann Surg Oncol* 2001;**8**:801−6.