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RESEARCH ARTICLE

LOCALLY ADVANCED RECTAL CANCER; PREOPERATIVE CHEMO RADIOTHERAPYOUTCOME AND TOLERABILITY; CENTER EXPERIENCE

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ABSTRACT

Background and objective: Preoperative treatment with chemo radiotherapy for rectal cancer is a standard approach for certain patients group with cancer rectum. This study reports on overall survival and disease-free survival, down staging and toxicity in rectal cancer patients who received combined chemo radiation therapy followed by curative surgery. Patients and methods:in oncology department, Bahrain and between December 2009 and November 2012, 30 patients with clinical preoperative stage II–III underwent chemo radiotherapy followed by radical surgery for middle and lower rectal adenocarcinoma. Preoperative radiotherapy (total 50.4 Gy was delivered in 1.8-Gy daily fractions, five times per week over a period of approximately 6 weeks) and chemotherapy (5-fluorouracil 350 mg/m^2/day and leucovorin 20 mg/m^2/day, bolus on days 1–5 and 29–33).
Results: All patients successfully completed the planned treatment course. Pathological complete response (pCR) was found in 5 patients (16.67%). The pathological staging were 12 patientsas stage I, 8 patients were stage II, and 5 patients were stage III. Grade 3 to 4 toxicity occurred in 11 cases (36.67%). Three-year actuarial disease-free survival and overall survival rates were 87.5% and 93.7%, respectively. Local recurrences were found in one patient, 2 patients had distant metastases. Two patients died (1 of cancer related causes), 25were alive and disease free, and 3 are alive with disease.
Conclusions: Our center experience showed that preoperative chemo radiotherapy approach seems to improve the disease-free survival and overall survival of selected patients with rectal cancer. However, a longer follow-up time is required to confirm these results and define the failure pattern for our patients with possible palmed factors

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INTRODUCTION

Survival and local recurrence rates after surgical treatment for rectal cancer vary greatly in series reported in literature. In most randomized trials with a surgery-alone control arm, the local recurrence rate is approximately 30% (Blomqvist, 2000). Adjuvant therapy is widely used, with a view to reducing local failure and improving survival. In the Gastrointestinal Tumor Study Group and the Mayo/North Central Cancer Treatment Group (Allaix, 2013 and Kulinna *et al*., 2004) trials, the 5-year overall survival (OS) and disease-free survival (DFS), after combined postoperative chemo radiation therapy, were better than those after surgery alone.

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Based on findings in these trials, the treatment recommended forstage II–III rectal cancer is postoperative combined radiotherapy (RT) and chemotherapy (Badger, 2007). However, this treatment method has been questioned because, in 61% of patients, it causes toxicity that is severe, life threatening, or fatal (Beaumont *et al*., 2013). Moreover, almost 35% of the patients in the above trials did not complete all the chemotherapy cycles planned (Allaix, 2013 and Kulinna, 2004). Short-course preoperative radiation treatment alone (25 Gy in 1 week) is accompanied by a lower local recurrence rate (Meredith, 2009 and Heald, 2006), moreover, according to the Swedish Rectal Cancer Trial (Taylor *et al*., 2011), it is also followed by a better OS; after a minimum follow-up time of 5 years, 58% of patients who had received preoperative RT were alive, compared with 48% in the surgery-alone control group. This treatment method has caused concern because RT fractionation is considered suboptimal (Badger, 2007), and

long-term bowel function after irradiation is poor (Bipat, 2004). In view of its potential advantages (Badger, 2007), several investigators have evaluated the preoperative combined chemo radiation method in patients with unresectable (Brown, 2004; Beets, 2010; Sugita, 2010), and in those with potentially resectable, rectal cancer (Chua, 2012; Rödel, 2012; Artioukh, 2010; Folkesson *et al*., 2005; Ciabatoni, 2003; Orrom *et al*., 1990; Sauer *et al*., 2003). The aim of the current study was to evaluate our practice in Bahrain oncology center using preoperative combined RT and 5-fluorouracil (5-FU)-based chemotherapy and to define this practice approach on the OS and DFS of patients with transmural or node-positive middle and lower rectal carcinoma who underwent curative resection. Secondary end points were to ascertain the acute toxicity rate, down staging, and surgical morbidity.

Patients and Methods

Data collected for the patients who were treated in our center between December 2009 and November 2012, 30 patients with clinical preoperative stage II–III underwent chemo radiotherapy followed by radical surgery for middle and lower rectal adenocarcinoma.

Eligible patients should have

- histological or cytological diagnosis of rectal adenocarcinoma,
- clinical stage II-III according to TNM staging.
- 18 and up to 65 years of age.
- Eastern cooperative oncology group (ECOG) performance status of 0-2,
- normal renal, liver, and hematological profile.
- no prior radiation therapy or chemotherapy.

Pretreatment evaluation included patient history, clinical examination, laboratory investigations (blood count, liver function tests, renal function tests, carcinoembryonic antigen {CEA}) radiological studies (chest x-ray, computerized tomography of the chest, pelvi-abdominal ultrasound, MRI of the pelvis). Trans-rectal ultrasound (TRUS), bone scan and procto-colonic endoscopy.

Treatment methods

Radiotherapy and concomitant chemotherapy

A total irradiation dose of 50.4 Gy was delivered in 1.8-Gy daily fractions, five times per week over a period of approximately 6 weeks. Patients were irradiated in a prone position using a belly board to minimize exposure of the small bowel. A three- or four-field box technique using 18 MV LINAC machine. The clinical target volume, according to the International Commission on Radiation Units and Measurements guidelines, included the sacrum, the presacral space, the posterior walls of the bladder and prostate/vagina, and the regional lymph nodes extending to the common iliac artery. The upper border of the field was the interspace between L5/S1 or between L4/L5, depending on the extent of macroscopically involved nodes. Ventral extension of the lateral fields to include the external iliac nodes was permitted in the case of clinically detectable lymph node involvement. The lower field border was 5 cm below the macroscopic tumor. The anal canal was not irradiated unless the tumor extended close to the anus. Fluorouracil (5-FU) 350 mg/m2/day and low dose leucovorin 20 mg/m2/day bolus were given for 5 days on days 1 to 5 and 29 to 33 during radiotherapy (RT). Surgery was planned 4 to 7 weeks after preoperative chemo radiotherapy.

Fields arrangements

We used of complex; multiple field arrangement utilizing wedges filters, tissue compensators, field weighting, and bolus to achieve an adequate coverage of the target volume.

Gross target volume (GTV)

Accurate delineation of gross tumor volume of primary cancer depends on positive findings obtained from all diagnostic modalities used in pretreatment evaluation, including computed tomography whichever was positive or magnetic resonance imaging (MRI) scans.

Planned target volume (PTV)

The treatment volume encompasses the primary tumor with a 2cm safety margin around and draining lymphatic system.

Dosimetric evaluation

The 3-D computer planning system was used to have the best dose homogenicity to cover the target volume into the 95 % isodose curve. Doses to normal tissues were kept within the tolerance limits to reduce sequelae and morbidity. Weekly verification of the target volume was done. Patients were assessed on daily bases for proper repositioning and tolerance to radiation therapy. Also weekly CBC was done for any hematological toxicity detection.

Surgical Procedures

Standard lymph node dissection with total mesorectal excision (TME) was used. The surgical procedure was considered curative if all macroscopic disease was removed, and if the resection margin was disease free at histology.

Postoperative Adjuvant Therapy

All patients received six cycles of chemotherapy after surgery; 5-FU 375 mg/m^2/day and leucovorin 20 mg/m^2/day; bolus, days 1–5 every 28 days.

Evaluation of response and Toxicity

Response evaluation was performed at the end of induction chemotherapy, plus concomitant chemo radiotherapy, and at completion of all therapy. Response assessment included a repeat clinical and endoscopic examinations plus CT or MRI scans. Response and toxicity were evaluated according to WHO criteria as follows

- Complete response (CR): was defined as complete disappearance of all measurable lesions for a minimum of 4 weeks.

- Partial response (PR): was defined as a 50% or more decrease in the sum of the products of perpendicular diameters of all measurable lesions for a minimum of 4 weeks.
- Stable disease (SD): was defined as a less than 25% decrease in the sum of products of measurable lesions or a less than 25% increase.
- Progressive disease (PD): was defined as a 25% or more increase in the size of measurable lesions or the appearance of new lesions.

All toxic reactions are graded 0-5 implying: none (0), mild (1), moderate (2), sever (3), life threatening (4); and fatal (5)[9].

Follow-Up

Patients were examined at routine follow-up controls, made 3, 6, 12, and 18 months after surgery, and then yearly. At each follow-up visit, carcinoembryonic antigen concentration and liver ultrasonography were performed. A chest x-ray and colonoscopy were performed yearly. OS was considered the interval between the start of preoperative combined modality therapy and the date of the last follow-up control or death. DFS was considered the interval between surgery and the date of the last follow- up control, death, or recurrence. No patients were lost to follow-up. The median overall follow-up time was 27 months (range, 3–63 months).

Statistical Analysis

Statistical package for social sciences (SPSS) version 16 was used for data base construction and analysis. Quantitative variables were summarized using mean and SD, median minimum and maximum values. Qualitative data were summarized using frequencies and percentage. The starting point was the date of diagnosis for survival and response while it was the end of treatment for the time to relapse. Immediate local failure was counted whenever residual tumor is detected. Survival analysis was done using Kaplan- Meier, comparisons between survival curves was done using Log-rank test. Differences were considered significant when p was <0.05 and highly significant when p<0.01. (17).

RESULTS

Patient characteristics

The study population had a median age of 58 (range, 28–64) years. Male were predominant (M:F = 18/12). The mean distance from the anal verge to the caudal tumor edge was 5.5 (range, 2–9) cmand the median duration of postoperative hospital stay was 11 days (range, 7–70 days).

All patients completed the planned treatment schedule. Patient characteristics are summarized in Table 1.

Table 1. Clinical Patients Characteristics

No. of Patients	30
Male/Female	18/12
Median age, years (range)	58 (28–64)
Distance between anal verge and tumor distal margin (cm), mean (range)	5.5 (2–9)
Distance between external sphincter and distal margin (cm), mean (range)	3.9 (1.3–7.5)
Craniocaudal length of tumor (cm), mean (range)	6.4 (4–9)

Tumor Response (down staging)

A pathological complete response (pCR) was found in 5 patients (16.67%). Thirteen patients had pathological stage I (T1N0, 2 patient; T2N0, 11 patients), 8 patientshad pathologicalstage II (all T3N0), and 4 patients had pathological stage III (T2N1, 2 patients and T3N1, 2 patients). Tumor differentiation was poor in 2 patients. No tumors were considered T0–2 N0 at the preoperative evaluation; whereas 18 patients (60%) had tumors with pathological stage T0-2 N0 (Table 2).

Table 2. Tumor down staging after preoperative combined chemo radiotherapy in 48 rectal cancer patients

	TNM Stage	Clinical		Pathological	
		No.	%	No.	%
0	T0N0	0	0	5	16.67
I	T1N0	0	0	2	6.66
	T2N0	0	0	11	36.66
II	T3N0	8	26.66	8	26.66
	T4N0	2	6.66	0	0
III	T2N+ve	2	6.66	2	6.66
	T3N+ve	14	60.5	2	6.66
	T4N+ve	4	13.33	0	0
Total		30	100	30	100

Acute Toxicity

When multiple toxicity episodes in the same patients were scored as a single event, 6 (20%) patients had no acute toxicity, 15 (50%) had grade 1 to 2, and 9 (30 %) grade 3 to 4 toxicity (Table 3). Diarrhea and leukopenia were the most common grade 3 to 4 complications, occurring in 5 and 3 patients, respectively. All patients with grade 4 toxicity had febrile neutropenia. Although RT and/or chemotherapy were temporarily suspended in 2 cases, all patients completed the planned treatment.

Table 3. Acute toxicity associated with preoperative combined chemo radiotherapy

	Grade I		Grade II		Grade III		Grade IV	
Non hematological	No.	%	No.	%	No.	%	No.	%
Nausea/vomiting	7	23.33	1	3.33	1	3.33	0	0.00
Diarrhea	5	16.67	3	10.00	5	16.67	0	0.00
Mucositis	2	6.67	0	0.00	1	3.33	0	0.00
Dermatitis	4	13.33	1	3.33	1	3.33	0	0.00
Hematological								
Leukopenia	10	33.33	4	13.33	1	3.33	1	4.20
Anemia	3	10.00	3	10.00	1	3.33	0	0.00
Thrombocytopenia	1	3.33	1	3.33	0	0.00	0	0.00

Recurrence and Survival

Two patients developed distant metastases; none had local recurrence. One patient had both lung and liver metastases while the other patient got liver metastases only. At the end of this study, 2 patients have died one of them died from non-cancer related cause (acute myocardial infarction). One was alive with the disease, and the remaining 28 patientswere alive and disease free. The 5-year actuarial DFS (Fig. 1) and OS (Fig. 2) rates were 87.5% and 93.7%, respectively.

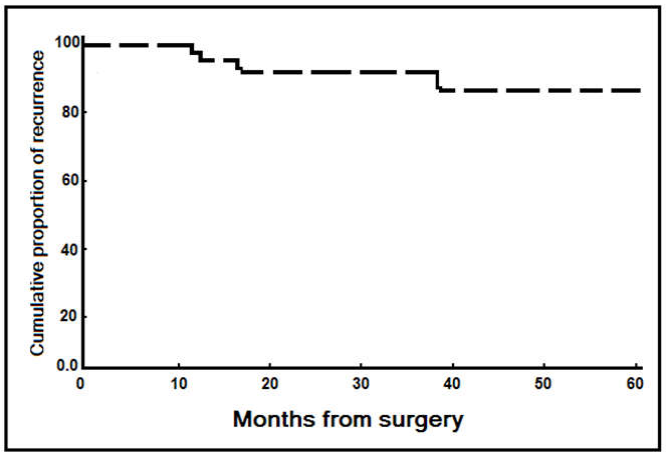

Fig. 1. Disease-free survival in 48 rectal cancer patients who received preoperative combined chemo radiotherapy

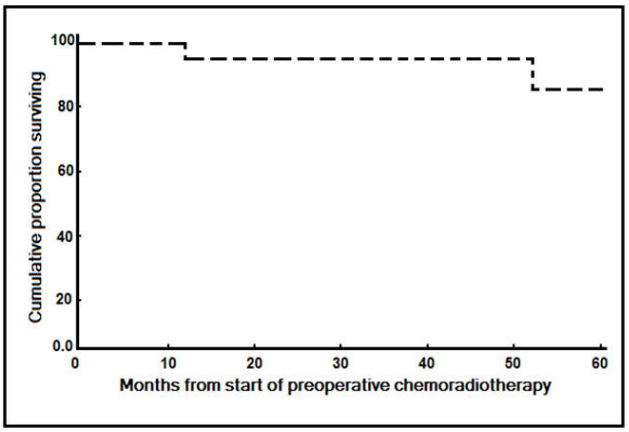

Fig. 2. Overall survival in 48 rectal cancer patients who received preoperative chemo radiotherapy

DISCUSSION

This study is reporting our management experience in middle and lower rectal cancer patients who underwent combined RT and 5-FU-based chemotherapy followed by radical surgery. In view of the selection of patients, the size of the study group, and the relatively short follow-up time, our data should be interpreted with caution. Moreover, surgical technique and skill are independent predictors of outcome in patients who undergo surgery for rectal cancer (Park *et al*., 2014; Evans, 2011). In selected series from single institutions (Puli, 2009; Wang *et al*., 2005; Beets-Tan *et al*., 2001) cancer-specific mortality and local recurrence rates after surgery alone for rectal cancer are even lower than those reported in prospective trials using adjuvant therapy (Kulinna, 2004; Allaix *et al*., 2013; Meredith *et al*., 2009; Heald *et al*., 2006; Taylor *et al*., 2011) TME is a complete, precise, and sharp excision of the entire rectum and mesorectum under direct vision. A local recurrence rate of 5% has been reported after the use of this technique in Dukes' B2 and C middle and lower rectal cancer cases [25]. Because our study was non-randomized and all our patients underwent TME, we were not able to distinguish between the influence of preoperative chemo radiotherapy and that of surgical technique on results. One randomized trial comparing results after preoperative RT with or without combined 5-FU, failed to demonstrate that this method had any advantage for OS [12, 17]. The low doses of RT used in this trial, the differences in both surgical and RT technique, and patient selection make any comparison with the results in our series somewhat questionable.

In several studies, (Chua, 2012; Rödel *et al*., 2010; Artioukh *et al*., 2010 Folkesson *et al*., 2005; Ciabatoni *et al*., 2003 and Sauer *et al*., 2003) a positive effect was found on both DFS and OS in clinically resectable rectal cancer patients who received preoperative chemo radiation therapy. With median follow-up times ranging from 22 to 38 months in some series (Chua *et al*., 2012; Rödel *et al*., 2010; Artioukh *et al*., 2010; Ciabatoni *et al*., 2003; Samdani *et al*., 2014; Sauer *et al*., 2003), and a mean follow-up time of 39 months in another,[9] the local recurrence rates reported are 0% to 11%, and DFS and OS range from 60% to 80% and 72% to 100%, respectively. The median follow-up time of 27 months in our series is comparable to those in other studies, and the actuarial 5-year DFS of 87.5% and OS of 93.7% are among the highest percentages reported. However, no definite conclusions can yet be drawn, because, as stated by Ahmad and Nagle, (Ahmad *et al*., 1997) a follow-up time of almost 5 years is required to detect 80% of all failures in patients who have undergone preoperative chemo radiotherapy for rectal cancer. Comparisons between series are hindered by several factors. The size and clinical stage of study populations reported on vary. Some studies (Rödel *et al*., 2010; Folkesson *et al*., 2005; Sauer, 2003) consider T3 tumors only, and others (Chua, 2012; Artioukh, 2010; Ciabatoni, 2003) [5,7,10]include T1 to T2 tumors. Our series also included three T4 tumors, but it did not include patients with microscopic residual disease at the time of surgery. Other studies (Sauer *et al*., 2003) have included patients with distant metastases. Moreover, in view of the differences between evaluations for preoperative staging, and between ranges of accuracy for both TRUS and pelvic CT scan, (Mercury, 2007) a selection bias is highly probable. The distance of the tumor from the anal verge, length of follow-up time, and types of surgical and adjuvant therapy used also vary. The highest local recurrence rates are reported by authors who include only patients with rectal carcinoma of the distal third, (Ciabatoni *et al*., 2003) who use RT doses of less than 45 Gy, (Rödel, 2012) and who undertake a longer follow-up period (Rödel, 2012 and Ciabatoni, 2003). The rate of sphincter-saving procedures in rectal cancer patients ranges from 17% (Chua *et al*., 2012) to 84.3% (this study). Moreover, in the series reported by Ciabatoni *et al*. (2003) 37 of 118 patients were found to have a complete response after preoperative chemo radiation therapy, and, therefore, they were not operated on. This policy is questionable, because, as

reported by Folkesson *et al.* (2005) only 36% of patients with negative biopsies after preoperative chemo radiation therapy have no residual tumor at pathology. Although a complete response was found at the time of the pathological examination in 16% of our cases, the surgical procedure performed was that planned before administration of preoperative chemo radiotherapy and was, therefore, unaffected by post treatment down staging. A further confounding variable, which may influence the comparison between these institutional series, is the use of different drugs at different doses and with different administration techniques. None of the authors considered herein used the same chemo radiotherapy regimen, and few of them (Folkesson, 2005; Ciabatoni *et al*., 2003; Sauer, 2003) used postoperative adjuvant chemotherapy.

The 30% of grade 3 to 4 toxicity found in our study is not unimportant. It is, however, only slightly higher than the 21% to 25% reported by other authors (Chua, 2012; Folkesson, 2005 and Ciabatoni, 2003) and toxicity was never severe enough to require a permanent suspension of treatment. Diarrhea and leukopenia were the most common grade 3 to 4 complications, occurring in 5 and 3 patients, respectively. All patients with grade 4 toxicity had febrile neutropenia (Table 3). Two authors used a regimen similar to ours (Orrom *et al*., 1990; Park *et al*., 2014). Sauer *et al*. (Orrom *et al*., 1990) reported an overall grade 3 to 4 toxicity rate of 25% (13% had grade 3 diarrhea and 12% had grade 3–4 leukopenia). Ciabatoni *et al*. (2003) reported that an overall 26.5% of non hematological toxicity, requiring temporary suspension of treatment, occurred in 26.5% of their patients. After review of studies on preoperative radiochemotherapy for rectal cancer, (Chua, 2012; Rödel *et al*., 2012; Artioukh *et al*., 2010; Ciabatoni, 2003; Sauer, 2003) it seems that permanent suspension of treatment is rare, whereas a temporary suspension is required in 7% to 26.5% of cases. A lower acute toxicity rate is reported with doses of RT of less than 40 Gy [6]. Although none of our patients required permanent suspension of treatment, toxicity still remains a concern.

Conclusion

Our findings confirm that preoperative chemo radiotherapy is an effective approach for patients with stage II-III rectal cancer. The actuarial 5-year OS and DFS in our series is encouraging, as is the sphincter-preserving rate for surgical procedures.

Recommendations

Longer follow-up time and larger number of patients are required to figure out the center experience in comparison to globally published data.

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