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# Side effects and disease-free survival with capecitabine compared to 5FU for concurrent radiochemotherapy of rectal cancer: A 5-year review

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## ABSTRACT

***Background:*** Considering the ease of administration of capecitabne instead of infusional 5FU for concurrent radiochemotherapy (RcT) of rectal cancer, the use of capecitabine has increased significantly in our radiation oncology department in the past years. Thus we decided to compare the safety and survival with these 2 drugs by a retrospective review.

***Methods:*** Files of all patients receiving RcT either pre- or post-operatively for rectal cancer in our department in the 5 years of 2004-2008 were reviewed. Side effects were compared for all patients treated by capecitabine versus 5FU; while for homogeneity of data, disease-free survival was only compared in the patients treated pre-operatively.

***Results:*** During the review period, 322 rectal cancer patients had received concurrent RcT in our department. Radiation dose-fractionation regimens were mostly 45 or 50 Gy in 25 fractions or 5040 in 28 fractions. The use of pre-operative treatments increased from 33% in 2004 to 67% in 2008. The use of capecitabine versus 5FU also went up from 2% in 2004 to 65% in 2008. The grades of leucopenia, thrombocytopenia and radiation dermatitis were significantly higher in the 5FU group ($p<0.05$). There was only one case of hand-foot syndrome, observed in the capecitabine group.

In the102 patients (66.7% male with a mean age of 53.7 years) who had received pre-operative RcT,mediandisease-free survival was 53% for all patients,with no statistically significant difference between the patients treated bycapecitabine and 5FU.

***Conclusion:*** The use of capecitabine for concurrent RcT of rectal cancer in our patients was easy and safe, with a favorable acute side-effect profile compared to 5FU, and comparable survival.

***Keywords:*** ***Rectal carcinoma, Radiochemotherapy, 5FU, Capecitabine***



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## Introduction

Colorectal cancer is the third common cancer and the second cause of cancer death in the world.[1] The maintherapy in patients with rectal cancer is surgery, but more studies in this field have proved that the pre- or post-operative radiochemotherapy for locallyadvanced rectal cancer (T3, T4 or N+)can improve disease-free survival.[2,3,4,5] Therefore concurrent chemotherapy such ascontinuous intravenous infusion 5-fluorouracil or bolus 5FUwith radiotherapyhas become a standard treatment for these patients.[6] But effective prescription of 5FU requiresthe placementof a central venous catheter and use of a portalinfusionpumpwhich can negatively affect patients' quality of life.[7] Capecitabine is an oral fluoropyrimidine carbamate prodrug of 5FU,which by a three-step enzymatic cascade(more in tumor tissue comparedto normal tissues)is converted to 5FU. It has been developed because of its oral usage, convenient method of administration,and somewhat specificantineoplastic activity.[8,9]

In thestudies conducted to compare the complications of 5FU andcapecitabine,the latter had lower gastrointestinal and hematologiccomplicationsbut higher complications like hand-and-foot syndrome.[6,8,9]

Considering the ease of administration of capecitabne for concurrent chemoradiation of rectal cancer, and also considering the difficulty of arranging treatment with 5FU infusion pumps in our centre, the use of capecitabine has increased significantly in our radiation oncology department in the past years. Thus we decided to compare the side effects and survival with these 2 drugs by a retrospective review.

## Methods

Files of all patients receiving radiochemotherapy either pre- or post-operatively for rectal cancer in our department in the years of 2004-2008 were reviewed. Also we attempted telephone follow-up for all the patients with incomplete information in their files.Acute side effects were recorded according to Common Terminology Criteria for Adverse Events v3.0 (CTCAE).[10] Side effects were compared for the patients treated by capecitabine versus 5FU. For completeness and homogeneity of data and comparison, disease-free survival was analyzed only in the patients treated pre-operatively. The data analyses were done with the Statistical Package of Social Science (SPSS) for windows version 18. P-valuesof<0.05 were considered statistically significant.

## Results

This retrospective study included 322 patients with colorectal cancer, of which 102 patients (66.7% male with a mean age of 53.7 years) had received pre-operativeradiochemotherapy in our department.

The use of pre-operative treatments increased from 33% in 2004 to 67% in 2008, for a total of 42% in the 5 years. The use of capecitabne versus 5FU also went up from 2% in 2004 to 65% in 2008, for a total of 29%.

The most common concurrent chemotherapy regimen was 750mg/m2/day bolus injection for 4 days in the 1st and 4th weeks of radiation for 5FU, and 825/m2 twice a day in all radiation days for capecitabine.Also Radiation dose-fractionation regimens were mostly 45 or 50 Gy in 25 fractions or 50.4 Gy in 28 fractions.

The numbers of the patients with grade 2-4 acute side effects with 5FU and capecitabine were 16 and 3 for leucopenia, 5 and none for anemia, 10 and 2 for thrombocytopenia, 2 and 1 for diarrhea, and 9 and none for dermatitis in the radiation fields, respectively. There was only one case of hand-foot syndrome, observed in the capecitabine group. The grades of leucopenia, thrombocytopenia and radiation dermatitis were significantly higher in the 5FU group (P<0.05, **Fig. 1**).

Kaplan-Meier disease-free survival (DFS) analysis was only performed for the 102 patients treated pre-operatively, andis shown in **figure 2**. Median DFS was 53 months for all these patients.In log rank test, there was no significant difference for DFS between patients who took 5FUand capecitabine.

We could not see any statistically significant effect of gender, age, T or N stage, and dose of radiation and chemotherapy on DFS, or any difference in this regard between the two groups of patients.

## Discussion

Significant advances have been made in reducing the re-

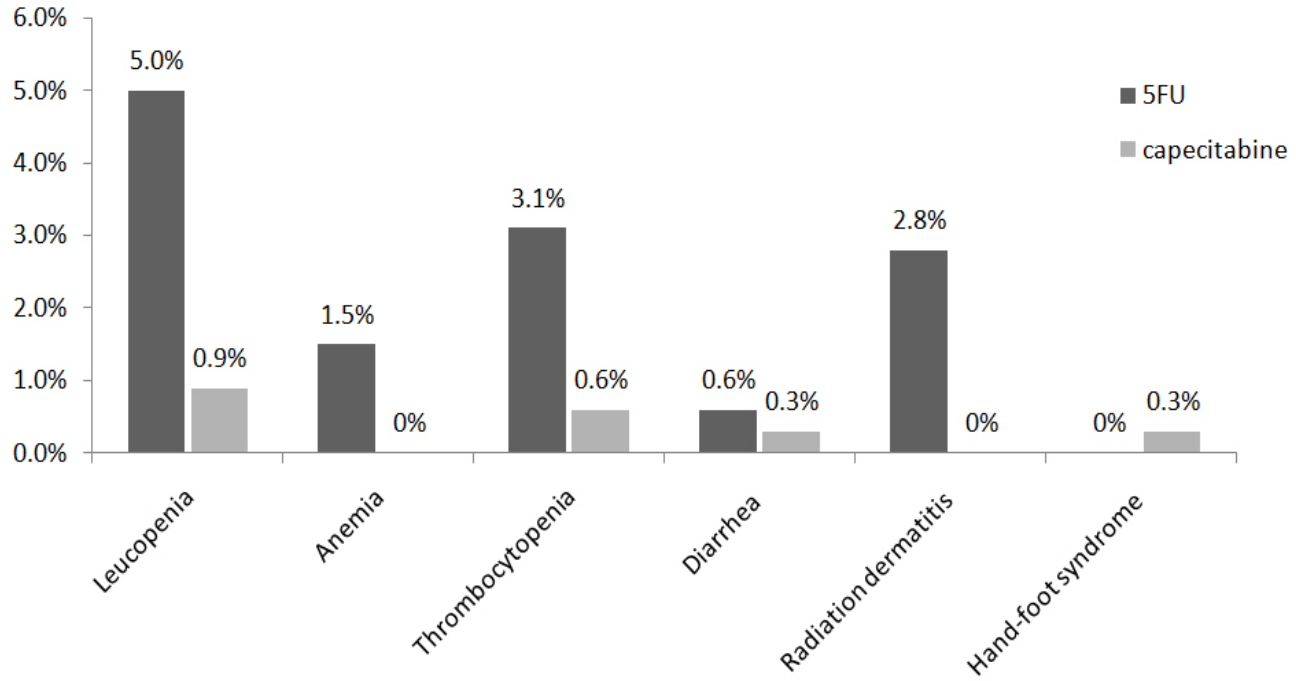


**Figure 1. 5FU and capecitabine side effects on 322 rectal cancer patients**

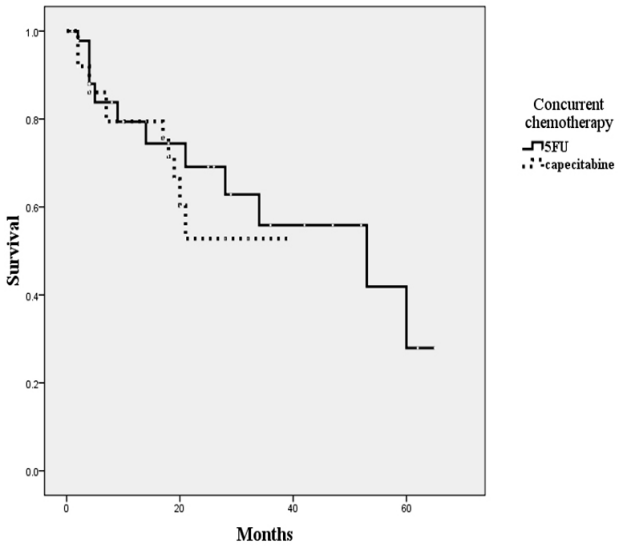


**Figure 2.The effect of concurrent chemotherapy type on disease-free survival for 102 rectal carcinoma patients treated in a pre-operative setting.**

currence of rectal cancer while surgery is combined with pre- or post-operative radiochemotherapy (RcT). A meta-analysis published in 2001 indicated that preoperative RcT decreased the yearly risk of local recurrence by 46% (p=0.0001),but post-operative RcT decreased that risk by 37% (p=0.002).[3]

From a scientific view, pre-operative RcT is associated with several advantages compared to post-operative RcT. First RcT is more effective in surgically undisturbed well oxygenated tissue. Second, pre-operative only approach may result in down staging and downsizing effect. Third, pre-operative RcT may have less toxic effect to the small bowel compared to post-operative RcT. As shown in this study the use of pre-operative chemoradiation increased from 33% to 67% during 2004 to 2008 in our institute in accordance with the new findingson the benefits of neo-adjuvant RcT.

Several chemotherapeutic agents act as radiosensitizers and increase the effectiveness of radiotherapy. Many institutional experiences suggest significantly higher response rates, with or without improving overall survival rates, by using pre-operative RcT.[11] Although new drugs including oxaliplatin, irinotecan, and capecitabine have recently been tested concurrent with radiotherapy, capecitabine utilized in RcT has shown similar response rates as 5FU; therefore this drug appears a reasonable substitute in the neo-adjuvant therapy.[12,13] Efficacy of each chemoradiation regimen and its side effects are two most influential factors while choosing the regimen for treatment. It is believed that oral agents are more preferred

by patients. As an oral fluoropyrimidine, capecitabine is a more convenient alternative to intravenous infusions of 5FU.

Chan showed that both capecitabine and 5FU have comparable pathologic tumor response, local control and disease-free survival rates in rectal cancer when administered concurrently with preoperative radiotherapy.[14]

In a randomized phase III study, the efficacy and safety of capecitabine and 5FU in the neo-adjuvant chemoradiation setting were compared. All patients received adjuvant capecitabine or bolus 5FU-leucovorin. At a median of 52 months, the investigators noted non-inferiority of capecitabine for 5-year overall survival (P=0.0004) and no difference in local recurrence (P=0.665); 3-year disease-free survival was superior in the two arms (P=0.034).[15]

In our study, as mentioned in the result, there are no statistical differences in disease-free survival between capecitabine and 5FU.Acute toxicities such as diarrhea, stomatitis, nausea, and bone marrow suppression were also somewhat less with capecitabine than with 5FU. In another similar study with 30 patients, pre-operative capecitabine plus radiotherapy had a good safety profile.[16]

In a study by Veerasarn et al, pre-operative capecitabine 2,000 mg/m2/day concurrent with whole pelvic irradiation was effective and well tolerated. The common toxicities were diarrhea, hand-foot syndrome and skin dermatitis in radiation treatment area.[17] Our study too demonstrated a relatively low rate of hand-foot syndrome (only one patientin the capecitabine group), which is comparable with similar studies.[15,18,19]

Our study had several limitations. As always in a retrospective research, we were faced with difficulties of incompleteness of the data in clinical files and in follow-up of the patients, even though we attempted telephone contacts for this purpose. For this reason and also to obtain a more homogenous sample of the patients' data to compare 5FU and capeciabine in, we had to perform our survival analysis only in the patients treated in the pre-operative setting, which lowers the staistcal power and validity of our findings.

## Conclusion

According to this study pre-operative Radiochemotherapy with capecitabine for rectal cancer is efficacious and comparable to 5FU, with acceptable and tolerable toxicity profile in Iranian patients. Considering the limitations of this retrospective study, we hope that further research (specially the randomized clinical trials) going on now in our department, in tandem with the major international efforts over the world, can help clarify the issue of the best regimen for the neo-adjuvant radiochemotherapy of rectal cancer.

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