ABSTRACT

Purpose: The aim of the current study is to assess the response rate and toxicity profile in patients with locally advanced rectal cancer using brachytherapy (BT) boost following external beam radiotherapy (EBRT), concomitant with chemotherapy as a component of the neoadjuvant treatment.

Patients and Methods: This is a prospective phase II study of neoadjuvant chemo-radiation therapy for patients with locally advanced rectal cancer who presented to the department of radiation oncology, King Abdul-Aziz University Hospital, Jeddah, Kingdom of Saudi Arabia. Seventeen patients had been included in the study. Radiation therapy was given as: phase I, 45 Gy/25 fractions/5 weeks of EBRT, followed by brachytherapy boost (within one week after the end of EBRT) using high dose rate iridium 192 ($^{192}$Ir) aiming at 800 cGy given in 2 fractions (each 400 cGy) separated by 1 week. All patients received the same concomitant chemotherapy in the form of Capecitabine and Oxaliplatin. The clinical and pathological response rates, together with the toxicity profile were assessed.

Results: Seventeen patients had been studied; the majority (14; 82%) were males, while 3 only (18%) were females, their mean age was 57.4 years. All patients had low anterior resection (LAR). The clinical response rate, assessed by digital rectal examination ± endoscopy examination 4 weeks after the end of EBRT and BT, revealed that complete clinical response (cCR) was noted in 3 patients (18%), clinical partial response (cPR) in 14 patients (82%); while the pathological response rate was: complete pathological response (pCR) in 8 patients (47%), pathological partial response (pPR) in 9 patients (53%). The toxicity profile showed that grade III radiation proctitis was seen in one patient (6%), grade III dermatitis in 2 (12%), while no patients developed grade III cystitis. For chemotherapy toxicities, three patients (18%) developed grade III nausea and/or vomiting, 2 (12%) developed grade III diarrhea.

Conclusion: The use of high dose rate brachytherapy as a boost in the neoadjuvant chemotherapy and radiation therapy setting in locally advanced rectal cancer is an acceptable modality with an appreciable clinical and pathological response rates as well as an acceptable toxicity profile.

Key Words: Rectal cancer – Neoadjuvant chemotherapy and radiation therapy – Brachytherapy.

INTRODUCTION

In Saudi Arabia colorectal cancer is considered the second most common type of malignancy according to the Cancer Incidence Report of Saudi Arabia for the year 2004 [1].

Abdominoperineal resection (APR) has been considered to be the standard operation for lower rectal tumors with a distal edge up to 6 cm from the anal verge. Although it results in excellent local control and survival, the APR entails a permanent colostomy and a high incidence of sexual and urinary dysfunction. So, for patients with larger or more invasive tumors, neoadjuvant radiation therapy and chemoradiotherapy have been utilized to promote tumor regression in an attempt to convert a planned APR to a sphincter-sparing surgical procedure [2-5].

Neoadjuvant chemoradiation therapy in rectal cancer resulted in a high sphincter preservation rate from 41 to 95 percent, averaging 68 percent [6-13]. The aim of the current study is to assess the efficacy of brachytherapy boost...
after external beam radiation therapy concomitant with chemotherapy in terms of clinical and pathological response rates, as well as toxicity profile of both combined modalities in addition to brachytherapy.

**PATIENTS AND METHODS**

The study was conducted in the department of radiation oncology, King Abdul-Aziz University Hospital, Jeddah, Kingdom of Saudi Arabia, whereby seventeen patients with locally advanced rectal cancer referred for neoadjuvant chemoradiation therapy before definitive surgery had been evaluated.

Patients involved in the study included those diagnosed between May 2006 and June 2007 (inclusive). This is a prospective phase II study done on patients with locally advanced rectal cancer who should fulfill the following inclusion criteria: pathologically proven rectal carcinoma; locally advanced (T3, or T4) lesions, with no evidence of distant metastases as proved by CT scan chest abdomen and pelvis, and bone scan before the start of treatment. Patients should be able to sign an informed consent. Tumor (T) and lymph node (N) stages were identified by rectal MRI or trans-rectal ultrasound. Baseline hematological, renal and electrolyte profiles should be within normal range to start chemotherapy. Exclusion criteria included patients with unproved pathological diagnosis of rectal cancer, patients with metastatic disease at presentation, patients with history of previous pelvic irradiation, or patients who were involved in other clinical trials.

All patients received neoadjuvant chemotherapy during the course of irradiation consisting of Oxaliplatin 50 mg/m² intravenous (IV) given on days 1,8,22,29 and Capecitabine 825 mg/m² PO BID daily from day one to day 14, followed by 1 week rest and resumed at day 22 for 2 weeks.

CT planning for all patients was done in the treatment position (prone) for phase I (whole pelvis) and phase II (brachytherapy boost to rectum). Radiation therapy was given in phase I as whole pelvic irradiation, aiming at 45 Gy/25 fractions/5 weeks given as daily treatments, for 5 days per week and two days rest. Each radiation fraction dose was 180cGy using a linear accelerator with 3 fields; one direct posterior and two lateral fields. The energy used was 6MV in the posterior field and 18 MV in the lateral fields. Patients were treated in the prone position with full bladder to reduce small bowel toxicity.

After phase I (EBRT); patients were assessed clinically (by digital rectal examination) before phase 2, which entailed delivering brachytherapy within one week after the end of EBRT using an iridium 192 (Ir¹⁹²) high dose rate source inserted as remote after loading in a rectal cylinder applicator given as an outpatient procedure once per week for 2 fractions (each is 400cGy) for a total of 800cGy. The dose prescription would be at 0.5 cm from the applicator surface taking care to block the uninvolved areas with lead blocks mounted in the applicator cylinder. The upper and lower margins were of the treatment length usually selected to cover the tumor and 2 cm above and below the tumor edge with every attempt to spare the anal verge.

During the brachytherapy procedure, the patient lies in the prone position on the table, lidocaine gel 2% for mucous membrane with xylocaine gel were introduced around the anus and for a short distance inside the rectum to facilitate the entrance of the applicator. Examination was done to assess the extent of the lesion. The applicator was introduced in the rectum through the anus with the predetermined length and fixed to the table through the fixation arm to prevent movement of the patient during the procedure. The connected transfer tube was introduced into the tandem of the applicator and connected to the HDR machine (Figs. 1-6).

We have two diameters of the rectal cylinder 2.6 and 3 cm each one with two lengths, 6 cm and 10 cm, to accommodate the tumor with acceptable safety margins.

Computerized planning was then done with determination of the dwell time and position of the source according to the treatment length using the Brachy Vision V 7.3.10 planning system.

Acute reactions from radiation therapy were recorded according to the Radiation Therapy Oncology Group (RTOG) toxicity criteria [14] as maximal reported reactions through the whole
course of radiation, either during EBRT or at the end of the whole radiation treatment (Phase 1 and 2), as the gap between the EBRT and brachytherapy was one week or less in most of cases, so the contribution of the toxicities to which modality could not be clearly identified. Also, the same was applied to the radiation and chemotherapy toxicities. The toxicities reported might have been due to one of the two modalities or both, so identification of which toxicity belonged directly to any modality was difficult to determine precisely (the separation of radiation from chemotherapy toxicities can not be identified separately due to the use of the concomitant chemoradiation treatment).

Patients were referred for definitive surgery (either APR or LAR) 4 weeks after the completion of neoadjuvant chemoradiation therapy. Histopathological assessment of response to neoadjuvant radiation and chemotherapy was performed. Complete pathological response (pCR) referred to complete clearance of tumor cells from the resection specimen; the presence of residual tumor cells in resection specimen was referred to as pathological partial response (pPR). No response means no change from the pretreatment view [15].

Follow-up after surgery was done as clinical evaluation (both general physical assessment and rectal examination) every 3 months for the first 2 years. Proctosigmoidoscopy was done on a yearly basis; however, if local symptoms occurred (i.e. progressive constipation or bleeding), an immediate proctosigmoidoscopy was done. Radiological evaluation (CT scan chest abdomen and pelvis; and bone scan) were requested if patient got symptomatic.

Statistical analysis: Was done using the SPSS software, and descriptive statistics were used for patient criteria evaluation. The prognostic significance of different variables was assessed regarding its influence on the response rate using the Cross Tabulation Test.

RESULTS

Seventeen patients with histopathological diagnosis of rectal cancer had been identified and were referred for neoadjuvant chemoradiation therapy at the department of radiation oncology, King Abdul-Aziz University Hospital, Jeddah, Kingdom of Saudi Arabia, during the period from May 2006 to June 2007 (inclusive). Their ages ranged from 35 to 72 years (mean 57.4±11.6 years). Clinical and pathological features of patients involved in the study are shown in table (1).

The mean duration of treatment for all patients with radiation therapy (EBRT+BT) was 6.7 weeks (±0.75 weeks).

The mean follow-up period was 14.2 months, with Standard Error of the Mean (SEM) 2.91; (95% Confidence Interval; CI: 8.56-19.97) with a range from 1.5 to 39 months, while the median follow-up was 9 months with SEM 1.37 (95% CI: 6.31-11.69).

Due to the short follow-up period, analysis of the disease free survival and overall survival is sub optimal (needs longer follow-up), while our aim was to focus on assessment of the pathological response and toxicity profile.

Assessment of radiation toxicity was done as per RTOG toxicity criteria [14] and is shown in table (2).

All patients had low anterior resection (LAR). Only 2 patients (12%) developed wound infection one to two months following the operation, which healed spontaneously with medical treatment. One patient developed a stricture with partial intestinal obstruction one year after the operation and was treated conservatively with no further surgical interference. The pathological response rate was complete response (pCR) in 8 patients (47%), partial response (pPR) in 9 patients (53%). Complete clinical response rate (cCR) before surgery was founded in 3 patients (18%) and clinical partial response (cPR) in 14 patients (82%).

The toxicity profile included proctitis grade III which developed in one patient (6%), dermatitis grade III in 2 patients (12%), while no patients developed grade III cystitis Table (2).

Three patients (18%) developed grade III nausea and/or vomiting, 2 patients (12%) developed grade III diarrhea Table (3).

Comparing the pathological response rate with other clinical and pathological variables revealed that there was no correlation between the pathological CR and overall duration of radiation therapy in weeks (p=0.25), T stage (p=0.68), or N stage p=0.41).
Table (1): Clinical and pathological features of patients in the study.

<table>
<thead>
<tr>
<th>Feature</th>
<th>Number</th>
<th>Percentage (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Sex:</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>14</td>
<td>82</td>
</tr>
<tr>
<td>Female</td>
<td>3</td>
<td>18</td>
</tr>
<tr>
<td><strong>Histopathological grade (G):</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>G1</td>
<td>2</td>
<td>12</td>
</tr>
<tr>
<td>G2</td>
<td>14</td>
<td>82</td>
</tr>
<tr>
<td>G3</td>
<td>1</td>
<td>6</td>
</tr>
<tr>
<td><strong>Tumor (T) stage:</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>T3</td>
<td>12</td>
<td>71</td>
</tr>
<tr>
<td>T4</td>
<td>5</td>
<td>29</td>
</tr>
<tr>
<td><strong>Lymph node (N) stage:</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>N0</td>
<td>14</td>
<td>82</td>
</tr>
<tr>
<td>N1</td>
<td>3</td>
<td>18</td>
</tr>
<tr>
<td><strong>Distance from the anal verge:</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Less than 5 cm</td>
<td>7</td>
<td>41</td>
</tr>
<tr>
<td>More than 5 cm</td>
<td>10</td>
<td>59</td>
</tr>
</tbody>
</table>
DISCUSSION

There is much debate regarding the relative merits and disadvantages of adjuvant versus neoadjuvant combined modality therapy in the treatment of patients with non-metastatic rectal carcinoma. Three randomized trials have directly compared the two approaches [16], and in all of them the overall survival was not different in the two approaches; however, the rate of sphincter preservation and local disease control were higher among the neoadjuvant combined modality approach.

In phase II studies of neoadjuvant chemoradiation therapy in locally advanced rectal cancer, the rates of complete pathological response were higher following preoperative 5 FU-based chemoradiotherapy than they were in series using radiation therapy alone [17-26].

The standard neoadjuvant chemoradiation therapy is based on 5 FU-Leucovorin concomitant with pelvic irradiation aiming at 50.4 Gy/28 fractions/5.5 weeks. A lot of different techniques were developed to compare this standard approach against different radiation therapy protocols.

In a Polish randomized trial involving 316 patients with T3-4 rectal cancer [27], patients were randomized between the standard radiation therapy and concomitant 5FU-Leucovorin arm and a short course of high dose per fraction of radiation RT (5 x 5 Gy) followed by surgery. In an early report, the pathological response rate was significantly higher in the chemoradiotherapy group (16 versus 1 percent), and there were fewer cases of radial margin positivity (4 versus 13 percent), but the rate of sphincter preservation in both groups was comparable (58 and 61 percent, respectively). Toxicity was much higher in the short course high dose per fraction arm. Local failure and survival rates were not reported.

In the current trial, we studied in a prospective way a new technique in the preoperative chemoradiation therapy for rectal cancer in which the standard chemoradiation therapy was followed by a rectal brachytherapy boost, whereby phase I 4500cGy/25 fractions/5 weeks was given as an external beam irradiation followed by a brachytherapy boost to the rectum aiming at 800cGy in 2 fractions given by a high dose rate brachytherapy iridium192 source. The clinical and pathological response rates, together with the toxicity profile were assessed.

After completion of the study, it was found that the pathological response rate was complete response (pCR) in 8 patients (47%), pathological partial response (pPR) in 9 patients (53%). Complete clinical response rate (cCR) before surgery was founded in 3 patients (18%) and clinical partial response (cPR) in 14 patients (82%). This emphasizes the superiority and more accuracy of the pathological assessment in this setting.

The toxicity profile showed that grade III radiation proctitis was seen in one patient (6%); grade III dermatitis in 2 (12%), while no patients had grade III cystitis. As regards chemotherapy toxicity, 3 patients (18%) developed grade III nausea and/or vomiting, 2 patients (12%) developed grade III diarrhea.

There is no much data about the use of brachytherapy as a boost to the external beam radiation therapy in the neoadjuvant setting in rectal cancer in the literatures. The biggest trial about brachytherapy in rectal cancer had been done in Canada by Vuong et al. [28], whereby forty-nine patients underwent staging with endoscopic endorectal ultrasound, and the tumor dimensions were determined with MRI of the pelvis. Patients with resectable rectal cancer (stages T2, T3, or early T4) were treated with

<table>
<thead>
<tr>
<th>Toxicity feature</th>
<th>Number (percentage)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Grade 0</td>
</tr>
<tr>
<td>Proctitis</td>
<td></td>
</tr>
<tr>
<td>Dermatitis</td>
<td>3 (18%)</td>
</tr>
<tr>
<td>Cystitis</td>
<td>11 (64%)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Toxicity feature</th>
<th>Number (percentage)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Grade 0</td>
</tr>
<tr>
<td>Nausea and/or vomiting</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>6 (35%)</td>
</tr>
</tbody>
</table>

Table (2): Radiation toxicity profile of the patients in the study.

Table (3): Chemotherapy toxicity profile of the patients in the study.
preoperative high-dose-rate endorectal brachytherapy concomitant with the standard 5FU-Leucovorin chemotherapy followed by surgery 6–8 weeks later. The treatment planning was done with the use of a CT simulator, and the treatment was delivered using a flexible endorectal applicator with eight catheters arranged around the circumference of the applicator and a high-dose-rate brachytherapy remote afterloading system with an Iridium-192 source. Digitally reconstructed radiographs were used as references for daily treatment. A tumor dose of 26 Gy in four fractions was prescribed. Forty-nine patients received planned treatment, and all but 2 patients underwent planned surgery. The pathology specimens showed a complete macroscopic response in 64% of the patients and tumor downstaging in 67% of the patients. This study showed the impact of preoperative brachytherapy on gross tumor control but not on microscopic remission as in the current study.

Conclusion: The use of brachytherapy as a boost to external beam radiation with concomitant chemotherapy in patients with locally advanced rectal cancer is an effective modality in terms of pathological complete response rate with an acceptable toxicity profile. The significance of this modality in terms of disease-free and overall survival was not clear in this study. So, it is recommended to do similar studies on a larger number of patients with longer follow-up periods to have more solid data.

REFERENCES


