Pre-operative Chemoradiotherapy with Oral Capecitabine in Locally Advanced, Resectable Rectal Cancer

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Abstract. *Purpose: The aim of the study was to evaluate the efficacy and tolerance of pre-operative chemoradiotherapy with oral capecitabine in Greek patients with locally advanced, resectable rectal cancer. Materials and Methods: Thirty patients, 16 men and 14 women with a median age of 58 years (range, 21-75 years), with potentially resectable T3N0 (30%), T3N1 (53%) and T4N0-1 (17%) rectal cancer, were treated with capecitabine (825 mg/m^2, twice daily for 7 days/week) and concomitant radiotherapy (50.4 Gy/28 fractions) for 5.5 weeks. Patients underwent surgery with total mesorectal excision 4-6 weeks later followed by 4-months of post-operative treatment with capecitabine. The primary end-point was to determine the clinical and pathological response, safety profile, preservation of the sphincter mechanism and rate of peri-operative complications. Results: The median distance of rectal tumors from the anal verge was 7 cm. All patients had curative resection. Downstaging rate was 84% (25/30) on endorectal ultrasonography and 75% (22/30) on pathology findings. Pathological complete response rate was 23% (7/30). No patient had grade 4 toxicity. Grade 3 toxicity occurred in 3 patients (10%) and consisted mainly of leucopenia (6%) and hand-foot syndrome (4%). Mild or moderate toxicity was frequent, but always reversible. Twenty-four patients (80%) received sphincter-preserving surgical procedures. Peri-operative complications were seen in 6 (20%) patients and included mechanical ileus (3%), delayed wound healing (7%), wound infection (7%) and anastomotic leakage (3%). Conclusion: Pre-operative chemoradiotherapy with oral capecitabine in locally advanced, resectable rectal cancer achieves significant rates of tumor downstaging and sphincter preservation with a favorable safety profile.*

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Pre-operative radiotherapy with concurrent 5-fluorouracil (5-FU)-based chemotherapy has been recently proposed as an acceptable therapeutic alternative in the treatment of locally advanced, resectable rectal cancer. Although short-term pre-operative radiation therapy alone followed by immediate surgery can increase local control (1, 2) and survival (1) with an acceptable safety profile (3), combined chemoradiotherapy seems to be more attractive because of the possibility to promote increased rates of sphincter-preservation as a result of a significant downstaging effect (4).

In the treatment of rectal cancer, several new chemotherapeutic agents, including capecitabine, have been introduced. Capecitabine is an oral fluoropyrimidine carbamate, which is converted to 5-FU preferentially in tumor cells through exploitation of high activity of the enzyme thymidine phosphorylase in tumor as opposed to normal tissue. The tumor-preferential activation of capecitabine reduces systemic exposure to 5-FU and potentially improves cytotoxic efficacy and safety. As an oral agent, capecitabine can achieve a continuous exposure to 5-FU mimicking infusional regimens but avoiding the risk of central venous access complications. It also seems that concurrent radiotherapy has a selective synergistic effect with capecitabine (5, 6).

Based on these considerations, the clinicopathological response, safety profile, sphincter-preserving surgery and post-operative complications were prospectively evaluated in a Greek population with stage II-III, resectable rectal cancer treated with capecitabine-based neoadjuvant chemoradiotherapy.

Materials and Methods

Eligibility criteria. Inclusion criteria for the study were as follows: (a) histologically proven rectal adenocarcinoma; (b) distal margin of tumor located within 10 cm from the anal verge on fiberoptic endoscopy; (c) extension of the primary tumor through the rectal wall or evidence of regional lymphadenopathy on endoscopic

ultrasound and computerized tomography (clinical stage T3 or T4, N0 or N1); (d) age≤75 years; (e) Eastern Cooperative Oncology Group performance status of 2 or below; (f) adequate hematological, liver and renal function; and (g) no evidence of distal metastatic spread at diagnosis. Patients were excluded from the study if they had other than adenocarcinoma tumor histology, prior chemotherapy or radiotherapy in the pelvic region, other serious medical conditions, or familial cancer syndromes.

Pre-treatment evaluation and monitoring during treatment. Baseline assessment and staging included history and physical examination, flexible colonoscopy with histological confirmation of the tumor, pelvic and abdominal computerized tomography, endorectal ultrasound, chest X-ray and complete hematological and biochemical profile, including tumor markers.

During chemoradiotherapy, the patients were examined weekly for the safety evaluation and compliance. Complete blood count, biochemical tests and a documentation of body weight were recorded. Safety was evaluated according to the National Cancer Institute Toxicity Criteria version 2.0 (7).

Radiation therapy. A radiation dose of 45 Gy was given to the posterior part of the pelvis to include the tumor, the mesorectum, the posterior walls of the bladder and prostate/vagina, as well as the internal and external iliac nodes, followed by a boost of 5.4 Gy limited to the tumor and corresponding mesorectum with a 2 cm margin, for a total radiation dose of 50.4 Gy. A conventional fractionation of 1.8 Gy/day, 5 days a week, was used for an overall treatment time of 5.5 weeks. Patients were radiated in the prone position using a dedicated device to minimize exposure of the small bowel. A three- or four-shaped field box-technique with high-energy photons (10 MV) was used. A computerized tomography-based treatment planning system was utilized to define the necessary target volume.

Chemotherapy. Capecitabine was administered orally at a dose of 825 mg/m^2 twice daily throughout the whole radiotherapy course, without weekend breaks. The first daily dose was given approximately 2 h before radiation treatment with the second dose taken 12 h after. Adjuvant chemotherapy after surgical resection was started 4 weeks post-operatively and consisted of four cycles of capecitabine with or without the addition of oxaliplatin, upon the medical oncologist's discretion.

Surgery. Surgery was planned 4 to 6 weeks after the completion of chemoradiotherapy. In all cases, resection was performed according to the principles of total mesorectal excision, meaning sharp dissection under direct vision along the parietal pelvic fascia, preserving the pelvic hypogastric nerve supply. The decisions regarding which type of surgery (low-anterior or abdominal-perineal resection) and whether a temporary colostomy should be performed were left to the discretion of the surgical oncology team. In sphincter-preserving procedures, a 2-cm disease-free distal resection margin, both clinically and pathologically, was necessary in order for surgery to be regarded as a complete curative resection. Peri-operative complications included adverse events occurring within 30 days after surgery.

Response to treatment. Evaluation of response was defined both clinically and pathologically. Clinical response was measured using the same clinical and imaging diagnostic tools employed prior to chemoradiotherapy. A tumor and/or nodal down-staging was considered when pathological T (pT) and/or pathological N (pN) was lower than clinical T and/or N as defined by endorectal ultrasound and computed tomography. Pathological response was defined according to the pTNM staging system. Serial sectioning of the specimen was performed and tumor site, with or without macroscopic residual disease, was entirely sampled for histological examination.

Table I. *Patient characteristics.*

	No. of patients (N=30)	%
Age (years)		
Median	58	
Range	21-75	
Gender		
Male	16	53
Female	14	47
ECOG		
0	26	87
1	4	13
Distance from the anal verge (cm)		
Median	7	
Range	4-12	
TNM clinical stage		
T3N0	9	30
T3N1	16	53
T4N0-1	5	17

Results

Patient characteristics. Between June 2004 and June 2006, a total of 30 patients with locally advanced rectal cancer were enrolled in this study. Their clinical and demographic characteristics are shown in Table I. They included 16 men and 14 women with a median age of 58 years (range 21-75). The majority of patients (53%) had T3, N1, M0 stage of disease. The median distance from the lower pole of the primary tumor to the anal verge was 7 cm (range 4-12 cm). All patients had a good performance status. All 30 patients were able to complete the treatment protocol and become evaluable for clinical response and safety profile, as well as pathological response and down-staging.

Treatment compliance and toxicity. All patients enrolled in the study completed the pre-operative chemoradiation as initially planned. Treatment was well tolerated. Neither grade 4 toxicity nor treatment-related deaths were recorded.

Grade 3 toxicity occurred in 3 patients (10%) and consisted mainly of leucopenia (6%) and hand-foot syndrome (4%). These toxicities were the reason for temporary capecitabine interruption and dose reduction. Most adverse events were mild to moderate in intensity and all of them recovered spontaneously with supportive management. Such frequent

Table II. *Perioperative complications.*

Complications	No. of patients	%
Mechanical ileus	1	3
Delayed wound healing	2	7
Wound infection	2	7
Anastomotic leakage	1	3
Total	6	20

Table III. *Pathological tumor response.*

T Stage	pT0	pT1	pT2	pT3	pT4
T3	7	3	8	7	-
T4	-	-	2	2	1
Total	7	3	10	9	1

grade 1 and 2 toxicity mainly included leucopenia (46%), diarrhea (40%), fatigue (30%) and radiation proctitis (13%).

Clinical response. Every patient was evaluated for clinical response after completion of chemoradiotherapy and before definitive surgery. Tumor response was assessed by endorectal ultrasound and computerized tomography. Overall response was recorded in 25 patients (84%). 5 patients (17%) had complete response, 8 patients (27%) showed microscopic residual disease and 12 patients (40%) had macroscopic residual disease after treatment. In particular, down-staging in T-category was observed in 20 patients (70%) and in N-category in 16 patients (53%). Down-staging on both T- and N-category was achieved in 14 patients (47%). Stable disease was observed in 4 patients (13%), whereas disease progression on primary tumor was seen in 1 patient (3%). Two patients had liver metastases at pre-operative restaging or at operation, with partial response on the primary tumor. These metastases were completely resected at surgery.

Surgical results. All patients treated with pre-operative capecitabine and radiation therapy underwent curative surgical resection. Twenty-four (80%) patients received sphincter-preserving surgery, either as a low anterior resection (21 patients) or as a coloanal anastomosis with temporary diverting colostomy (3 patients). Six (20%) patients underwent abdominal-perineal resection.

No peri-operative deaths were recorded. One patient developed anastomotic leakage and underwent transient diversion procedure. No severe peri-operative complications necessitating major intervention were encountered (Table II).

Pathological response. Complete disappearance of the primary tumor on the pathology specimen was observed in 7 patients (23%). Overall tumor down-staging was reported in 22 patients (75%). Nodal down-staging was observed in 16 (53%) (Table III).

Discussion

Pre-operative combined modality treatment with radiotherapy and 5-FU-based chemotherapy is now a well accepted approach in the management of patients with locally advanced and potentially resectable rectal adenocarcinoma. The introduction of new effective drugs, such as oral capecitabine, provides the opportunity to explore novel radio-chemotherapeutic combinations in stage II-III rectal cancer. Capecitabine, which offers the advantage of avoiding central lines, concentrates its action on tumor cells, is up-regulated by radiation and improves the possibility of drug-enhanced radiosensitization (8).

Dunst *et al.* (9) using escalating doses of capecitabine combined with radiotherapy (50.4 Gy with 1.8 Gy daily fractions) in the pre-operative and post-operative setting, defined a recommended for safety dose of 825 mg/m^2 twice daily, on a 7 day/week schedule. Ours is the first reported series on pre-operative chemoradiotherapy with capecitabine in Greek patients suffering from locally advanced rectal cancer. Although it consists of a limited number of patients, this report is part of a prospective study based on a demographically and biologically solid subpopulation.

Of the 30 patients enrolled in the study, 25 (84%) had a clinical response including 5 (17%) complete and 20 (67%) partial responses. These data are comparable with other experiences, which generally report a 70%-90% clinical response rate (10, 11) and much better than recent ones using the same protocol (12). It should be kept in mind, however, that evaluation of clinical response with endoscopic ultrasound, CT or MRI remains a difficult problem in this tumor site because of locoregional changes that impede the correct differential diagnosis between residual tumor and postchemoradiation fibrosis.

Compared with clinical stage at baseline, pathological tumor down-staging was observed in 22 (75%) patients including 7 patients (23%) with a complete pathological response (pCR). From the few preliminary reports on neo-adjuvant chemoradiotherapy with oral capecitabine, the complete pathological response rate varies from 4% to 31% (4, 6, 9, 12, 13). It is unlikely that the difference of treatment make such a wide range in the pathological complete response rates because most studies, including ours, used conventional doses of radiation and capecitabine. In addition to the extent of pathological examination and the quality control of chemotherapeutic compliance, it

seems that the proportion of T4 lesions is the most probable reason. Studies with clinical T4 tumors in less than 20% of cases, as in the GERCOR trial (13) and a recent study by De Paoli *et al.* (12), showed pCR rates over 20%. In contrast, when T4 lesions represented 50% of cases (9), the pCR rate was much smaller (4%). The results of the present study are in full agreement with this observation.

Our results also compare well with those reported with ci-5-FU (14) and with those recently published by randomized trials using bolus 5-FU/LV and radiotherapy (15, 16), both reporting a pCR rate ranging from 14% to 29%.

The incidence of acute toxicity during capecitabine-radiotherapy was very low. As expected, no grade 4 toxicity was reported and grade 3 side-effects were observed in only 3 patients (10%). Similarly, low toxicity rates have been reported in other capecitabine-radiotherapy phase II trials (13, 17). In our study, even if mild and moderate toxicity were common, all patients enrolled were finally able to receive the whole capecitabine planned dose. These data confirm the safety and feasibility of the treatment program, as well as the high level of compliance achieved.

All patients underwent curative surgical resection and most of them (24 out of 30) had a sphincter-preserving operation. These data on conservative surgery compare fairly well with other studies (10, 11, 14). The National Surgical Adjuvant Breast and Bowel Project reported a trend to sphincter preservation in the pre-operative chemoradiation arm (18) and the randomized study by Sauer *et al.* (4) showed that pre-operative chemo-radiotherapy enhanced sphincter preservation rate among those who required abdominoperineal resection before randomization. Although Bujko *et al.* (19), comparing two different preoperative approaches, showed no significant increase in sphincter preservation despite adequate clinical response rate, other investigators demonstrated a strong correlation between response to pre-operative chemoradiotherapy and the possibility of a sphincter-preserving procedure (20).

Although several authors using pre-operative chemoradiotherapy suggested 1-cm as a safe distal margin of resection (21, 22), Phang *et al.* reported that local and overall recurrences were significantly affected by the distance between the tumor and the anus (23), which might be partly due to insufficient distal margin, especially in the sphincter-preserving procedures. The 2-cm distal resection margin used as a prerequisite in our small series, in combination with the achieved rates of curative surgery and sphincter-preservation, is of particular importance.

In the present study, post-operative complications were uncommon and comparable to those reported in similar studies (24), as well in the short-term pre-operative (3) and the conventional post-operative fractionated radiotherapy (25).

Conclusion

Pre-operative chemoradiotherapy with oral capecitabine in locally advanced, resectable rectal cancer is an encouraging therapeutic approach achieving significant rates of tumor down-staging and sphincter-preservation with a favorable safety profile.

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