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ORIGINAL ARTICLE

Neoadjuvant treatment for locally advanced rectal adenocarcinoma with concomitant radiotherapy and oral capecitabine

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Summary

Purpose: *Concomitant chemoradiotherapy prior to surgery of locally advanced rectal carcinoma (clinical T3-4, and/or N+) might improve the therapeutic results. We report on our clinical experience with 34 patients receiving concurrent preoperative radiotherapy and capecitabine.*

Patients and methods: *Between September 2001 and March 2003, 34 patients with a median age of 62 years (range 18-75 years) were treated for adenocarcinoma of the rectum. Capecitabine was administered orally at a dose of 825 mg/m² twice-daily concomitantly every day during pelvic irradiation. The planned total dose of radiotherapy was 50.4 Gy, given with daily fractions of 1.8Gy, 5 days a week, over a period of about 5.5 weeks. Large pelvic dose (PTV-1) was 45.0 Gy/25 fractions in 5 weeks. Higher dose up to 50.4 Gy in further 3 fractions was given using boost fields (PTV-2). Radiotherapy was performed with high-energy photon beam (18 MV) linear accelerator using 3-dimensional (3D) treatment planning for 3 or 4 fields technique.*

Results: *Toxicity was low: grade (G) 3 local dermatitis in 2 (6%), G3 diarrhea in 3 (9%) and G3 leucopenia in 1 (3%) patients. However, 2(6%) patients required drug dose reduction by 80%. Sphincter-sparing surgery was possible in 25 (76.5%) patients while 9 (26%) patients had radical surgery with removal of all macroscopic disease. Tumor mass downstaging by TNM criteria has been achieved in all of the treated patients. Pathological (p) complete response (CR) was verified in 7 (21%) patients and minimal microscopic residual cancer was found in 6 (17%) patients, for a total of 13 (38%) patients with substantial disease remission.*

Conclusion: *Preoperative concomitant radiotherapy and oral capecitabine chemotherapy for locally advanced rectal adenocarcinoma appears to be an effective and safe therapeutic choice, improving the chance for rectal-sparing surgery. The follow-up time is rather short to evaluate time to progression and survival.*

Key words: capecitabine, chemoradiation, downstaging, preoperative radiotherapy, radiosensitization, rectal cancer

Introduction

Colorectal carcinoma is one of the most common malignant diseases [1]. Its incidence in the Czech Republic amounts to approximately 25.6 per 100,000 men and 14.5 per 100,000 women, which is the highest in worldwide statistics. Seven percent of all cancer deaths are due to rectal adenocarcinoma. The prognosis of this disease is dependent on the stage at the time of diagnosis, being more severe in cases with distal rectal cancer.

Rectal cancer occurs in the region of bowel below the peritoneal reflection, including approximately 15 cm of intestine above the anal verge. The risk of local recurrence is related to the disease extension beyond the rectal wall and the involvement of lymph nodes. Locoregional failure occurs in 20-50% of patients with transmural or node-positive cancers [2-6]. Recently, it has been shown that preoperative radiotherapy reduces local recurrences and improves over-

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all survival, and a benefit regarding locoregional control was demonstrated even in cases with suboptimal surgery [7-9].

Considering the high risk of a local relapse, postoperative adjuvant chemoradiotherapy has become a standard recommendation for the therapy of locally advanced tumors (T3-4). This approach leads to a reduction of risk of local relapses, distant dissemination and to improvement of 5-year survival. Randomized studies proved that using preoperative radiotherapy for locally advanced rectal adenocarcinomas (T3-4,N1-3) enables better local disease control but also lower toxicity (myelotoxicity, skin toxicity) compared with postoperative radiotherapy. Major study groups have shown that adjuvant and neoadjuvant chemoradiotherapy, based on radiosensitization by 5-fluorouracil (5-FU) offer a clear benefit in relation with tumor control and survival [10].

In patients with primary, locally advanced or unresectable disease, preoperative chemoradiation increases the resectability rate and provides downstaging of the tumor with 10-30% pCR. About 60-90% of the preoperatively treated patients are able to undergo surgery with curative intent. Nevertheless, the local failure rate in patients with histologically negative surgical margins is still 10-30%. Lately, attention has been drawn to a strategy of concomitant chemoradiotherapy for locally advanced rectal cancer. The potential advantage of this approach is the different mechanism of action of chemotherapy and radiation on a heterogeneous tumor population. The interaction of concurrent radiation and the appropriate cytotoxic drugs increases the therapeutic index compared with sequential administration of the two modalities. Therefore, tumor reduction after neoadjuvant therapy can prevent mutilating abdominoperineal rectal resection [11-14].

Preoperative radiation treatment with concomitant intravenous (i.v.) infusion of 5-FU is known to be effective in shrinking and downstaging of tumors. However, i.v. chemotherapy has often been limited by its toxicity and poor patients´ compliance.

Capecitabine is a rationally designed oral tumor-activated and tumor-selective fluoropyrimidine carbamate, with the aim of preferential conversion to 5-FU at the tumor site by exploiting the higher levels of thymidine phosphorylase (TP) found in tumor tissues compared to normal tissues. It is one of a series of 5´-deoxy-5-fluorocytidine (5´-DFCR) derivatives, which were synthesized with the objective of having them converted to 5-FU via 5´-DFUR under the action of liver carboxylesterase, and then cytidine deaminase present in the liver or tumor tissue and then to 5-FU by TP which is also found in the gastrointestinal tract [15,16].

Therefore, concomitant chemoradiotherapy with capecitabine theoretically represents a much more practical alternative than the so far used radiosensitizer 5-FU [17,18].

Patients and methods

Combination of capecitabine with standard preoperative radiotherapy of the pelvis were administered to patients with locally advanced rectal carcinoma without distant dissemination. From September 2001 to March 2003 34 patients were prospectively included in this study which was approved by the Ethics Committee of Masaryk Memorial Cancer Institute.

Study objectives

The primary objective of the study was to determine the pCR rate in patients treated preoperatively with capecitabine and standard-technique radiotherapy of the pelvic region after optimal surgery.

Secondary objectives were the evaluation of the effectiveness of the combined modality treatment (tumor response) and the evaluation of toxicity.

Eligibility criteria and diagnostic work-up

Locally advanced rectal cancer was defined as tumor extension through the bowel wall and/or with perirectal nodal involment without evidence of distant metastases. Eligibility criteria included histology of adenocarcinoma; clinical stage T3-T4 or N1-N3 according to the TNM 1997 staging system; fixed inoperable tumor; age 18-75 years; Eastern Cooperative Oncology Group (ECOG) performance score 0-2; no prior malignancy other than nonmelanoma skin or *in situ* cervical cancer; no prior chemotherapy, immunotherapy, or radiotherapy to the pelvis; no serious active infection; no pregnant or lactating woman; adequate heart function; no significant neurological or psychiatric disorders; life expectancy >3 months; neutrophils $>2\times10^9$/L, platelets $>100\times10^9$/l, serum creatinine ≤ 140 mmol/L (1.6 mg/dL), or creatinine clearance >60 mL/min; written informed consent.

Pretreatment work-up included physical and digital rectal examination, pelvic and abdominal CT, transrectal ultrasonography, chest X-ray, colonoscopy and proctoscopy with biopsy, gynecologic and urologic examinations, serum CEA levels, and blood tests (full blood count, renal and liver function tests).

Patient population

Four to 5 weeks after the end of preoperative chemoradiotherapy, the patients were evaluated for possible surgery. Colostomy before or during therapy was allowed if necessary. The patient characteristics are summarized in Table 1.

Capecitabine

All of the patients received oral capecitabine therapy (Xeloda®, Roche) in two divided doses every day (Monday to Sunday) of the week during radiotherapy (5.5 weeks). Capecitabine was administered at a dose of 825 mg/m^2 twice-daily, with doses 12h apart within 30min after the end of a meal (breakfast, dinner). The a.m. dose should have been taken approximately 2h ± 30min prior to radiotherapy at the same time every day.

Radiotherapy

Three-dimensional conformal radiotherapy was delivered using linear accelerator with 18 MV photon beams and with an isocentric technique (source-axis distance of 100 cm). Radiotherapy was given in conventional fractionation. The daily fraction dose was 1.8 Gy, and a total dose of 50.4 Gy was delivered with 5 weekly fractions over a period of 5.5 weeks. The dose was referred to the axis intersection (ICRU Report 50). Simulation and irradiation were performed with full bladder in prone position. During simulation rectal contrast with barium sulfate enema was used (Figure 1).

The planning target volume 1 (PTV 1) included the primary tumor, mesorectum, and internal iliac nodes (plus external iliac nodes for T4 tumors). The classic box or 3-field convergent technique was used: the lateral border of postero-anterior radiation field was 1.5 cm outside the widest bony margin of the true pelvic side walls; the inferior border of all fields was 3 cm below the primary tumor or at the inferior aspect of the obturator foramen. The superior border of all fields was at L5/S1 interspace. The posterior border of the lateral fields was at 1-1.5 cm behind the anterior bony sacral margin. The anterior border was at the posterior margin of the symphysis pubis (to treat only internal iliac nodes) or at the anterior margin of the symphysis pubis (to include the external iliac nodes in T4 tumors). The planning target volume 2 (PTV 2) included primary tumor with 3 cm margin added in all directions. PTV 1 received 45 Gy/25 fractions in 5 weeks. Higher dose up to 50.4 Gy with 3 further fractions was given using PTV 2 (Figure 2, 3).

Surgery

Surgery was performed about 6 weeks after the completion of concurrent chemoradiotherapy. The choice of the surgical procedure (abdominoperineal resection – APR, low anterior resection, local excision) was at the surgeon's discretion.

Table 1. Patient (n=34) and tumor characteristics

Characteristic	*n (%)*
Age (years)	
median (range)	62 (33-76)
Sex	
male	24 (71)
female	10 (29)
ECOG performance status	
0	21 (62)
1	9 (26)
2	4 (4)
Tumor distance from anal verge (cm)	
0-5	12 (29)
6-10	19 (59)
10-15	3 (12)
Histology (adenocarcinoma)	
tubular	6 (18)
gelatinous	4 (12)
cylindroid	1 (3)
unspecified	23 (67)
TNM (clinical)	
II	5 (15)
IIIA	23 (67)
IIIB	6 (18)

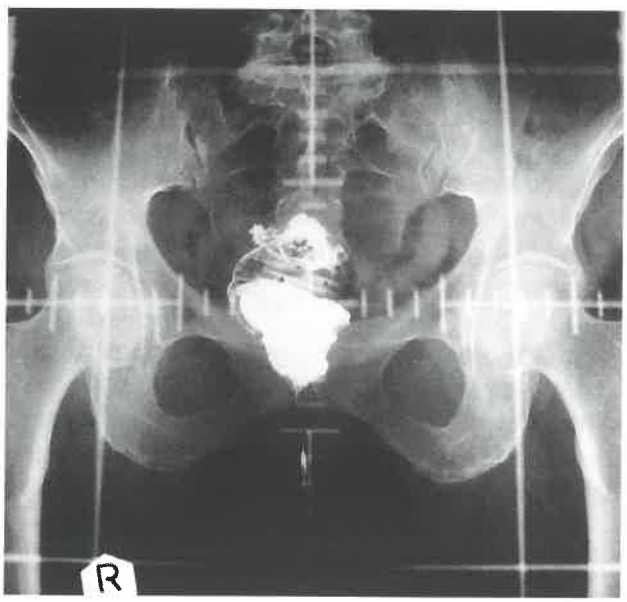


Figure 1. Simulator radiograph of the pelvis with barium sulfate contrast.

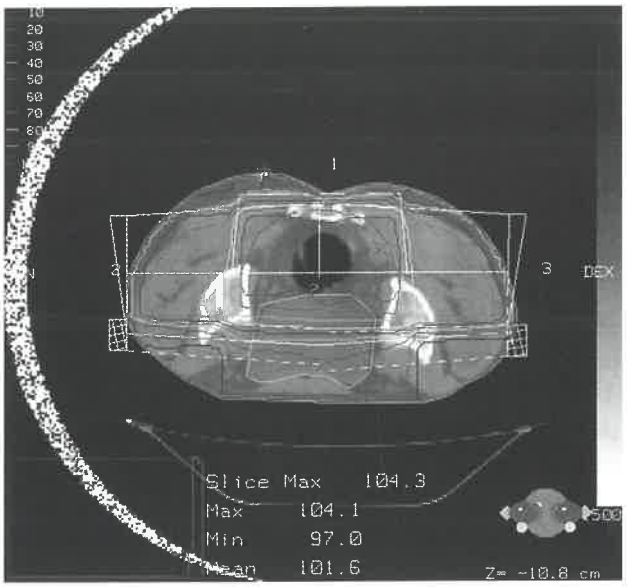


Figure 2. Isodoses plan – planning target volume 1 (PTV 1, small pelvis).

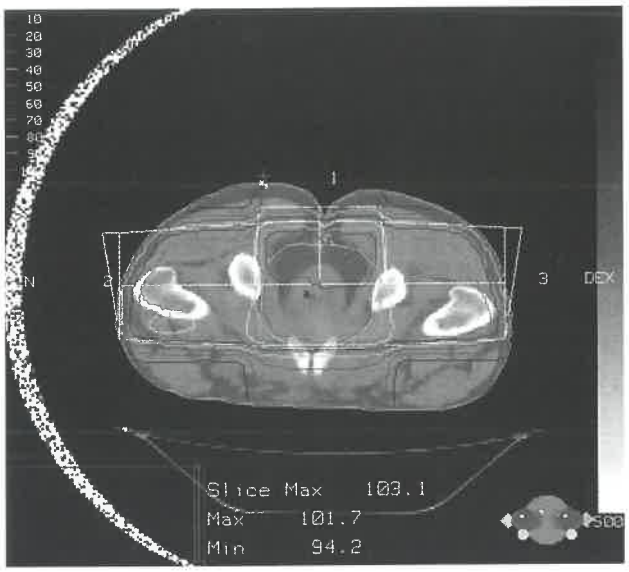


Figure 3. Isodoses plan – planning target volume 2 (PTV 2, tumor volume).

Postoperative chemotherapy

Adjuvant chemotherapy was recommended after surgery for patients with pT3, pT4 and/or pN+. These patients received 4 cycles of capecitabine monotherapy. Capecitabine was administered at a dose of twice-daily 1250 mg/m^2 on days 1-14 every 3 weeks.

Follow-up

Patients' routine follow-up schedule included visits every month for the first 3 months, every 3-4 months for 2 years, every 6 months up to 5 years, and yearly thereafter. The patients were seen jointly by a radiation oncologist, medical oncologist and surgical oncologist. In addition to clinical examination, proctoscopy, pelvic CT, abdominal CT (or liver ultrasonography), serum CEA values, and chest X-ray were carried out every 6 months for 2 years and yearly thereafter. Surveillance colonoscopy was performed at 1-3 year intervals.

Results

Acute toxicity

The acute toxicity was low: G 3 local dermatitis in 2 (6%), G 3 diarrhea in 3 (9%) and G 3 neutropenia in 1 (3%) patients. No G4 toxicity was seen. Capecitabine dose reduction to 80% of the planned dose was necessary for 2 (6%) patients (G3 diarrhea and G3 leucopenia). One patient suffered from urethrocystitis. No treatment-related death was observed. During neoadjuvant therapy no performance score deterioration or weight loss was registered in any patient. The most frequent adverse effects were perineal skin reaction, hand-foot syndrome, diarrhea, leucopenia and thrombocytopenia (Table 2).

Surgery

Thirty-three patients underwent radical surgical resection of residual cancer. The lower rectum (distance between the tumor and the anorectal ring: 0-5 cm) was affected in 12 patients, the middle rectum (5-10 cm) in 19 patients and the upper rectum (>10cm) in 3 patients. In 25 (76.5%) of them sphincter-preserving surgery was possible, while in the remaining 9 patients with tumor in the lower rectum abdominoperineal resection with colostomy was performed.

Response

Pathological CR was confirmed in 7 (20.6%) patients. Only minimal microscopic cancer was found

Table 2. Acute toxicity according to RTOG scoring system

Organ/symptom	*Number of patients*		
	Grade 1	*Grade 2*	*Grade 3*
Skin reactions (perineal)	9	7	2
Hand-foot syndrome	3	1	0
Diarrhea	4	1	2
Leucopenia	5	6	1
Trombocytopenia	0	0	0

in 6 more patients, making 13 (38%) patients with a substantial response. TNM tumor mass and imaging downstaging was achieved in all of the patients (Table 3, Figure 4,5). From 11 patients with primarily elevated serum CEA (median 10.2 ng/ml) 9 (82%) showed marker normalization.

During neoadjuvant chemoradiotherapy, symptoms and signs due to rectal carcinoma (bleeding, pain) disappeared or were greatly improved in all of the patients.

Postoperative adjuvant chemotherapy with 4 cycles of capecitabine was administered to 13 (38%) patients who were found with pT3-4 residual cancer or with pathologically positive regional nodes.

Table 3. Pathological disease response to chemoradiotherapy

Clinical TNM* (on starting neo-adjuvant treatment)	pTNM response (CR,PR) n (%)	cTNM response (CR,PR) n (%)
II (n=5)	3CR, 2PR (100)	5 (100)
IIIA (n=23)	2CR, 9PR (50)	23 (100)
IIIB (n=6)	2CR, 8PR (100)	6 (100)

*AJCC Cancer Staging Manual (6th edition), March 2002

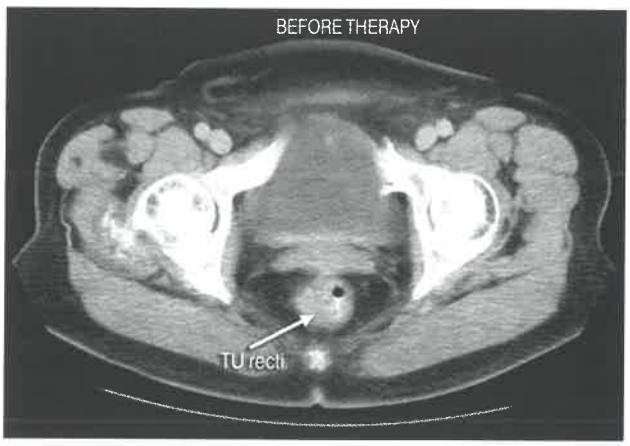


Figure 4. CT scan of rectal carcinoma (arrow) before chemoradiotherapy.

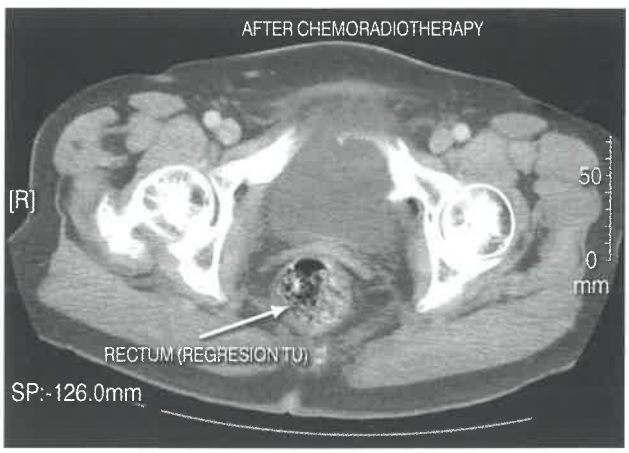


Figure 5. Regression of tumor (arrow) after chemoradiotherapy.

Follow-up

The median follow-up time is 7 months (range 4-18 months), which is very short to evaluate the time of progression and survival.

Discussion

Neoadjuvant chemoradiotherapy has been successfully used as a curative treatment method for anal carcinoma since 1970s. Considering chemo and radiosensitivity of this disease, the curative results of preoperative chemoradiotherapy are comparable with those taken by mutilating anorectal resection [1-3].

Although rectal adenocarcinoma has a different biological behavior from anal carcinoma, the positive impact of preoperative chemoradiotherapy in clinical stage II and III concerning local relapse rate, distant dissemination and improvement of 5-year survival, is supported by randomized clinical studies [4-6,10]. On the contrary, disadvantages of postoperative radiotherapy include higher risk of including the small intestine into the irradiated volume, potentially less response of the hypoxic tumor bed to radiotherapy, and extention of the field to the area of the perineal scar.

Preoperative radiotherapy has become a standard therapy for locally advanced rectal cancer in many institutions. With demonstrated better tolerance of preoperative radiotherapy (*versus* postoperative radiotherapy) and the synergistic effect of radiotherapy and chemotherapy, it is logical to use this combined curative modality in the neoadjuvant setting of rectal adenocarcinoma.

The main advantages of the preoperative approach of the combined treatment of rectal cancer are sphincter preservation and lower incidence of acute toxicity [19]. In recent years, several phase II studies of preoperative chemoradiation in locally advanced resectable rectal cancer have been published, showing interesting results in tumor downstaging and in sphincter preservation, with low toxicity. In all of these studies, chemotherapy included 5-FU administration by bolus injection or by continuous infusion or in combina-

tion with other drugs [20,21]. In fact, the ability of 5-FU to enhance the tumoricidal action of radiotherapy has already been known from the studies by Vietti et al. [22] and Byfield [23]. Since the early investigations, 5-FU has been a known radiosensitizer. Extensive preclinical data generated by Byfield has shown that synergism of 5-FU and radiotherapy is a postirradiation phenomenon, and, based on the 5-FU pharmacokinetic data, sensitization is likely to be achieved by infusional 5-FU. Preoperative toxicity is lower than postoperative, but it varies according to the method of 5-FU delivery; with bolus 5-FU the incidence of diarrhea and leucopenia is higher than with infusional 5-FU, where the incidence of nausea, vomiting, and mucositis is more common. The incidence of nausea, vomiting, diarrhea, and hand-foot syndrome in the present study is comparable to that seen in studies with infusional 5-FU. The radiosensitizing effect of 5-FU is dependent on the continuous exposure of cancer cells to the drug after radiation [24-26].

In the preoperative setting, radiotherapy combined with chemotherapy (e.g. 5-FU/leucovorin and protracted 5-FU i.v. infusion) has been shown to be feasible. Data of radiotherapy for rectal cancer combined with protracted infusion of 5-FU, as a very promising concept of radiosensitization, showed 29% of pCR rate and 68% of sphincter-saving surgery in resectable disease, and 13% pCR rate and 62% of resectability rate in unresectable disease [27].

The acute side effects of pelvic radiotherapy are diarrhea, weight loss, anorexia and pollakisuria. The acute radiotherapy bowel reaction usually begins 3 weeks after the start of radiotherapy and continues from 2 up to 6 weeks after the end of radiotherapy. Acute toxicity of radiation is low compared to chemoradiation [1-3]. Our patients were operated on the 6th week after the end of concomitant chemoradiotherapy.

The incidence of severe complications in our study was minimal (G3 – diarrhea 9%, skin reaction 6%, leucopenia 3%); it is also comparable to other studies with 5-FU and radiotherapy [22-28].

The results of a retrospective study from Erlangen University showed reduced acute toxicity for the preoperative approach. Fifty-six patients received preoperative chemo(5-FU)radiation, and 64 patients were treated postoperatively with 5-FU. Radiation was given by the box technique, with daily fractions of 1.8 Gy and total dose 50.4 Gy. During the 1st and the 5th week of radiation, 5-FU was administered by continuous infusion (1000 mg/m^2/day). Acute G3 toxicity occurred mainly as diarrhea (33%), perineal skin reaction (37%), and leucopenia (10%). Patients after abdominoperineal resection had significantly more toxic side effects (diarrhea, leucopenia). After preoperative chemoradiation there was a significant reduction of G3 – diarrhea compared with postoperative chemoradiation (11% *versus* 29%, respectively) [28].

Capecitabine has the additional important advantage of its predominant conversion to 5-FU within the malignant cells. In the present study one dose of capecitabine (1650 mg/m^2/day) was used. Tumor response and acute toxicity of our study were comparable with other published results [29-31].

Vaishampayan et al. showed their first experience with concurrent capecitabine and radiation therapy in gastrointestinal malignancies (rectal and colon carcinoma, pancreatic cancer, gallbladder carcinoma, oesophageal tumors and gastroesophageal junction malignancies; in all 32 patients). The median dose of capecitabine was 1600 mg/m^2/day orally for 5 days per week during radiation therapy. Thirty patients received a total radiation dose ranging from 45 to 64 Gy over 4-6 weeks. G3-4 toxicities observed were neutropenia in 3 patients and diarrhea, trombocytopenia, fatigue and myocardial infarction in one patient each. No treatment-related febrile neutropenia episodes or deaths were observed. The predominant minor toxicities consisted of G1 nausea in 11 patients and G1 diarrhea and hand-foot syndrome in 9 patients each. Patients in the higher-dose group (>1600 mg/m^2) had an increased incidence of hand-foot syndrome. The incidence of toxicities was not significantly different between the two groups. Of 11 evaluable patients with advanced disease or preoperative therapy, 4 demonstrated a response to therapy (2 CR and 2 PR) for an overall response rate of 36.4% [32].

A phase I trial of capecitabine with concurrent radiotherapy for rectal carcinoma used 1650 mg/m^2 daily during irradiation without any G3-4 toxicity. Five of 6 patients undergoing neoadjuvant treatment for locally advanced rectal cancer achieved downstaging [29]. Other phase I trials with concomitant chemoradiotherapy for locally advanced rectal carcinoma using capecitabine also describe minimal severe complications [30-33].

Protracted infusional chemotherapy is unfortunately inconvenient for patients, expensive and more labor-intensive for the medical and nursing staff. The new fluoropyrimidine-carbamate capecitabine achieves long-term inhibition of thymidylate synthase and, in this way, mimics protracted infusional 5-FU chemotherapy by oral administration [34-36].

Achieving tumor downstaging may be important for the resectability of advanced disease and may increase the rate of sphincter-saving surgery in low-lying rectal tumors [37,38]. Allen et al. describe tu-

mor downstaging in 86% and sphincter preservation in 79% of their patients by using neoadjuvant concomitant chemoradiotherapy (continuous infusion of 5-FU 300 mg/m^2/day, 5 days per week, radiotherapy 52.5 Gy) [39]. In our series, except one patient who refused surgery for personal reasons (CR after chemoradiotherapy), all of the patients were downstaged and underwent surgery with curative intent.

Tannapfel et al. described a clinical-to-pathologic downstaging after preoperative chemoradiotherapy for locally advanced rectal carcinoma in 25/32 (78%) patients. In that study, the apoptotic index was significantly increased in almost every case examined [40]. The treatment results of combined preoperative chemoradiotherapy followed by surgery for patients with initially nonresectable primary rectal cancer were reviewed by Leong et al. After preoperative therapy (radiotherapy 50.4-54 Gy, concurrent chemotherapy with 5-FU during the 1st and 5th weeks of irradiation), the resectability rate was 91% and pCR rate was 10% [41]. The pCR rate of our study (20.6%) was comparable (13-17%) to those reported using radiotherapy and 5-FU-based chemotherapy [42-44].

According to the relevant literature, the sphincter-saving surgery after preoperative chemoradiotherapy is possible in 44-86% of patients [19,37,45,46]; in our study it was 76.5%.

The growing interest of placing neoadjuvant chemoradiotherapy to a curative algorithm in locally advanced rectal carcinoma arises from the possibility of increasing the number of curative resections and sphincter-saving operations considering the regression of tumors.

The choice of an optimal anticancer agent is a subject of many clinical studies. The combination of preoperative irradiation with capecitabine facilitates the application of chemoradiotherapy. It is highly practical for the patients and therefore offers a potential for replacing bolus or infusional administration of 5-FU.

Neoadjuvant concomitant radiotherapy and oral capecitabine chemotherapy for locally advanced rectal adenocarcinoma is feasible and appears to be an effective (high dowstaging rate) and safe (low toxicity) therapeutic choice, improving the chances for sphincter-sparing surgery.

In conclusion, capecitabine can be safely administered with irradiation. The optimal dose and schedule of capecitabine and radiotherapy must be defined in future prospective trials. However, 1650 mg/m^2/day of capecitabine with standard radiotherapy has acceptable toxicity. In the present study the follow-up time is very short to evaluate other important parameters such as time to progression and survival.

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