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Capecitabine-based Neoadjuvant Chemoradiation Therapy in Locally-advanced Rectal Cancer

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Purpose: The aim of the study was to evaluate the efficacy and the toxicity of preoperative treatment with capecitabine in combination with radiation therapy (RT) in patients with locally-advanced, resectable rectal cancer.
Methods: Thirty-five patients with locally-advanced rectal cancer (cT3/4, N-/+) were treated with capecitabine (825 mg/m^2, twice daily for 7 days/wk) and concomitant RT (50.4 Gy/28 fractions). Surgery was performed 6-8 wk after completion of the chemoradiation followed by 4-6 cycles of adjuvant capecitabine monotherapy (1,250 mg/m^2, twice daily for 14 days every 3 wk).
Results: The chemoradiation program was completed in all but 2 patients, for whom both capecitabine and RT were interrupted for 2 wk because of grade-3 diarrhea. A R0 resection under the principle of total mesorectal excision (low anterior resection, 26; intersphincteric resection, 6; abdominoperineal resection, 2) was performed in all but one patient with a low anterior resection with positive circumferential margin (R1). Primary tumor and node downstaging occurred in 57% and 60% of patients, respectively. The overall rate of downstaging, including both the primary tumor and node, was 77% (27 patients). A pathological complete response of the primary tumor was achieved in 4 patients (11%). No patient had grade-4 toxicity, and the only grade-3 toxicity developed was diarrhea in 2 patients (6%) during chemoradiation. During a median follow-up of 38 mo, distant metastases developed in 4 patients (multiple lung metastases, 2; aortocaval nodal metastases, 2), and another 2 patients showed local recurrence. The three-year disease-free survival was 83%.
Conclusion: This study suggests that preoperative capecitabine-based chemoradiation therapy is an effective and safe treatment modality for the tratment of locally-advanced, resectable rectal cancer.

Keywords: *Rectal cancer; Neoadjuvant chemoradiation; Capecitabine*

INTRODUCTION

Neoadjuvant concomitant chemoradiation therapy (CCRT) has increasingly become a standard treatment protocol in stage II and III rectal cancer. Compared to postoperative modality, the advantages of preoperative application of CCRT include improved compliance, reduced toxicity, and downstaging/downsizing of the tumor in a substantial number of patients.[1,2] These biological merits may enhance R0 resectability in cases of locally-advanced rectal cancer (LARC), permit sphincter preservation in patients with low-lying tumors, and have a positive impact on the quality of life.[2-4]

Although several chemotherapeutic agents are being investigated in combination with radiation treatment (RT), 5-fluorouracil (5-FU) in continuous infusion remains the standard radiosensitizer in preoperative CCRT schedules. It provides the biological advantage of achieving a prolonged exposure of tumor cells to effective levels of 5-FU, thereby enhancing the radiosensitization activity of 5-FU.[5,6] However, the need for a long-term vascular access port may limit the use of continuous 5-FU infusion therapy, and complications resulting from long-term central venous access, such as bleeding and thrombosis, are not uncommon.[7]

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Capecitabine (Xeloda®, Hoffmann-La Roche Ltd, Basel, Switzerland) is an oral fluoropyrimidine carbamate, which is converted to 5-FU preferentially in tumor cells through exploitation of a higher activity of the enzyme thymidine phosphorylase (TP) in tumor tissue compared with normal tissue.[8] This tumor-preferential activation of capecitabine reduces systemic exposure to 5-FU and potentially improves its efficacy and safety.[9] In addition, preclinical studies have shown that RT can up-regulate the TP expression in tumor cells, resulting in a selective synergistic effect between RT and capecitabine.[10] As an oral agent, it mimics the pharmacokinetics of continuous 5-FU infusion,[11] while avoiding the potential complications associated with central venous access. Therefore, capecitabine may be an alternative to protracted intravenous 5-FU in combination with RT, making CCRT more patient-friendly.

The aim of the present study was to evaluate the efficacy and the toxicity of preoperative treatment with capecitabine in combination with RT in patients with locally-advanced, resectable rectal cancer (LARC). In addition, the impact of neoadjuvant CCRT on oncologic outcome was analyzed.

MATERIALS AND METHODS

Patient population

From the database of colorectal cancer under the care of the Department of Surgery, Dong-A University Medical Center since 2003, patients with LARC in which neoadjuvant capecitabine-based CCRT followed by surgical resection and in which follow-up till recurrence or of 3 yr or more was matured were considered in this retrospective study. Inclusion criteria for this study were as follows: clinical stages T3 or T4, and N0 or N+ rectal cancer located within 10 cm from the anal verge. Patients with distant metastatic disease at the time of pretreatment evaluation were excluded from the study. A total of 35 consecutive patients with histologically-proven rectal adenocarcinomas received capecitabine in combination with neoadjuvant RT between June 2004 and July 2005.

Pretreatment evaluation

Baseline assessment included a complete history and physical examination, rigid rectosigmoidoscopy and/or colonoscopy, abdominal and pelvic computed tomography (CT), endorectal ultrasound (EUS) and/or pelvic magnetic resonance imaging (MRI), chest X-ray, ECG, and blood chemistry, including carcinoembryonic antigen (CEA).

Treatment protocol

A radiation dose of 45 Gy was given to the whole pelvis in 25 fractions over 5 wk, followed by a boost of 5.4 Gy in 3 fractions to the primary tumor and corresponding mesorectum. For the whole-pelvis field, the clinical target volume was defined to cover the small pelvis from the L5-S1 interspace to 3-4 cm below the primary tumor. The lateral borders were 1.5 cm outside the true bony pelvis to encompass internal iliac lymph nodes. For the lateral field, the posterior margin was 1.5 cm behind the anterior bony sacral margin. The dose was prescribed to cover the planning target volume with a 95% reference isodose (95% of the ICRU point dose). Radiation was delivered with 15-MV photons by using a three-field technique (posterior and both laterals), and the treatment plan was performed by using computerized dosimetry. Patients were treated in the prone position. They were instructed to have a full bladder during irradiation, and no devices were used to displace the small bowel out of the irradiated field. A multi-leaf collimator was used for shaping the fields and for protecting normal tissues.

Concurrent chemotherapy using capecitabine was delivered on an outpatient basis. It was administered orally at a dose of 825 mg/m^2 twice a day throughout the RT course (including weekends). The first daily dose was administered approximately 2 hr prior to irradiation, with the second dose being taken 12 hr later. During treatment, patients were evaluated weekly to assess acute toxicity and compliance with the treatment schedule. Clinical examinations, complete blood counts (with differential count), and blood chemistries were performed. The intensity of toxic side effects were assessed and graded according to National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) version 3.0.[12]

Definitive surgery was scheduled 6-8 wk after completion of the CCRT. Surgery was performed based on a principle of total mesorectal excision (TME), and decisions regarding which form of surgery (abdominoperineal resection, intersphincteric resection, or low anterior resection) and whether a temporary diverting

ileostomy should be performed were left to the surgeon's discretion.

Following surgery, patients received an additional 4-6 cycles of adjuvant capecitabine. It was administered at a dose of 1,250 mg/m^2 twice daily for periods of 14 days spaced three weeks apart.

Analysis of response to neoadjuvant chemoradiation treatment

The effect of neoadjuvant CCRT on downstaging of the tumor (TD) and/or the lymph node (ND) was assessed by comparing the radiologically-determined pretreatment clinical TNM stage with the postoperative final pathologic TNM stage. TD and/or ND were defined as reductions in the T and/or the N stages, at least, by one level. Overall response was defined as occurrence of either TD or ND. A pathological-complete response (pCR) was defined as the absence of any residual cancer cells in the resected specimen (pT0N0). According to the tumor regression grade (TRG) proposed by Mandard et al.[13] for esophageal carcinomas, it corresponds to TRG1. The impact of TD, ND, and pCR after neoadjuvant CCRT on the oncologic outcomes was analyzed in terms of the 3-yr disease-free survival (DFS).

Statistical analysis

Data were entered into a spreadsheet program and were subsequently imported into a statistics program (Prism™ ver. 4; GraphPad Software Inc., San Diego, CA, USA). Survival curves were calculated using the Kaplan-Meier method and were analyzed usibg the log-rank test. A P-value of <0.05 was considered statistically significant.

Table 1. Acute toxicity during chemoradiation therapy

Toxicity	Grade		
	1	2	3
Hematologic			
Anemia	5 (14)	1 (3)	
Leukopenia	8 (23)	3 (9)	
Thrombocytopenia	2 (6)		
Non-hematologic			
Diarrhea	9 (26)	3 (9)	2 (6)
Radiation dermatitis	13 (37)	6 (17)	
Hand-foot syndrome	5 (14)	1 (3)	

Values are presented as number (%).

RESULTS

There were 27 men and 8 women, with a median age of 58 yr (range, 26 to 76 yr). The extents of the diseases after combining the radiologic findings were as follows: T3N0, 6; T3N+, 26; T4N0, 1; T4N+, 2. The median distance from the anal verge to the lower margin of the tumor was 7 cm (range, 2 to 10 cm). Eight patients had the disease located less than 5 cm proximally from the anal verge and required a definite abdominoperineal resection (APR) or intersphincteric resection (ISR), 19 had the disease located between 5 and 8 cm and were thought to have a probability of requiring an APR or ISR, while others had the disease located more than 8 cm proximally.

Treatment compliance and toxicity

Overall, preoperative treatment with capecitabine in combination with RT was well tolerated and in no patient was the treatment schedule permanently interrupted by severe adverse effects. Neither grade-4 toxicity nor treatment-related deaths were reported. Common acute toxicities encountered during treatment are shown in Table 1. The most common non-hematologic toxicities of grade 1 or 2 were radiation dermatitis (54%), diarrhea (35%), and hand-foot syndrome (17%). In no patients with grade-1/2 non-hematological toxicity was either capecitabine or RT interrupted. Two patients manifested diarrhea of grade 3, which required both capecitabine and RT interruption for 2 wk. No hema-

Table 2. Surgery and postoperative pathologic characteristics

Characteristics	All patients
Operative procedure	
Low anterior resection	27
Intersphincteric resection	6
Abdominoperineal resection	2
Pathologic stage*	
Complete response, N0	4
T0N1	1
T1N0†	4
T2N0	4
T2N1	3
T2N2	1
T3N0‡	9
T3N1	5
T3N2	4

*Staging by AJCC/UICC classification; †Two patients with tumor regression grade 2 (TRG2) are included; ‡One patient with TRG2 is included.

tologic toxicities encountered in this study were severe enough to cause either capecitabine or RT interruption.

Surgery

All 35 patients underwent surgical resections. Twenty-seven patients underwent a LAR, 6 underwent an ISR, and 2 underwent an APR. A diverting ileostomy was constructed routinely after an ISR, but in no patient receiving a LAR was an ileostomy performed in this study. Overall, sphincter-preserving surgery was achieved in 33 of 35 patients (94%). Of 8 patients where the lower margin of the tumor was less than 5 cm from the anal verge, 6 (75%) received a sphincter-preserving procedure. There was neither perioperative mortality nor severe complications requiring surgical re-intervention. Postoperative surgical and pathologic data are shown in Table 2.

Table 3. Pretreatment clinical vs. postoperative pathologic T classification

	pCR/pT0N1	pT1	pT2	pT3	Total
cT3	4/1	4*	8	15†	32 (91.4)
cT4				3	3 (8.6)
Total	4 (11.4)/ 1 (3)	4 (11.4)	8 (22.9)	18 (51.4)	35 (100)

Values are presented as number or number (%).
*Two patients with tumor regression grade 2 (TRG2) are included; †One patient with TRG2 is included.
pCR=pathologic complete response.

Table 4. Pretreatment clinical vs. postoperative pathologic N classification

	pN0	pN1	pN2	Total
cN0	7			7 (20)
cN+	14	9		28 (80)
Total	21 (60)	9 (25.7)	5 (14.3)	35 (100)

Values are presented as number or number (%).

Pathologic response

Pathologic examination of the surgical specimens of the 35 patients who underwent surgery confirmed that a radical R0 resection was attained in all patients but one on whom a LAR had been performed and the circumferential margin had been microscopically involved by the tumor. Overall, TD was reported in 20 of 35 (57%) patients (Table 3), and ND in 14 of 21 (60%) patients (Table 4). As shown in Table 5, the overall rate of downstaging, including the primary tumor and/or node, was 77% (27 patients). A pCR of the primary tumor was reported in 4 patients (11%). Another 3 patients was reported to be TRG2. Interestingly, for one patient with TRG2, microscopic residual cancer cells were found within the perirectal adipose tissue (pT3).

Tumor recurrence and disease-free survival

During a median follow up of 38 mo (range, 9 to 49 mo), a total of 6 patients (17%) developed either local or distant recurrence. Local recurrence occurred in 2 patients (6%) and was documented 11 and 21 mo after a LAR. Distant metastatic disease in the lungs and in aortocaval lymph nodes developed in 2 patients each. In particular, one patient with pCR developed meta-

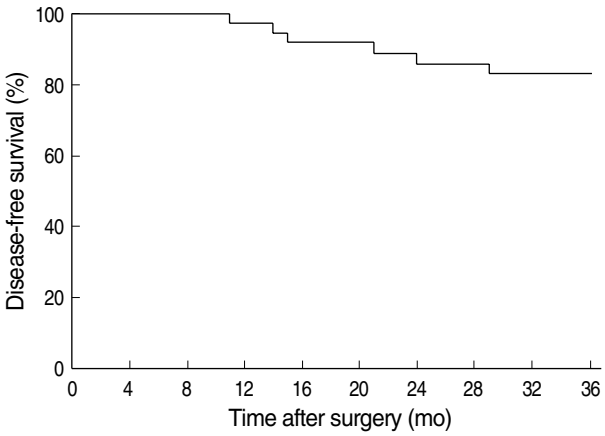

Fig. 1. Kaplan-Meier survival curves. The 3-yr disease-free survival for the 35 patients was 83%.

Table 5. Pretreatment clinical vs. postoperative pathologic TN classification

	pT0N0	pT0N1	pT1N0	pT2N0	pT2N1	pT2N2	pT3N0	pT3N1	pT3N2	Total
cT3N0	1		3	1			1			6
cT3N+	3	1	1	3	3	1	6	5	3	26
cT4N0							1			1
cT4N+							1		1	2
Total	4	1	4	4	3	1	9	5	4	35

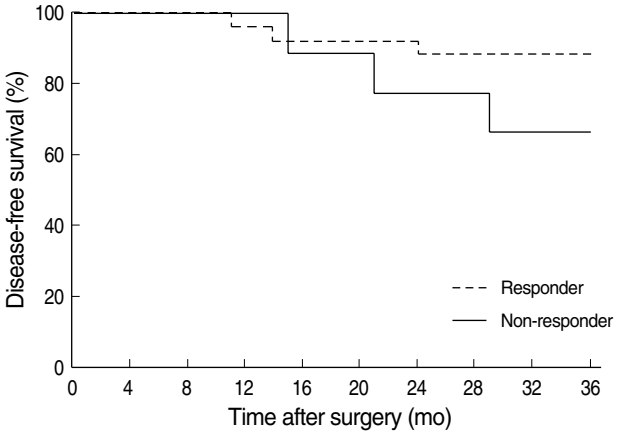

Fig. 2. Kaplan-Meier survival curves for responders and non-responders to the neoadjuvant concurrent chemoradiation. The difference in terms of 3-yr disease-free survival was not statistically different (88% vs. 67%; P=1.158; Hazard ratio, 0.334).

static disease in the aortocaval lymph nodes 24 mo after a LAR. The 3-yr DFS for the 35 patients in this study was 83% (Fig. 1). When survivals were compared between responders and non-responders (Fig. 2), the difference in terms of 3-yr DFS was not statistically different (88% vs. 67%; P=1.158; Hazard ratio, 0.334).

DISCUSSION

Neoadjuvant 5-FU-based CCRT has increasingly become a gold standard in the treatment of LARC. A recent trial comparing preoperative to postoperative CCRT clearly showed the benefits of the preoperative modality as evidenced by a decrease in the local recurrence rate from 13% to 6%, a decrease in the long-term toxicity of radiation treatment, and an apparent increase in the rate of sphincter-sparing surgery from 19% to 39%.[1] Currently, fluoropyrimidine 5-FU is the chemotherapeutic agent most widely used as a radiosensitizer in clinical practice.[14] Given the short half-life of 5-FU in plasma and its intracellular metabolites, it should be administered in the form of protracted intravenous infusions during the course of fractionated RT in order to act as a radiosensitizer.[15,16] As an alternative to protracted 5-FU, an oral fluoropyrimidine, capecitabine, is now increasingly in use. As a result of two phase-I dose-finding studies, the recommended dose of capecitabine with RT is 825 mg/m^2 twice daily administered from the first to the last day of standard pelvic irradiation.[17,18]

With oral capecitabine, pCR rates ranged from 4% to 31% and downstaging from 49% to 84% in several phase-II studies.[19-26] In the present study, the pCR and the downstaging rates were 11% and 77%, respectively. Reasons for the wide range in the pCR and downstaging rates in the literature are not clear yet. Kim et al.[19] and Velenik et al.[24] suggested that the main reason for these discrepancies might be the unfavorable distribution of T- and/or N-tumor stages; in 83% of patients T4 and/or N+ were the preoperative stages in this study. Kim et al.[19] also suggested that the extent of pathologic examination might be another possible reason for the wide range in the pCR rate. This suggestion may be evidenced by the finding in this study that one patient with no tumor cells in the primary tumor showed positive lymph-node metastasis (1 of 7 nodes) and that, in another patient with TRG2, microscopic residual cancer cells were found within the perirectal adipose tissue (pT3). These tumors might have been counted as pCR on an ordinary examination. If they had not detected, the pCR rate might have been increased to 20%. For these reasons, it would be important for pathologists to bear in mind that the gross residual tumor and its surrounding tissue should be examined thoroughly and that additional sections should be prepared to find viable tumor cells if there were no tumor cells in those representative sections.

The incidence of acute toxicity during capecitabine-based CCRT was very low. In the study by Dunst et al.,[20] myelosuppression was the most frequent toxicity observed in about half of the patients, and the most relevant adverse effect was diarrhea, which was associated with severe symptoms in 7 patients (7%; 6% grade 3, 1% grade 4). In another study, the most common grade-2/3 toxicities were diarrhea (25%) and local skin reactions (20%).[23] In the present study, the incidence of acute toxicity during CCRT was much lower. Neither grade-4 toxicity nor treatment-related deaths were reported, and the most common grade-2 adverse events were radiation dermatitis (17%), diarrhea (9%), and leukopenia (9%). The only grade-3 toxicity observed was diarrhea in 2 patients (6%). These data compare favorably with those reported for preoperative 5-FU-based chemoradiation treatment. The reported pCR rate in randomized studies was 8% both in a National Surgical Adjuvant Breast and Bowel Project protocol R-03 (NSABP R-03) with bolus infusion of 5-FU[27] and in a German study by Sauer et al.[1] with continuous infusion of 5-FU. However, bolus infusion of 5-FU seems to be associated with a lower rate of pCR

or downstaging. In a meta-analysis of pCR following preoperative CCRT for rectal cancer, continuous infusion of 5-FU and capecitabine appeared to be associated with a higher rate of pCR (24% and 23%, respectively; bolus, 13%).[28] However, preoperative protracted 5-FU-based CCRT shows a higher incidence of grade-3 or higher toxicity than capecitabine-based CCRT. In the German study by Sauer et al.,[1] grade-3 or -4 acute toxic effects occurred in 27% of the patients. In this study, even though mild and moderate toxicities were observed, only 2 patients with grade-3 diarrhea required both capecitabine and RT interruption for 2 wk, and no adverse effects were severe enough to be a reason for either permanent capecitabine or RT interruption. A large randomized phase-III trial (NSABP R-04) is ongoing to compare RT plus either continuous infusional 5-FU or capecitabine as a preoperative therapy in patients with resectable rectal cancer.

In summary, our results suggest that capecitabine in combination with preoperative RT is well tolerated and is an effective modality, as measured by the downstaging and the pathological response in patients with LARC. Therefore, oral capecitabine represents an attractive alternative to conventional protracted intravenous 5-FU in neoadjuvant CCRT from the standpoint of safety and downstaging potential.

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국문 초록

직장암에서 Capecitabine을 이용한 수술 전 화학방사선치료

최홍조 · 박기재 · 이태무 · 하상식 · 이호영 · 이형식[1]
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목적 : 이 연구는 절제가능한 진행성 직장암 환자에서 수술 전 치료로서 capecitabine을 병용한 화학방사선치료의 효능과 안전성을 평가하고자 시행되어졌다. **방법** : 진행성 직장암 환자(*c*T3/4, N−/+) 35명을 대상으로 수술 전 화학방사선치료로서 경구 capecitabine (방사선치료 기간 동안 매일 825 mg/m^{2}를 하루 두 번) 투여와 방사선치료(총 방사선량 50.4 Gy를 28 분획)를 동시에 시행하였으며, 수술은 화학방사선치료 완료 6−8주 후에 시행하였다. 수술 후에는 보조적 항암화학치료로서 4−6주기의 capecitabine (3주 간격으로 1,250 mg/m^{2}를 하루 두 번 2주간)을 투여하였다. **결과** : 두 환자에서 3도 설사로 2주간 capecitabine 투여와 방사선치료를 중단했던 경우를 제외하고는 모든 환자에서 계획된 화학방사선치료를 완료하였다. 수술은 저위전방절제술 후 환상절제연 양성(R1)이었던 1예의 환자를 제외하고는 모든 환자에서 전직장간막절제술의 원칙하에 잔존종양 음성의 근치절제(R0)가 시행되었다(저위전방절제술, 26예; 괄약근간절제술, 6예; 복회음절제술, 2예). 원발종양과 림프절의 병기하강(downstaging)은 각각 57%와 60%에서 관찰되었으며, 원발종양과 림프절을 포함한 전체 병기하강률은 77%(27예)였다. 원발종양의 병리학적 완전관해율은 11%로서 4예에서 관찰되었다. 화학방사선치료 기간 동안 4도 독성은 관찰되지 않았으며 3도 독성도 2예(6%)의 설사가 유일하였다. 추적기간 38개월 동안 4예의 환자에서 원격전이가 관찰되었으며(다발성 폐전이 2예; 대동정맥림프절, 2예), 다른 2예의 환자에서 국소재발이 확인되어 3년 무병생존율은 83%였다. **결론** : 절제가능한 진행성 직장암 환자에서 capecitabine을 병용한 수술 전 화학방사선치료는 효과적이며 안전한 치료양식으로 판단된다.

중심단어: 직장암; 수술전 화학방사선치료; Capecitabine

편집인의 글

진행성 직장암 치료에 수술전 화학방사선 치료는 많은 장점으로 인하여 직장암 치료의 표준으로 인정되어 있으며 병용 투여하는 5-FU는 방사선 감수성 증강물질로 사용된다. 특히 5-FU의 지속 주입이 방사선 치료중 5-FU의 농도가 충분하게 유지 되기 때문에 가장 효과적인 표준 투여 방법이지만 여러 가지 기술적인 합병증과 환자의 불편 등에 의하여 같은 효과를 보일 수 있는 방법으로 경구용 5-FU 제제를 사용하는 방법이 연구되었다. 특히 capecitabine은 5-FU의 전구 물질로 투여되어 암세포에서 thymidine phosphorylase (TP)에 의하여 5-FU로 변환된다. 또한 방사선 치료에 의하여 암세포에서 TP의 발현이 증가되는 것으로 밝혀져 capecitabine의 5-FU로의 변환이 방사선 치료를 받는 암조직에서 증가되어 전신적인 독성은 없이 국소적으로 암 조직에서의 활성 및 방사선 감수성 증강 효과가 증가될 것으로 기대되어 많은 연구가 진행되었다.[1] 여러 전통적인 방법인 간헐적 혹은 지속적 5-FU/Leucovorin 투여와 capecitabine을 방사선 치료와 병용하여 비교한 연구들에서 병리학적인 병기하강, 병리학적 관해율, grade 3-4의 합병증 발생, 국소 재발, 무병 생존율 등에서 두 군간에 차이가 없다고 보고하였다.[2] 본 논문에서는 원발 종양과 임파절 병기하강이 각각 57%, 60%이며 전체 병기 하강은 77%로 보고하였다. 완전 관해율은 11%, 무병 생존율은 83%로 보고하였으며 grade 3-4 정도의 독성은 거의 관찰되지 않았다. 다른 보고들에서도 완전 관해율은 약 20% 전후, 종양 T 병기 하강은 약 60%, 무병 생존율 80% 이상, grade 3-4의 합병증이 거의 발생하지 않았다고 보고하여 진행성 직장암에서 capecitabine을 병용 투여하는 수술전 화학방사선 치료가 효과적이며 안전한 방법이라 할 수 있다.[3]

그러나 capecitabine에 다른 약제들(oxaliplatin 혹은 cetuximab)을 추가하여 수술 전 화학방사선 치료를 시행하였을 때는 oxaliplatin이나 cetuximab에 의한 추가 장점이나 이득이 없어 아직은 사용을 추천하지는 않는다.[4,5]

다만 수술전 화학방사선 치료에 반응하지 않는 군을 원발 종양에서의 TP 수치 혹은 다른 분자 생물학적 요인들에 의하여 치료 전에 미리 구별할 수 있다면[6] 더 좋은 치료 효과를 얻을 수 있고 환자들에게도 더 적절한 치료를 제공할 수 있을 수 있어 이에 대한 연구들이 필요하리라 생각한다.

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