

Histologic response after neoadjuvant chemoradiotherapy in locally advanced rectal adenocarcinoma: experience from Sudan.

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Abstract

Background: Locally advanced rectal cancer can be down staged by neoadjuvant therapy and the resultant tumor response can be quantified histologically. This study aimed to assess pathological response of neoadjuvant chemoradiation in patients with locally advanced rectal cancers treated in Wad Medani Teaching Hospital (WMTH) and National Cancer Institute (NCI), Wad Medani, Sudan.

Patients and methods: A total of 36 consecutive patients with locally advanced rectal cancer that were managed in WMTH and NCI during the period from 2006-2011 were reviewed. Preoperative pelvic radiotherapy was delivered. Total of 46 Gray were delivered concurrently with 5- fluorouracil (5-FU) on the first and last week of radiation. Total mesorectal excision of the rectal tumour either by anterior or abdominoperineal resections was planned at 6-8 weeks from completion of preoperative treatment. The pathological response to therapy was assessed by histopathology examination of the surgical specimen.

Results: Initial clinical staging of patients revealed 58.3% of them were stage T3/T4N2M0 and 41.7% were stage T3N0M0. Down-staging to stage T1/T2N0M0 was found in 36.1% and stage T3N0M0 in 30.6%. No response was seen in 8.3% of cases with stage T3/T4N2M0 while complete clinical response (no residual) was seen in 25.0%. Complete histological response was observed in 13.8%. Positive lymph-nodes metastasis was confirmed in 8.3% of cases.

Conclusion: Neoadjuvant chemoradiation is a reasonable option for cases of rectal cancer and deserves further evaluation.

Keywords: Neoadjuvant, rectal cancer, chemoradiation, pathological response.

DOI: <http://dx.doi.org/10.4314/ahs.v16i3.15>

Cite as: Abdalla AAE, Alawad AAM, Ali HAM. Histologic response after neoadjuvant chemoradiotherapy in locally advanced rectal adenocarcinoma: experience from Sudan. *Afri Health Sci* 2016;16(3): 750-754. DOI: <http://dx.doi.org/10.4314/ahs.v16i3.15>

Introduction

Rectal cancer accounts for nearly 30% of all colorectal cancers cases¹. Surgical resection is the cornerstone of curative therapy. Following a potentially curative resection, the 5-year survival rate varies according to disease extent^{2,3}. After establishing the diagnosis and completing the staging work-up, a decision is made whether to pursue immediate resection or administer preoperative chemoradiotherapy (CMRT)⁴.

The use of preoperative radiotherapy (RT) combined or not with chemotherapy (CM) has been used in the treatment of rectal cancer for the past two decades and its use gradually increased as adjuvant therapy, especially in T3/T4 and/or N1/N2 tumors^{5,6}. The strategy of performing preoperative instead of postoperative treatment, has the proven advantages of lower acute toxicity⁷, lower total dose of radiation needed⁸ and eventual tumor regression and down-staging to enable curative resection and even sphincter preservation⁸⁻¹³.

The objective of this study is to assess the pathological response of neoadjuvant chemo radiation in patients with locally advanced rectal cancers treated in WMTH & NCI in the period 2006-2011 and to compare our results with the reported standards.

Patients and methods

This is a retrospective review of patients with locally ad-

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vanced rectal cancer that were managed in WMTH and/or NCI during the period from 2006-2011. In all 36 patients records are revised for symptoms. Digital rectal examination findings for all patients were recorded pre-operatively at the combined onco-surgical clinic, and all patients biopsy from the mass were taken as punch biopsies either bed side or during endoscopic examination. Radiological examination was performed evaluating the stage of the tumor and TNM staging system was used.

Neoadjuvant chemo radiation regimens were as follows: Pelvic radiotherapy delivered with total central dose of 46 Gray in 23 sessions. Bolus 5-FU was delivered (400 mg/m²) during the first and last weeks of radiation. 5-fluorouracil was given 30 minutes prior to radiation sessions. All patients had been seen at the combined clinic after 6-8 weeks of radiation. Clinical and radiological assessments were then repeated. Finally, the combined clinic decided on type of surgery according to the initial site of the tumor and response to treatment.

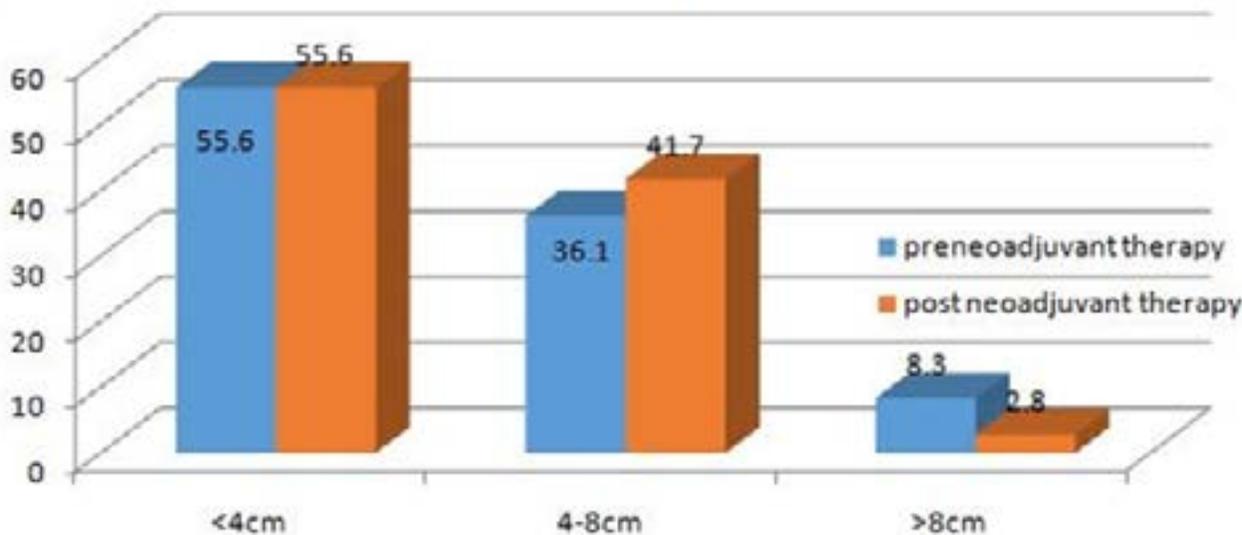
Review of the postoperative histopathology report took place addressing the presence of cancer or viable malig-

nant cells, extent of invasion and number of involved lymph nodes, a modified pathologic staging system was used. The Rectal Cancer Regression Grade (RCRG), which simplified the classification to three levels, RCRG 1: the tumor is either sterilized or only microscopic foci of adenocarcinoma remain; RCRG 2: marked fibrosis, but with macroscopic tumor still present; and RCRG 3: little or no fibrosis in the presence of abundant macroscopic tumor. RCRG 1 and 2 were considered to represent significant tumor regression¹⁴. Report included presence of lymph-nodes and if they were involved or not. Data was introduced and analyzed by computer program (SPSS version 17). To determine the statistical significance of differences, the Pearson test was used and probability test (P. value) with $p < 0.05$ considered as significant.

Results

The total number of cases was thirty six with female to male ratio of 1.25:1. All patients were seen in combined clinic. More than 55% of cases have tumor less than 4 cm from the anal verge (Figure 1).

Figure 1: The distance from the anal verge pre and post Neoadjuvant therapy



In this study, 97.2% (n=35) of patients received full course of CMRT and the dose of radiation ranging be-

tween 45-50 Gray Pre and post neoadjuvant therapy clinical staging is shown in (Table 1).

Table 1: Clinical staging using images pre and post CMRT therapy

CMRT therapy Clinical staging using images (CT/MRI) Pre-treatment	Clinical staging using images (CT/MRI) post-treatment
15 stage T3N0M0	4 stage T0N0M0 5 stage T1N0M0 4 stage T2N0M0 2 stage T3N0M0
21 stage T3/T4N2M0	5 stage T0N0M0 4 stage T1N0M0 9 stage T3N0M0 3 stage T4N2M0

In this study 91.7% of cases underwent APR, 8.3% cases underwent Anterior Resection (AR) which was done using staplers and one patient offered no surgery. Post neoadjuvant therapy histological assessment showed RCRGI in 41.7% of cases [of them 5 out of 15 there were com-

plete sterilization of the specimen. 13.8%], RCRGII in 27.8%, and RCRGIII in 30.6%.

Only 8.3% were found to have metastatic lymph nodes deposits. In cross tabulation between the results of the histology post CMRT and the grade of the tumors, we found that a significant relationship ($P=0.031$) between patients grade and response (Table 2).

Table 2: Correlation between post Neoadjuvant histological response and tumor grade

Histopathology post Neoadjuvant therapy	Tumor grade		
	Grade 1	Grade 2	Grade 3
RCRG 1	11	3	1
RCRG 2	2	6	2
RCRG 3	2	7	2
P. value	0.031		

Discussion

Advances in colorectal cancer treatment create a development of a neoadjuvant CMRT which became widely accepted now¹⁵. Neoadjuvant CMRT is very effective in reducing the tumor mass as seven out of 36 cases showed

no palpable mass, per digital rectal examination (DRE), after neoadjuvant CMRT. All cases were amenable for surgery after neoadjuvant CMRT including those who presented with fixed tumor (69.4%). This reflected the effectiveness of neoadjuvant CMRT in this study.

The results of this study can be compared with Dunst et al study done in Germany¹⁶ who found clinical response rate of 68% (95% confidence interval: 57-78%), and they have used a total irradiation dose of 50.4-55.8 Gray with conventional fractions. Capecitabine was given at an oral dosage of 825 mg/m² bid on each day of the radiotherapy period with the first daily dose applied 2 h before irradiation, followed by surgery 6 weeks later¹⁶.

In this series 58.3% of patients (n=21) were found to have stage T3/T4N2M0 and post therapy, only 3 cases had this stage 8.3% and in 41.7% of patients (n=15) with stage T3N0M0 prior to treatment, the down-staging was seen in (13/15). Radiological complete resolution was observed in 25.0% of cases. The overall down-staging in this study was observed in (31/36). In comparison with a study done by Rashid A et al they showed down-staging was found in 56.7% of cases¹⁷. Duke's university study showed down-staging in 82% of cases, and this was compatible with our findings¹⁸.

In a study conducted in Shanghai (2001-2005) published in 2007, 105 patients were studied, of these 13 patients showed complete tumor response after neoadjuvant therapy and they spared the operation¹⁹. In our study, we were following the case who experienced complete clinical and pathological response, and who remained free since 2009. Pathological complete response which was observed in this study was comparable to the findings of Dunst et al¹⁶ they have pathologically complete response was achieved in six patients (7%, 95% confidence interval: 3-14%). In another study conducted in Karachi; Rashid A et al found that pathological complete resolution of tumor was achieved in 3.3%¹⁷.

In cross tabulation between the results of the histology post CMRT and the grade of the tumors, we found a significant relationship (P=0.031) between patients grade and response. Eleven out of 15 tumors with grade I showed RCRGI, on the other hand only 3 out of 16 tumors grade 2 showed RCRGII, while only one tumor with grade 3 (out of five) showed complete response RCRGIII. This signifies that the tumor grade may predict the response to treatment (Table 2).

In 8.3% of our patients there were lymph nodes retrieved in the specimen after surgical resection, this correlates well with the series reported by De laFuente SG et al²⁰,

who found fewer total lymph-nodes were retrieved in the neoadjuvant therapy patients compared to those who did not receive preoperatively therapy (Neo 14.6 +/- 0.6 vs. No-Neo 17.2 +/- 1.1).

In conclusion, neoadjuvant chemoradiation in locally advanced rectal cancer in Sudanese patients provide a significant pathological response and it deserves further evaluation.

Acknowledgements

There was no grant or other financial support for this article.

Conflict of interest

None to declare.

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