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ORIGINAL ARTICLE

Preoperative radiotherapy with capecitabine and mitomycin C in locally advanced rectal carcinoma

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Abstract
Purpose To evaluate the efficacy and safety of preoperative radiotherapy with capecitabine and mitomycin C in patients with locally advanced rectal cancer.
Methods A prospective, open-label, non-randomized, phase II study was performed on 49 patients with locally advanced rectal cancer. Preoperative radiotherapy was conducted on linear accelerators (15 or 18 MV) with a tumor dose of 45 Gy in 25 fractions over 5 weeks, combined with mitomycin C 7 mg/m^2 on days 1 and 29 and oral capecitabine 825 mg/m^2 twice daily on days 1–35. Surgery was performed 5–6 weeks after the end of chemoradiation. The primary study endpoint was histopathological complete regression rate (pCR; Dworak grade 4).
Results Disease stage at diagnosis was T3 in 34 patients (69%) and T4 in 15 patients (31%). Positive lymph nodes were diagnosed in 28 patients (57%). Toxicity (all grades) was documented in 35 patients (71%). Grade 3 toxicities were radiation dermatitis (25%), diarrhea (2%), neutropenia (2%), and granulocytopenia (2%). No patient experienced grade 4 toxicity. A pCR was seen in 8 (16%, 95% CI 9–29%) patients, a major response was noted in 24 (49%) patients and a minor response in 14 (29%) patients. R0 resection was performed in 46 patients (93.9%) and R1 in 3 patients (6.1%). Histopathological tumor downstaging was documented in 26 patients (53%). One-year disease-free survival was 93.3% and 1-year survival was 97.7%.
Conclusion Preoperative chemoradiation with capecitabine and mitomycin C appeared to be effective with low toxicity in patients with locally advanced rectal cancer.

Keywords Capecitabine · Mitomycin C · Radiotherapy · Rectal cancer · Locally advanced disease

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Introduction

Preoperative chemoradiotherapy is widely accepted as a standard treatment option in locally advanced rectal cancer. Studies have shown that preoperative chemoradiotherapy results in better local control (i.e., a reduction of local recurrence rate by 20–50%), increased histopathological complete regression rate (pCR) by 10–30%, increased likelihood of curative and sphincter-preserving resection, and increased long-term survival [1–4].

The most commonly used neoadjuvant treatment in locally advanced rectal cancer involves radiotherapy 45–50.4 Gy with concurrent 5-fluorouracil (5-FU) administered either as bolus doses during the first and last weeks of radiotherapy or as a continuous infusion during the whole radiotherapy treatment period. The rationale for

combining cytotoxic agents and radiotherapy is based on the ability of some drugs to act as radiosensitizers [5]. The current research is focused on identifying the best combination of chemotherapy agents to be used with radiotherapy.

Capecitabine is an oral fluoropyrimidine that is converted to 5-FU via thymidine phosphorylase in the tumor tissue. Radiation has been shown to preferentially increase tumor thymidine phosphorylase levels by induction of tumor necrosis factor [6]. In a fluoropyrimidine-resistant, colorectal cancer xenograft model, exposure to capecitabine before irradiation demonstrated a supra-additive effect compared with radiation alone [7].

Mitomycin C is a cytostatic drug that has been widely used in the treatment of metastatic colorectal cancer for many years with good treatment results and low toxicity. It has also been used as a neoadjuvant agent in locally advanced rectal cancer in combination with radiotherapy and other cytotoxic agents [8]. Mitomycin C inhibits DNA and RNA synthesis by interfering with DNA cross-linking, primarily at guanine and cytosine pairs. Although mitomycin C is not cell cycle specific, it is known to induce marked cell-cycle arrest at the G2–M transition [8]. In combination with radiation, mitomycin C acts as a hypoxic cell sensitizer and is thought to prevent repopulation, although the exact mechanism remains elusive [5, 8]. Mitomycin C is also known to upregulate the tumor levels of thymidine phosphorylase in rectal cancer tissues, which may enhance the efficacy of capecitabine [9].

The purpose of this study was to evaluate the safety and efficacy of preoperative capecitabine plus mitomycin C and radiation therapy in patients with locally advanced rectal cancer.

Materials and methods

Study design

This was a prospective, open-label, non-randomized, phase II study, conducted at two centers, the Institute for Oncology and Radiology of Serbia and the Institute for Gastrointestinal Diseases, University Clinical Center of Serbia. The primary endpoint of the study was pCR. Secondary endpoints were clinical response, disease-free survival, overall survival, and toxicity. The study was approved by a local ethics committee and was performed in accordance with the ethical standards laid down by the Declaration of Helsinki.

Patient population

The study inclusion criteria were as follows: minimum age of 18 years; histologically confirmed, locally advanced stage II (T3/T4, N0, M0) or stage III (T3/T4, N1/2, M0) rectal adenocarcinoma located up to 16 cm from the anocutaneous line; no pretreatment except formation of an artificial anus (e.g., due to imminent intestinal obstruction); Eastern Cooperative Oncology Group (ECOG) status ≤ 2; sufficient bone marrow function (i.e., leukocytes $> 3.5 \times 10^9$/l, neutrophils $> 1.5 \times 10^9$/l, thrombocytes $> 100 \times 10^9$/l, hemoglobin > 10 g/dl); sufficient liver function (bilirubin < 2.0 mg/dl, and aspartate aminotransferase, alanine aminotransferase, alkaline phosphatase, gamma glutamyl transpeptidase ≤ 3 times the upper limit of the normal range); serum creatinine < 1.5 mg/dl; and creatinine clearance > 50 ml/min. In addition, patients were explained the requirements of the study protocol and had given their written informed consent to participate.

Exclusion criteria included prior pelvic irradiation or chemotherapy; secondary malignancies, except basal cell carcinoma of the skin or in situ cervical carcinoma; pregnancy or breastfeeding; inability to comply with the protocol and to undergo treatment and follow-up examinations; unstable cardiac disease in spite of drug treatment; myocardial infarction within the past 6 months; neurological or mental disorders; active, uncontrollable infection or sepsis; active disseminated intravascular coagulation disorder; inflammatory bowel diseases; malabsorption syndrome; synchronous colic or rectal tumors; and other uncontrolled severe disease precluding administration of chemotherapy and radiation.

Study treatment

Patients received oral capecitabine 825 mg/m^2 twice daily on days 1–35. Mitomycin C 7 mg/m^2 was given on days 1 and 29 as a 2-h intravenous infusion in 500 ml of glucose 5%.

Radiotherapy was initiated on day 1 of chemotherapy after administration of mitomycin C. It was delivered at a dose of 1.8 Gy once daily according to the International Commission on Radiation Units and Measurements (ICRU) recommendations [10] five times per week, in 25 fractions over a period of 5 weeks, until a total reference dose of 45 Gy was reached. Radiotherapy was delivered with high-energy photons (15 or 18 MV) on linear accelerators.

Five to 6 weeks after completion of chemoradiotherapy, patients underwent surgery.

Depending on the tumor stage as determined by histopathology after surgery, and consistent with routine hospital practice, patients received adjuvant therapy consisting of 6 cycles of 5-fluorouracil and leucovorin.

Diagnostic work-up

Patients were assessed at baseline by digital rectal examination, total colonoscopy with biopsy of the rectal tumor,

and determination of the distance between the lower edge of the tumor and the anocutaneous line, pelvic MRI, abdominal CT, transrectal ultrasonography, and chest X-ray. All these examinations were repeated 5–6 weeks after completing chemoradiotherapy and before surgery.

Complete blood counts, biochemistry including liver function tests, and an assessment of clinical symptoms and toxicities were performed at baseline and weekly during chemoradiotherapy. Patients with grade 3 or 4 hematological toxicity were hospitalized, and a peripheral blood count was performed every day until recovery from the nadir values.

Efficacy and safety evaluations

Treatment response was evaluated 5–6 weeks after completing chemoradiotherapy according to RECIST criteria [11]. Overall survival was defined as the time from the start of chemotherapy (day 1) to death from any cause. Disease-free survival was defined as the time from the start of chemotherapy (day 1) to the date on which progression of disease was first noted. The National Cancer Institute Common Toxicity Criteria (NCI-CTC) were used to grade treatment-emergent toxicity [12].

Independent response review was performed by members of the joint interdisciplinary committee for gastro-intestinal tumors of The Institute for Oncology and Radiology of Serbia and The University Clinic for Digestive Diseases. Members of the committee were not involved in the study.

Histopathological examination

The standardized histopathological examination of the resected tumor specimens included the assessment of morphology (histological type and grade), tumor spread (ypTNM, R classification), and quality of the total mesorectal excision. For each patient, a histopathological assessment of tumor regression in accordance with the grading method established by Dworak et al. [13] was made: grade 0 = no regression; grade 1 = minimal regression (defined as a dominant tumor mass with obvious fibrosis and vasculopathy); grade 2 = moderate regression (defined as fibrotic changes dominant with few tumor cell nests easy to locate); grade 3 = good regression (defined as very few isolated tumor cells that are hard to find under the microscope, in predominantly fibrotic tissues and pools of mucus); grade 4 = complete regression (defined as no tumor cells, only fibrotic tissue). Responses were thus defined as complete or pCR (grade 4), major (grades 3 and 2), or minor (grade 1).

Follow-up examinations and analyses

Follow-up procedures were performed every 3 months within the first 2 years and every 6 months during years 3–5. Furthermore, long-term adverse effects were assessed using a standardized assessment form at l, 3, and 5 years after surgery. Follow-up examinations and analyses included survival status, physical examination, and tumor assessment.

Statistical analysis

All analyses were performed on an intention-to-treat basis. All subjects enrolled in the study who received at least one dose of study medication were included in the safety analyses. The overall rate of histopathologically confirmed complete remission or pCR (i.e., Dworak grade 4) was presented with 95% confidence intervals (CI). Kaplan–Meier procedures were used for time-to-event data. The Simon two-stage minimax design was applied to test the null hypothesis that the pCR rate was 15% versus the alternative hypothesis that the pCR rate was $\geq$30%; the minimal clinically meaningful change was set to be 15%. To detect such a change, with $\alpha = 0.05$ and $\beta = 0.20$, a sample size of 49 patients was required. Twenty-one patients were planned to be included in the first cohort. In case three or less responses were observed in the first 21 patients, the trial would have been terminated. Alternatively, four or more responses warranted continuation to the second stage with additional 28 patients included, for a total of 49 patients.

Results

From October 2006 to April 2008, a total of 49 patients were enrolled. The median follow-up was 18 months (range 6–29 months). All 49 enrolled patients were analyzed for clinical response, histopathological response, toxicity, overall survival, and disease-free survival.

All patients had measurable disease on an MRI scan. The median age of the study population was 58 years, and all patients had a baseline ECOG status of 0 or 1. The disease stage at diagnosis was T3 in 34 patients (69.4%) and T4 in 15 patients (30.6%). Positive lymph nodes were diagnosed in 28 patients (57.1%). In all patients, tumors were localized in either the distal (36 patients) or middle third (13 patients) of the rectum. Patient characteristics are listed in Table 1. The mean time from the end of chemoradiotherapy to surgery was 45 (range 35–60) days.

Table 1 Patient characteristics at baseline ($N = 49$)

Characteristics	No. of patients	Percent
Sex		
Female	8	16.3
Male	41	83.7
Race		
Caucasian	49	100.0
Age (years)		
Median	58	
Range	25–80	
Mean	56.2	
ECOG status		
0	28	57.1
1	21	32.9
Histopathology grading		
Well differentiated	31	63.3
Moderately differentiated	16	32.6
Poorly differentiated	2	4.1
T classification		
T3	34	69.4
T4	15	30.6
N classification		
N0	21	42.9
N+	28	57.1
M classification		
M0	49	100.0
M1	0	0

ECOG Eastern cooperative oncology group

Tumor response

Confirmed objective clinical tumor responses were seen in 40 (82%) patients (95% CI 69–90%) calculated on an intention-to-treat basis. Complete response was noted in 10 (20.4%) patients, partial response in 30 (61.2%) patients, and stable disease in 9 (18.4%) patients. No patient showed disease progression.

Pathologic tumor response expressed as ypTNM stage, and tumor regression grade were assessed in all patients (Table 2). Histopathological complete response (pCR) was achieved in 8 (16%, 95% CI 9–29%) patients, whereas 24 (49%) and 14 (29%) patients showed major and minor responses, respectively. No histopathological response was detected in 3 (6%) patients.

Surgery

All patients underwent surgery after chemoradiotherapy. Of the 49 patients, 23 (46.9%) underwent abdominoperineal resection secundum Milles, 25 (51%) underwent low anterior resection secundum Dixon and one patient underwent a Hartman procedure. R0 resection was achieved in 46 patients (93.9%) and R1 resection in 3 patients (6.1%). All histopathological non-responders had an R1 resection. No patient died during surgery. Tumor downstaging was noted in 26 patients (53.1%).

Major and minor postoperative complications were observed in 8 patients and consisted of anastomotic leakage (4 patients), delayed wound healing (3 patients), and perianal abscesses (1 patient).

Of the 49 patients who underwent surgery, 24 patients (49%) had positive lymph nodes (20 patients had pN1 and 4 patients had pN2) and received adjuvant chemotherapy according to the hospital protocol.

Table 2 Pathologic tumor response: correlation between ypTNM and tumor response grade ($N = 49$)

Stage	Grade 4	Grade 3	Grade 2	Grade 1	Grade 0
ypT0N0	8				
ypT2N0		5			
ypT2N1		1			
ypT3N0			9	4	
ypT3N1			9	7	
ypT3N2				3	
ypT4N0					1
ypT4N1					1
ypT4N2					1
Total	8	6	18	14	3

grade 0 = no regression; grade 1 = minimal regression, i.e., dominant tumor mass with obvious fibrosis and vasculopathy; grade 2 = moderate regression, i.e., fibrotic changes dominant with few tumor cell nests easy to locate; grade 3 = good regression, i.e., very few isolated tumor cells that are hard to find under the microscope, in predominantly fibrotic tissues and pools of mucus; grade 4 = complete regression, i.e., no tumor cells, only fibrotic tissue

ypTNM tumor classification after neoadjuvant therapy

Toxicity

Almost all patients received >90% of planned dose intensity for both drugs (capecitabine 92%, range 69–108%; mitomycin C 94%, range 54–105%). Of the 49 patients, toxicity (grades 1–4) was documented in 35 patients (71.4%). Radiotherapy was temporarily interrupted in one patient due to grade 3 diarrhea that lasted for 7 days. All patients completed radiotherapy. Chemotherapy was stopped in 2 patients (4.1%), due to phlebothrombosis (one patient) and grade 3 neutropenia and grade 3 diarrhea (one patient).

Hand-foot syndrome was noted in only 3 patients (6.1%), and it was low grade (grade 1 or 2) in all cases. Hematological toxicities occurred in 14 patients (28.6%) and non-hematological toxicities in 33 patients (67.3%). There were no treatment-related deaths.

Table 3 Hematologic toxicity: worst toxicity by patient ($N = 49$)

Toxicity	NCI-CTC grade (no. of patients)				
	Grade 0	Grade 1	Grade 2	Grade 3	Grade 4
Anemia	40	7	2	0	0
Neutropenia	38	3	7	1	0
Granulocytopenia	40	5	3	1	0
Thrombocytopenia	43	6	0	0	0

NCI-CTC National cancer institute common toxicity criteria

A summary of hematological toxicities is presented in Table 3. Grade 3 neutropenia was observed in only one patient. The nadir occurred on days 9–16 and was not associated with febrile episodes. No grade 3/4 anemia or thrombocytopenia and no grade 4 hematological events were observed.

A summary of non-hematological toxicities is presented in Table 4. The most common non-hematological adverse events were radiation dermatitis noted in 29 patients (59.2%) and diarrhea in 15 patients (30.6%). Non-hematological events were usually of short duration, reversible, and easy to manage. No grade 4 events were observed.

Long-term outcomes

The 1-year disease-free survival rate was 93.3%, and the 2-year disease-free survival rate was 82%. The 1-year overall survival rate was 97.7%. At the last follow-up, 5 of 49 patients had relapsed. One patient had died due to distant progression of disease (liver), two patients had local relapses, one patient had local relapse and lung and liver metastases, and one patient had lymphonodal dissemination.

Table 4 Non-hematologic toxicity: worst toxicity by patient ($N = 49$)

Toxicity	NCI-CTC grade (no. of patients)				
	Grade 0	Grade 1	Grade 2	Grade 3	Grade 4
Elevated creatinine	46	3	0	0	0
Elevated bilirubin	47	1	1	0	0
Elevated transaminases	48	0	1	0	0
Nausea	47	2	0	0	0
Vomiting	48	1	0	0	0
Diarrhea	34	6	7	2	0
Mucositis	49	0	0	0	0
Radiation dermatitis	20	7	10	12	0
Neurotoxicity	48	1	0	0	0

NCI-CTC National cancer institute common toxicity criteria

Discussion

Our results show that preoperative radiotherapy combined with capecitabine and mitomycin C has promising activity with a clinical tumor response rate of 82%, a pCR of 16%, and tumor downstaging rate of 53%. The regimen also has an acceptable tolerability profile. No grade 4 toxicity was observed and, with the exception of grade 3 radiation dermatitis that occurred in 25% of patients, other grade 3 events were documented in ≤4% of patients. By using a low cumulative dose of mitomycin C (14 mg/m^2) as part of our regimen, we avoided unwanted dose-related toxicities associated with this agent (i.e., thrombotic thrombocytopenic purpura–hemolytic uremic syndrome) [14].

It is of interest that our findings compare favorably with two studies that investigated combinations of 5-FU and mitomycin C with radiotherapy in the preoperative setting [15, 16]. In the FUMIR study [15], 83 patients were treated with mitomycin C 10 mg/m^2 on day 1 plus a 24-h continuous intravenous infusion of 5-FU 1,000 mg/m^2 on days 1–4 with concurrent radiotherapy (tumor dose 37.8 Gy, conventionally fractionated 1.8 Gy per day, 5 times per week). Almost all patients (98%) had T3 tumors. The response rate was 77% and pCR was 8%. Tumor downstaging was reported in 57% of patients. Hematological toxicity grade 3/4 was documented in 12% of patients, one of whom died from septic complications due to leucopenia. Grade 3 diarrhea was registered in 2% of patients. Treatment was temporarily interrupted in 11% of patients due to acute complications. Another study that investigated the combination of 5-FU and mitomycin C in the neoadjuvant setting was published by Chau et al. [16]. Thirty-six patients received a protracted intravenous infusion of 5-FU 300 mg/m^2/day for 12 weeks with mitomycin C 7 mg/m^2/day given by intravenous bolus every 6 weeks. At the beginning of week 13, the 5-FU dosage was reduced to 200 mg/m^2/day and combined with concomitant radiotherapy 50.4 Gy. Postoperatively, patients received 12 weeks of mitomycin C and 5-FU at the same doses as preoperatively. There was no grade 3 or 4 hematological toxicity. Nine patients (25%) had grades 3 and 4 non-hematological toxicity, such as diarrhea, stomatitis, infection, and hand-foot syndrome. The response rate was 81%. A pCR was confirmed in one patient, and 25 patients (74%) had downstaging of their primary tumor on histological examination. While the usual limitations of cross-trial comparisons should be taken into account, the findings from the present study suggest that preoperative radiotherapy with capecitabine and mitomycin C achieves a higher pCR rate and has a more favorable toxicity profile (especially with regard to hematological toxicity) than 5-FU and mitomycin C combined with radiotherapy. Furthermore, standard 5-FU-based regimens used in

combination with radiotherapy involve either intermittent bolus doses or a continuous infusion necessitating central line placement. Capecitabine, on the other hand, can be given as a convenient outpatient oral regimen which offers continuous cytotoxic exposure during radiotherapy without the need for a central line.

5-FU is commonly used in clinical practice as a radiosensitizer. However, capecitabine is now known to be at least as effective as intravenous 5-FU/LV in the treatment of colorectal cancer in both the metastatic [17, 18] and adjuvant settings [19]. Pharmacoeconomic benefits in terms of less medical resource utilization with capecitabine have also been documented [20]. Several phase III trials are currently comparing preoperative capecitabine and 5-FU combined with radiotherapy in patients with locally advanced rectal cancer. In a preliminary report from the ongoing German ML16646 study [21], improved tumor downstaging was reported with capecitabine versus 5-FU chemoradiotherapy in patients with locally advanced rectal cancer. The multinational NSABP R-04 trial, which is comparing preoperative radiotherapy plus capecitabine ± oxaliplatin versus radiotherapy plus 5-FU ± oxaliplatin in a planned sample of 1,606 patients, is also currently ongoing. The final results of these studies will help to determine the place of capecitabine versus 5-FU in this setting.

To our knowledge, no other clinical trial has investigated the efficacy of preoperative radiotherapy combined with capecitabine and mitomycin C in patients with locally advanced rectal cancer. However, this combination has recently been investigated in patients with anal cancer [22]. The EXTRA study [22] used a schedule that was similar to our own except that capecitabine was not given at weekends and mitomycin C was delivered as a single 12 mg/m^2 dose on day 1 rather than as two 7 mg/m^2 doses. The toxicity profile of this regimen was similar to that observed in our study. The major acute toxicity reported by Glynne-Jones et al. [22] was skin desquamation; grade 3 events were reported in 39% of patients. All other grade 3/4 toxicities (diarrhea, neutropenia, and thrombocytopenia) occurred in 3–10% of patients.

Although no studies have investigated the efficacy of preoperative radiotherapy combined with capecitabine and mitomycin C in patients with locally advanced rectal cancer, some insight can be gained by comparing our findings with those of phase II studies that investigated preoperative radiotherapy plus capecitabine alone in patients with locally advanced rectal cancer. In these studies, pCR rates ranged from 4 to 23% and downstaging rates from 42 to 84% [23]. Grade 3 diarrhea was observed in 3–13% of patients. As in our study, grade 3/4 hematological adverse events and grade 4 toxicities were rare or were not observed at all. The incidence of grade 3 dermatitis, however, appeared to be higher in our study (25%) than in studies that did not use mitomycin C (2–6%) [23]. A direct comparison of preoperative radiotherapy with capecitabine with or without mitomycin C is needed to clarify the relative merits of these two regimens.

In conclusion, preoperative radiotherapy with capecitabine and mitomycin C showed promising efficacy with a good tolerability profile in patients with locally advanced rectal cancer. Further research on this combination is merited.

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References

1. Valentini V, Glimelius B, Minsky B, Van Cutsem E, Bartelink H, Beets-Tan RG, Gerard JP, Kosmidis P, Pahlman L, Picciocchi A, Quirke P, Tepper J, Tonato M, Van de Velde CJ, Cellini N, Latini P (2005) The multidisciplinary rectal cancer treatment: main convergences, controversial aspects and investigational areas which support the need for an European Consensus. Radiother Oncol 76:241–250
2. Bujko K, Nowacki MP (2002) Emerging standards of radiotherapy combined with radical rectal cancer surgery. Cancer Treat Rev 28:101–103
3. Bosset JF, Calais G, Daban A, Berger C, Radošević-Jelić LJ, Maingon P, Bardet E, Pierart M, Briffaux A, EORTC Radiotherapy Group (2004) Preoperative chemoradiotherapy versus preoperative radiotherapy in rectal cancer patients: assessment of acute-toxicity and treatment compliance. Report of the 22921 randomized trial conducted by the EORTC Radiotherapy Group. Eur J Cancer 40:219–224
4. Gérard JP, Conroy T, Bonnetain F, Bouché O, Chapet O, Closon-Dejardin MT, Untereiner M, Leduc B, Francois E, Maurel J, Seitz JF, Buecher B, Mackiewicz R, Ducreux M, Bedenne L (2006) Preoperative radiotherapy with or without concurrent fluorouracil and leucovorin in T3-4 rectal cancers: results of FFCD 9203. J Clin Oncol 24:4620–4625
5. Seiwert YT, Salama JK, Everett EV (2007) The concurrent chemoradiation paradigm—general principles. Nat Clin Pract Oncol 4:86–100
6. Blanquicett C, Gillespie GY, Nabors LB, Miller CR, Bharara S, Buchsbaum DJ, Diasio RB, Johnson MR (2002) Induction of thymidine phosphorylase in both irradiated and shielded, contralateral human U87MG glioma xenografts: implications for a dual modality treatment using capecitabine and irradiation. Mol Cancer Ther 1:1139–1145
7. Sawada N, Ishikawa T, Sekiguchi F, Tanaka Y, Ishitsuka H (1999) X-ray irradiation induces thymidine phosphorylase and enhances the efficacy of capecitabine (Xeloda) in human cancer xenografts. Clin Cancer Res 5:2948–2953
8. Colvin OM, Friedman HS (2005) Alkylating agents—mitomycin C. In: DeVita VT, Hellman S, Rosenberg SA (eds) Cancer principles and practice of oncology, 7th edn. Lippincot Williams and Wilkins, Philadelphia, pp 332–344
9. Ogata Y, Matono K, Sasatomi T, Ishibashi N, Torigoe S, Fukumitsu T, Mizobe T, Yamashita N, Yanagawa T, Shirouzu K (2006) Upregulation of thymidine phosphorylase in rectal cancer tissues by mitomycin C. J Surg Oncol 93:47–55

10. ICRU Report 50 (1993) Prescribing, recording and reporting photon beam therapy. International Commission on Radiation Units and Measurements, Washington
11. Therasse P, Arbuck SG, Eisenhauer EA, Wanders J, Kaplan RS, Rubinstein L, Verweij J, Van Glabbeke M, van Oosterom AT, Christian MC, Gwyther SG (2000) New guidelines to evaluate the response to treatment in solid tumors. J Natl Cancer Inst 92:205–216
12. NCI-Common Toxicity Criteria (1999) Version 2.0. National Cancer Institute, Division of Cancer Treatment
13. Dworak O, Keilholz L, Hoffmann A (1997) Pathological features of rectal cancer after preoperative radiochemotherapy. Int J Colorectal Dis 12:19–23
14. Medina PJ, Sipols JM, George JN (2001) Drug-associated thrombotic thrombocytopenic purpura-hemolytic uremic syndrome. Curr Opin Hematol 8:286–293
15. Valentini V, Coco C, Picciocchi A, Morganti A, Trodella L, Ciabattoni A, Cellini F, Barbaro B, Cogliandolo S, Nuzzo G, Doglietto GB, Ambesi-Impiombato F, Cosimelli M (2002) Does downstaging predict improved outcome after preoperative chemoradiation for extraperitoneal locally advanced rectal cancer? A long-term analysis of 165 patients. Int J Radiat Oncol Biol Phys 53:664–674
16. Chau I, Allen M, Cunningham D, Tait D, Brown G, Hill M, Sumpter K, Rhodes A, Wotherspoon A, Norman AR, Hill A, Massey A, Prior Y (2003) Neoadjuvant systemic fluorouracil and mitomycin C prior to synchronous chemoradiation is an effective strategy in locally advanced rectal cancer. Br J Cancer 88:1017–1024
17. Van Cutsem E, Twelves C, Cassidy J, Allman D, Bajetta E, Boyer M, Bugat R, Findlay M, Frings S, Jahn M, McKendrick J, Osterwalder B, Perez-Manga G, Rosso R, Rougier P, Schmiegel WH, Seitz JF, Thompson P, Vieitez JM, Weitzel C, Harper P, Xeloda Colorectal Cancer Study Group (2001) Oral capecitabine compared with intravenous fluorouracil plus leucovorin in patients with metastatic colorectal cancer: results of a large phase III study. J Clin Oncol 19:4097–4106
18. Hoff PM, Ansari R, Batist G, Cox J, Kocha W, Kuperminc M, Maroun J, Walde D, Weaver C, Harrison E, Burger HU, Osterwalder B, Wong AO, Wong R (2001) Comparison of oral capecitabine versus intravenous fluorouracil plus leucovorin as first-line treatment in 605 patients with metastatic colorectal cancer: results of a randomized phase III study. J Clin Oncol 19:2282–2292
19. Twelves C, Wong A, Nowacki MP, Abt M, Burris H 3rd, Carrato A, Cassidy J, Cervantes A, Fagerberg J, Georgoulias V, Husseini F, Jodrell D, Koralewski P, Kröning H, Maroun J, Marschner N, McKendrick J, Pawlicki M, Rosso R, Schüller J, Seitz JF, Stabuc B, Tujakowski J, Van Hazel G, Zaluski J, Scheithauer W (2005) Capecitabine as adjuvant treatment for stage III colon cancer. N Engl J Med 352:2696–2704
20. Twelves C, Boyer M, Findlay M, Cassidy J, Weitzel C, Barker C, Osterwalder B, Jamieson C, Hieke K, Xeloda Colorectal Cancer Study Group (2001) Capecitabine (Xeloda) improves medical resource use compared with 5-fluorouracil plus leucovorin in a phase III trial conducted in patients with advanced colorectal carcinoma. Eur J Cancer 37:597–604
21. Hofheinz R, Wenz F, Post S, Matzdorff A, Laechelt S, Mueller L, Link H, Moehler M, Burkholder I, Hochhaus A (2009) Capecitabine (Cape) versus 5-fluorouracil (5-FU)-based (neo-)adjuvant chemoradiotherapy (CRT) for locally advanced rectal cancer (LARC): safety results of a randomized, phase III trial. J Clin Oncol 27:15s (suppl; abstr 4014)
22. Glynne-Jones R, Meadows H, Wan S, Gollins S, Leslie M, Levine E, McDonald AC, Myint S, Samuel L, Sebag-Montefiore D, National Cancer Research Institute Anal Sub Group and Colorectal Clinical Oncology Group (2008) EXTRA-a multicenter phase II study of chemoradiation using a 5 day per week oral regimen of capecitabine and intravenous mitomycin C in anal cancer. Int J Radiat Oncol Biol Phys 72:119–126
23. Glynne-Jones R, Dunst J, Sebag-Montefiore D (2006) The integration of oral capecitabine into chemoradiation regimens for locally advanced rectal cancer: how successful have we been? Ann Oncol 17:361–371