Original Article

Neoadjuvant chemoradiation for rectal cancer: analysis of clinical outcomes for patients treated in Wad Medani Teaching Hospital and National Cancer Institute (Sudan) in the period 2006-2011

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Abstract

Background
Locally advanced rectal cancer can be down-staged by neoadjuvant therapy and the resultant tumour response can be quantified histologically.
This study aimed to assess clinical response of neoadjuvant chemoradiation in patients with locally advanced rectal cancers treated in Wad Medani Teaching Hospital (WMTH) & National Cancer Institute (NCI) in the period 2006-2011.

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 meso rectal excision of the rectal tumour either by anterior or abdomino-perineal resections was planned at 6-8 weeks from completion of preoperative treatment.

Results
Initial clinical staging of patients revealed 58.3% Duke’s C and 41.7% Duke’s B. The
clinical response was obviously seen in rectal bleeding which dropped from 97.3% to 2.8% and the palpable tumour had disappeared in 19.4%. Down-staging to Duke’s A is found in 36.1% and Duke’s B in 30.6%. No response was seen in 8.3% of cases with Duke’s C while complete response (no residual) was seen in 25.0%. Complete histological response was observed 41.7%. 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.

**Key words:** Neoadjuvant, rectal cancer, chemoradiation, complete response

**Introduction**

Rectal cancer is no longer a disease for the generalist. Rather it has become the paradigm and test bed for the future multi-disciplinary specialists’ management of all solid tumours. The relative importance of surgical technique, modern radiotherapy (RT), and the arrival of the new drugs represent one of the most fascinating and complex scenarios in modern medicine\(^{(1)}\). Rectal cancer accounts for nearly 30% of all colorectal cancers cases\(^{(2)}\). The preoperative evaluation is critically important to treat the cancer optimally and achieve sphincter preservation. With this information, surgeons must individualize the treatment and care of each patient\(^{(3)}\). Surgical resection is the cornerstone of curative therapy. Following a potentially curative resection, the 5-year survival rate varies according to disease extent\(^{(4,5)}\).

Surgical and oncologic management varies greatly depending on the stage and location of the tumour within the rectum. Superficially invasive, small cancers may be managed effectively with local excision. However, most patients have more deeply invasive tumours that require major surgery, such as low anterior resection (LAR) or abdominoperineal resection (APR). Yet others present with locally advanced tumours adherent to adjoined structures such as the sacrum, pelvic sidewall, prostate, or bladder, requiring an even more extensive operation\(^{(3)}\).

After establishing the diagnosis and completing the staging work-up, a decision is made whether to pursue immediate resection or administer preoperative chemoradiotherapy (CMRT)\(^{(5)}\). The employment 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 employ gradually increased as adjuvant therapy, especially in T3/T4 and/or N1/N2 tumours\(^{(6,7)}\).

The strategy of performing preoperative instead of postoperative treatment, has the proven advantages of lower acute toxicity\(^{(8)}\), lower total dose of radiation needed\(^{(9)}\) and eventual tumour regression and down-staging to enable curative resection and even sphincter preservation\(^{(9-14)}\).

Concomitant chemotherapy includes 5-FU during first and last weeks of radiation\(^{(15)}\).

The objective of this study is to assess the clinical response of neoadjuvant chemoradiation in patients with locally advanced rectal cancers treated in WMTH & NCI in the period 2006-2011.

**Patients and methods**

This is non-interventional retro-prospective analytical observational hospital-based review of patients with locally advanced rectal cancer that were managed in WMTH and/or NCI during the period from 2006-2011. Combined onco-surgical clinic in NCI was established in 2005 and composed of surgeons, oncologists, radiologists, pathologists and a psychologist. For rectal cancers they follow local guidelines with main features which include joint clinical assessment, staging, preoperative chemoradiation for all cases with Duke’s B and C and finally post radiotherapy assessment and surgery for operable cases.

In all 36 patients history was taken addressing symptoms of localized disease (T1/T2) and locally advanced disease (T3/T4), and
constitutional symptoms like weight loss. Digital rectal examination findings for all patients were recorded preoperatively at the combined onco-surgical clinic, like the distance from the anal verge, site, fixity, and length of the tumour. For all patients biopsy from the mass was taken as punch biopsy. MRI pelvis or CT scan was done for all cases and interpreted with Duke's system was extracted from the study as confined to the mucosa was stage A and when infiltrate wall or reach the serosa and/or extend to the perirectal fat was stage B. Stage C for the lymph-nodes involvement. 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 tumour and response to treatment.

Review of the postoperative histopathology report took place addressing the presence of cancer or viable malignant cells, extent of invasion and number of involved lymph nodes, a modified pathologic staging system the Rectal Cancer Regression Grade (RCRG) was used. "Good" for response (I), "median" response (II) and "poor" response (III). RCRG I included complete histological response and when there were very few microscopic foci of adenocarcinoma. RCRG II was when some malignant cells were found in the specimen and RCRG III was when the tumour cells were found in the entire specimen. Report must include presence of lymph-nodes and if they were involved or not. Data introduced and analysed by computer program for statistical package for social sciences (SPSS). 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 and preoperatively MRI was performed for 52.8% while 47.2% were assessed by CT scan. Pre-treatment clinical staging using images revealed that 58.3% of cases have Duke’s C and 41.7% with Duke’s B. More than 90% of the patients have adenocarcinoma. In this study, 97.2% (n=35) of patients received full course of CMRT and the dose of radiation ranging between 45-50 Gray. The clinical assessment before neoadjuvant treatment is shown in Table 1. Post neoadjuvant chemoradiation therapy the anal mass persisted in one (2.8 %) patient and the other symptoms showed 100% response.

<table>
<thead>
<tr>
<th>Table 1: Initial symptoms at presentation.</th>
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<tbody>
<tr>
<td>Anal swelling</td>
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<td>-------------</td>
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<tr>
<td>Yes %</td>
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</tbody>
</table>

Marked response was seen in tumour mobility (69.6% to 2.8%) and to lesser extended in tumour regression, out of 97.2% presented initially with palpable mass there were 19.4% with no palpable mass after the neoadjuvant therapy. Pre and post neoadjuvant therapy clinical staging is shown in Table 2.
Table 2: Clinical staging using images pre and post CMRT therapy.

<table>
<thead>
<tr>
<th>CMRT therapy Clinical staging using images (CT/MRI) Pre-treatment</th>
<th>Clinical staging using images (CT/MRI) post-treatment</th>
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</thead>
<tbody>
<tr>
<td>15 Duke Stage B</td>
<td>4 No tumour seen</td>
</tr>
<tr>
<td>9 Duke Stage A</td>
<td></td>
</tr>
<tr>
<td>2 Duke Stage B</td>
<td></td>
</tr>
<tr>
<td>0 Duke Stage C</td>
<td></td>
</tr>
<tr>
<td>21 Duke Stage C</td>
<td>5 No tumour seen</td>
</tr>
<tr>
<td>4 Duke Stage A</td>
<td></td>
</tr>
<tr>
<td>9 Duke Stage B</td>
<td></td>
</tr>
<tr>
<td>3 Duke Stage C</td>
<td></td>
</tr>
</tbody>
</table>

The distance from the anal verge was approximately 1-9 cm. 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 complete tumour regression RCRGI in 41.7% of cases, RCRGII in 27.8%, and RCRGIII in 30.6% showed no response for treatment. 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 tumours, we found that a significant relationship (P=0.031) between patients grade and response (Table 3).

Table 3: Correlation between post neoadjuvant histological response and tumour grade.

<table>
<thead>
<tr>
<th>Histopathology post neoadjuvant therapy</th>
<th>Tumour grade</th>
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<tbody>
<tr>
<td></td>
<td>Grade 1</td>
</tr>
<tr>
<td>RCRG 1</td>
<td>11</td>
</tr>
<tr>
<td>RCRG 2</td>
<td>2</td>
</tr>
<tr>
<td>RCRG 3</td>
<td>2</td>
</tr>
<tr>
<td>P. value</td>
<td>0.031</td>
</tr>
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</table>

Discussion

Advances in colorectal cancer treatment create a development of a neoadjuvant CMRT which became widely accepted now. Neoadjuvant CMRT is very effective in stopping rectal bleeding as is shown in this study (97.2%).

In this study, tenesmus appeared in 77.8% (28 cases) and 25 of them experienced relief from this symptom, this finding is even better than what is being reported in literature. Presentation with anal pain which suggested involvement of the anal sphincters; cancers growing directly into the anal sphincter usually were not amenable to sphincter-sparing procedures. In this series all patient with anal pain (50%) became pain free after neoadjuvant treatment.

Seven out of 35 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 tumour (69.4%). This reflected the effectiveness of neoadjuvant CMRT in this study.

Taking these results (fixity, hardness, pain and lengthy tumours) indicated that these cases were presenting late and the risk of inoperability was high so the neoadjuvant treatment could help in making these tumours resectable.

In all previous results, we can extract a conclusion that clinically the response was very satisfactory regarding symptoms and clinical assessment using digital rectal examination. These results can be compared with Dunst et al study done in Germany (2008). They found clinical response rate of 68% (95% confidence interval: 57-78%), they have used the same protocol which we have used in this study.

In this study, we used MRI pelvis preoperatively in 52.8% (n=19) of patients and the others 47.2% (n=17) of patients assessed by CT scan, here we were lagging behind because the MRI have now replaced CT scan because it was better in T-stage and in detecting lymph-nodes in peri-rectal fat.
Endorectal ultrasound (ERUS) was more accurate than MRI\(^3\).

In this series 58.3% of patients (n=21) were found to have Duke’s C and post therapy, only 3 cases had this stage 8.3% in 41.7% of patients (n=15) with Duke’s B, 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 cases\(^19\). Duke’s university study showed down-staging in 82% of cases, and this was compatible with our findings\(^20\).

In study conducted in Shanghai (2001-2005) published in 2007, they studied 105 patients, of these 13 patients showed complete tumour response after neoadjuvant therapy and they spared the operation\(^21\). 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 Mátrai Z et al\(^16\), who studied 57 patients and found 10.5% patients had complete pathological response. In another study conducted in Karachi; Rashid A et al found that pathological complete resolution of tumour was achieved in 3.3% \(^{19}\).

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

In 8.3% of our patients there were lymph-nodes retrieved in the specimen after surgical resection, this correlate well with the series reported by De la Fuente SG et al\(^22\), 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, to draw a conclusive conclusion we need a large sample size study. But in this study the clinical response to neoadjuvant therapy was significant in the form of patients’ symptoms and clinical findings. Neoadjuvant therapy led to down-staging of the tumours in significant number of patients. Further studies are needed to demonstrate the outcome of patients who shows complete clinical and pathological response without surgery.

References


