ABSTRACT

Purpose: A prospective study was designed to randomize locally advanced rectal carcinoma patients between either preoperative radiotherapy (±postoperative chemotherapy) or postoperative adjuvant chemoradiation. Two end points were evaluated, local recurrence and survival, aiming at defining prognostic parameters that can help in the choice of the optimum treatment modality.

Patients and Methods: This is a prospective randomized clinical study including patients with locally advanced low rectal cancer treated at the National Cancer Institute (NCI), Cairo University, during the period from December 1994 to January 1999. Fifty patients with previously untreated rectal cancer were randomized into two groups, Group I: Subjected to surgery followed by radiation therapy (50Gy/5 weeks, 2Gy/fraction, 5 days/week) plus chemotherapy and Group II, subjected to preoperative radiotherapy (46Gy/4.5 weeks, 2Gy/fraction, 5 days/week) followed by surgery ± postoperative chemotherapy. Chemotherapy in the concomitant setting was given in the form of Leucovorin in a dose of 300mg/m² as a short i.v. infusion followed by 5-FU in a dose of 350mg/m² as a 6 hour i.v. infusion, whereas adjuvant chemotherapy consisted of 5-FU as 600mg/m² short i.v. infusion weekly for 48 weeks, in addition to levamisole tablets.

Results: The long-term treatment end results obtained showed that group I patients had a slightly higher 10-year overall survival (OS) rate when compared to group II patients (63% versus 60%, p=0.698). The corresponding figures for the 10-year disease-free survival (DFS) were 65% and 66%, respectively, p=0.816. Although the 10-year local failure rate (persistent/relapsed disease) was higher for the preoperative group, it was not of statistical significance, (30% Vs. 8%, p=0.057). On the other hand, the 10-year distant metastasis free survival was higher in the preoperative group (88% Vs. 72%), yet this difference did not reach statistical significance (p=0.16). The rate of acute radiation reactions was higher in the postoperative group, with no increase in the operative complications in the preoperative group. Moreover, none of the 50 patients had grade 3 or more late radiation/surgical squealae. There were no grade 3 or 4 chemotherapy related toxicities.

Conclusions: This work showed equal results for DFS and OS rates between preoperative and postoperative radiation therapy with the same acceptable acute and late radiation toxicity. High dose preoperative irradiation did not cause any significant increase in acute or late radiation induced reactions, delay in wound healing or increased postoperative morbidity when compared to postoperative adjuvant radiochemotherapy. Duke’s stage and response to preoperative irradiation proved to be of significance regarding DFS, while compliance to systemic therapy was of significance regarding both OS and DFS.

Key Words: Low Rectal cancer – Adjuvant chemoradiation – Neoadjuvant radiotherapy.

INTRODUCTION

The search for improved disease control and survival for resectable high-risk rectal cancers has led to studies that combine all 3 modalities (surgery, radiotherapy and chemotherapy), since local recurrence is a major cause of treatment failure that is difficult to treat [1]. There is a high incidence of local recurrence (15-68%) after conventional surgery alone according to pathological stage. Moreover, in the western countries, the 5-year survival rate of patients with rectal cancer undergoing surgery (with curative intent) alone is 50% [2]. In the Egyptian series, local recurrence rate was reported to be 35% due to the prevalence of locally advanced
disease [3]. Postoperative chemoradiation has been shown to improve both disease control (local and distant) and survival (disease-free and overall) and was recommended as standard adjuvant treatment at the 1990 National Institute of Health Colorectal Cancer Consensus Conference [4]. Several clinical trials were conducted to evaluate the impact of either pre- or postoperative radiotherapy on local control, overall survival (OS) as well as disease free survival (DFS) in rectal cancer. Mohiuddin and Ahmad [3], Friedman et al. [5], and Ezzat et al. [6] evaluated the effect of adding high dose preoperative radiation therapy on local control, a dose of 40Gy/4 weeks was found to improve the incidence of local control and, in some reports, survival. On the other hand, delivering 50Gy/25 fractions/5 weeks as postoperative adjuvant therapy achieved optimal significant reduction in local recurrence and improvement in DFS [7]. While addressing the problem of distant metastasis, addition of adjuvant chemotherapy to postoperative irradiation proved to significantly improve local control as well as survival when compared to postoperative irradiation alone [8]. The demonstration that 5-FU/levamisole can be an effective adjuvant therapy of colon cancer and the acceptance that 5-FU/leucovorin combinations are superior to 5-FU alone for metastatic colorectal tumors, have produced hope for further improvement in the systemic component of adjuvant treatment of rectal cancer [9]. Based on the promising results obtained with either preirradiation or postoperative concomitant chemoradiation, we report the 10-year follow-up results of the best high dose (46-50Gy/4.5-5 weeks) preoperative radiotherapy schedule compared to a combined postoperative chemoradiation schedule (50Gy/5 weeks plus 5-FU) combined with the biological response-modifiers.

PATIENTS AND METHODS

A controlled prospective randomized clinical study, open (with allocation concealment using closed envelope method) parallel group study was held at the NCI, Cairo University, during the period from December 1994 to January 1999. The study included 50 patients with previously untreated locally advanced resectable low rectal carcinoma. Patients were randomized into two groups:

**Group I:** Subjected to surgery followed by adjuvant radiation therapy (50Gy/5 weeks, 2Gy/fraction, 5 days/week) plus chemotherapy.

**Group II:** Subjected to preoperative radiotherapy (46Gy/4.5 weeks, 2Gy/fraction, 5 days/week) followed by surgery (± adjuvant chemotherapy).

Patients’ eligibility criteria included age less than 65 years with histopathologically proven low rectal carcinoma (all tumors were ≤7cm from the anal verge), no previous intervention (except biopsy), locally advanced [circumferential, obstructed rectum or partially fixed tumor (mobile only in one direction)], with no evidence of distant metastases. Pretreatment assessment included detailed clinical history, complete physical examination and laboratory tests. The radiological examination included endorectal ultrasonography, CT scan abdomen and pelvis, and chest X-ray. Sigmoidoscopy, tumor biopsy and DNA ploidy were also done. Patients were staged according to the Dukes classification system [10]. After informed consent had been obtained, 26 patients and 24 patients were randomly allocated into group I and II, respectively.

**Treatment protocols:**

**Surgery:** Abdominoperineal resection, posterior pelvic excentration or low anterior resection, were performed according to the site and extent of the tumor.

**Radiation therapy:** A 6MV linear accelerator was used. An isocentric technique was adopted at SAD of 100cm. All patients were treated in the prone position with a full bladder to displace the small bowel anteriorly and superiorly and to reduce the postero-anterior separation in obese patients. Irradiation was given in a dose of 50Gy/5 weeks for the postoperative group and 46Gy/4.5 weeks for the preoperative irradiation group. All the patients were treated with 2Gy/fraction, treating 5 days/week. For group II, after 2 weeks rest, reassessment for response was performed by digital rectal examination and endorectal ultrasonography. Surgery was performed 4 weeks after the completion of irradiation.

**Chemotherapy:** For group I (postoperative arm), chemotherapy, as radio-sensitizer, was administered during the first three days of the first and last week of postoperative irradiation,
in the form of Leucovorin in a dose of 300mg/m² as a short i.v. infusion over 1 hour followed in half an hour by 5-FU in a dose of 350mg/m² as short i.v. infusion over 4-6 hours. Chemotherapy, on an adjuvant basis, was continued immediately after the end of irradiation if complete blood picture and laboratory investigations were satisfactory. This entailed the delivery of 5-FU as 600mg/m² short i.v. infusion weekly for 48 weeks, in addition to levamisole tablets; 1 tablet 3 times per day for 3 days every other week, also for 48 weeks. As regard group II (preoperative arm), the same adjuvant chemotherapy was given for patients with pathologically positive lymph nodes and/or tumor had reached the pre-rectal fat, 4-6 weeks after surgery.

**Evaluation of patients during treatment:**

Postoperative sequelae were reported in both groups, namely time to wound healing, wound sepsis or dehiscence, and GIT complications. During irradiation, all patients were scored weekly for early normal tissue reactions using the RTOG/EORTC acute radiation morbidity scoring schema [11]. Patients were evaluated during radiation treatment once a week for assessment of tumor response in case of the preoperative arm. A change of a partially fixed tumor into a mobile one, or when a tumor that involves the whole circumference of the lumen changes into one that involves only a segment of the lumen, or more than 50% reduction in the size of the rectal mass, was considered as good partial response. On the other hand, patients who had complete disappearance of their disease were considered complete responders. All patients were evaluated for chemotherapy-related toxicity using the WHO grading system. Clinical examination, complete blood picture, liver and kidney function tests were done before each cycle.

**Evaluation of patients after treatment:**

Patients were followed-up monthly for the first 6 months after the end of their treatment, every 2 to 3 months for the following 2 years, every 6 months thereafter. The patients were scored for both local and systemic failures, and late treatment complications, using the RTOG/EORTC late radiation morbidity scoring schema [11]. Evaluation was done by clinical examination, CEA, periodic X-ray chest, abdominopelvic ultrasonography and CT pelvis. Locoregional and/or distant failure were diagnosed clinically and radiologically. Histopathological confirmation of the locoregional failure was done.

**Statistical analysis:** The overall survival was calculated from the date of randomization to the date of death from disease or last follow-up. Disease-free survival (DFS) was calculated from the date of surgery to the date of relapse (whether local, distant, or combined as confirmed clinically and/or radiologically using CT of the abdomen and pelvis). For statistical analysis, Stat View version 4.5 package (Abacus Concepts, Inc. Berkeley, CA) was used. Numerical data were described in terms of means and medians for central tendency and standard deviation and range, minimum and maximum for dispersion. Chi-square test was used to compare qualitative variables. Overall survival and relapse-free survival were determined using the Kaplan-Meier product limit method [12]. Comparison between survival rates of different groups was determined using the Log-Rank test [13]. Probability (p-value) ≤0.05 was considered to be significant.

**RESULTS**

Table (1) shows the characteristics of the 50 patients included in the study. There was no difference between the 2 groups as regard age, grade, surgical techniques, lymph node invasion, ploidy, and compliance to systemic treatment. However, more male patients were allocated in the preoperative arm, $p=0.005$. The preoperative arm had more patients with partially fixed lesions, $p<0.001$, and more patients with adeno-carcinoma in the preoperative arm, while the postoperative arm had more mucinous subtype of carcinoma, $p=0.037$.

Endorectal ultrasonography was performed in 40 patients. The accuracy to detect the depth of invasion of the primary tumor was better than that for detection of lymph node involvement, being 70% in the former and 50% in the latter when these findings were correlated to the histopathological examination of the specimens. Forty-two patients had pretreatment CT scans, which proved to be of value in detecting lymph node enlargement. In 16 of the evaluated patients who had pathologically negative nodes, the CT scan ruled out lymph node involvement in 13 cases, while the other 3 cases which
showed lymph node enlargement proved to be reactive hyperplasia. For the 26 patients with pathologically positive nodes, the CT scan was able to detect lymph node enlargements in 22 of them, thus giving a positive predictive value of 85% and a negative predictive value of 81%.

In Group I, abdominoperineal resection or pelvic excentration were done for 19 (73%) patients, and low anterior resection for 7 (27%) cases. In group II, 15 (62%) patients underwent abdominoperineal resection or pelvic excentration, and one patient had low anterior resection, \( p=0.127 \). For all patients, the median number of lymph nodes removed was 7.5 (range 2-34). For group I, positive lymph nodes were reported in 19 (73%) patients compared to 7 (29%) patients in group II, \( p=0.10 \). Out of the 26 patients in group I, 22 (84.6%) completed their systemic treatment as opposed to 16 (66.7%) in group II, \( p=0.190 \) (Table 1).

Patients were followed-up for a time period that ranged from 6 to 135 months (median 62.5 months). For the whole group, the 10-year overall survival (OS), disease-free survival (DFS) rates amounted to 67\( \pm 7\% \) and 62\( \pm 8\% \), respectively. The 10-year OS was 63\( \pm 10\% \) for Group I compared to 60\( \pm 14\% \) for Group II, \( p=0.698 \). As regard DFS, there was no difference between the 2 groups being 65\( \pm 10\% \) for group I and 66\( \pm 10\% \), \( p=0.816 \), (Table 2 and Figs. 1,2).

The median time to local failure and/or distant metastasis was 16 months. There were only three cases of locoregional recurrence (LR), 2 patients (8%) in group I and 1 patient in group II (4%). LRs in group I patients were located in the pelvis inside the irradiated field, 5 and 13 months after surgery. LR in group II patient occurred 34 months post surgery and was associated with a single liver deposit.

Distant metastasis occurred in 8 patients (16%) with 75% of these failures taking place within two years. Six patients (23%) were in group I and 2 patients (8%) in group II. The most common sites of metastasis were bone and lung (28.6% each) followed by the liver (14.3%). Five of the 10 patients who failed were still under their weekly systemic therapy and were all in Group I.

The correlation between the overall survival and DFS with the various prognostic factors is shown in Table (2). The only prognostic factor that showed a statistically significant effect on overall survival was patients’ compliance to their scheduled chemotherapy where the 10-year OS for complying patients was 67% as opposed to 47% for non-compliers, \( p=0.009 \). The same factor was of significance in the DFS setting, where complying patients had a DFS of 72% Vs. 50% for non-compliers, \( p=0.019 \). Response to preoperative radiotherapy was another factor with significance in the DFS of Group II patients where good responders (complete and partial remission) reported a 78% 10-year DFS, while non-responders’ rate fell down to 38\%, \( p=0.034 \). Patients with Duke’s stage B had a 10-year DFS of 92\% vs. 55\% for stage C patients, \( p=0.027 \). Patients refractory to treatment or locally relapsing patients had a 0\% 10-year OS as opposed to 68\% for the locally controlled patients, \( p=0.004 \). Patients having distant metastasis also had statistically lower 10-year OS of 13\% as opposed to 74\% for non-metastatic patients, \( p=0.0007 \). There were no operative mortalities in both groups.

In group I patients, wound healing ranged from 6 to 135 months (median 62.5 months). For the whole group, the 10-year overall survival (OS), disease-free survival (DFS) rates amounted to 67\( \pm 7\% \) and 62\( \pm 8\% \), respectively. The 10-year OS was 63\( \pm 10\% \) for Group I compared to 60\( \pm 14\% \) for Group II, \( p=0.698 \). As regard DFS, there was no difference between the 2 groups being 65\( \pm 10\% \) for group I and 66\( \pm 10\% \), \( p=0.816 \), (Table 2 and Figs. 1,2).

All 26 patients in group 1 (100%) received adjuvant chemotherapy, whereas only 16 patients (67\%) in group II (Duke C) received chemotherapy. None of the patients who re-
ceived adjuvant chemotherapy experienced grade 3 or 4 hematological or gastrointestinal toxicities necessitating treatment interruption. The commonest toxicities were oral mucositis (OM). In group 1, grade 1 OM occurred in 6/26 patients and grade 2 in 4/26 patients, whereas in group II, grade 1 OM occurred in 4/16 patients and grade 2 OM in 2/16 (Table 4).

As regard response to preoperative irradiation, out of the 20 patients with initially partially fixed tumors, 8 (40%) showed complete response, 6 (30%) showed partial response, and 6 (30%) showed no response to irradiation.

Grade 3 or higher radiation-induced late reactions occurred in only one patient in group I who underwent low anterior resection and developed stenosis of the rectal lumen around the line of anastomosis. It was managed by endoscopic dilatation. Apart from that, none of the patients experienced any grade 3 or 4 late radiation sequelae, whether cutaneous, intestinal or urogenital.

Table (1): Patients characteristics.

<table>
<thead>
<tr>
<th>Variables</th>
<th>Group I Post-operative</th>
<th>Group II Pre-operative</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years):</td>
<td>N=26 (%)</td>
<td>N=24 (%)</td>
<td></td>
</tr>
<tr>
<td>Range</td>
<td>20-55</td>
<td>15-59</td>
<td>0.193</td>
</tr>
<tr>
<td>Median</td>
<td>31.5</td>
<td>40</td>
<td></td>
</tr>
<tr>
<td>Gender:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>9 (34.6)</td>
<td>18 (75%)</td>
<td>0.005#</td>
</tr>
<tr>
<td>Female</td>
<td>17 (65.4)</td>
<td>6 (25)</td>
<td></td>
</tr>
<tr>
<td>Male : Female</td>
<td>0.5:1</td>
<td>3:1</td>
<td></td>
</tr>
<tr>
<td>PS:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>I</td>
<td>4 (15)</td>
<td>5 (20)</td>
<td>0.6</td>
</tr>
<tr>
<td>II</td>
<td>22 (85)</td>
<td>19 (80)</td>
<td></td>
</tr>
<tr>
<td>Mobility:</td>
<td></td>
<td></td>
<td>&lt;0.001#</td>
</tr>
<tr>
<td>Mobile</td>
<td>19 (73)</td>
<td>4 (16.7)</td>
<td></td>
</tr>
<tr>
<td>Limited mobility</td>
<td>7 (27)</td>
<td>20 (83.3)</td>
<td></td>
</tr>
<tr>
<td>Pathological cell types:</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Adeno-carcinoma</td>
<td>9 (34.6)</td>
<td>17 (70.8)</td>
<td>0.037#</td>
</tr>
<tr>
<td>Mucinous</td>
<td>13 (50)</td>
<td>5 (20.8)</td>
<td></td>
</tr>
<tr>
<td>Signet-ring</td>
<td>4 (15.4)</td>
<td>2 (8.3)</td>
<td></td>
</tr>
<tr>
<td>Grade:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>I-II</td>
<td>21 (80.8)</td>
<td>18 (75)</td>
<td>0.738</td>
</tr>
<tr>
<td>III</td>
<td>5 (19.2)</td>
<td>6 (25)</td>
<td></td>
</tr>
<tr>
<td>Surgical Technique*:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>APR/Excentration</td>
<td>19 (73.1)</td>
<td>15/16 (93.7)</td>
<td>0.127</td>
</tr>
<tr>
<td>LAR</td>
<td>7 (26.9%)</td>
<td>1/16 (6.6)</td>
<td></td>
</tr>
<tr>
<td>Pathological Duke's Stage:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>B</td>
<td>5 (19.2)</td>
<td>8 (33.3)</td>
<td>0.339</td>
</tr>
<tr>
<td>C</td>
<td>21 (80.8)</td>
<td>16 (66.6)</td>
<td></td>
</tr>
<tr>
<td>Lymph node*:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Positive</td>
<td>19 (73.1)</td>
<td>7/16 (43.7)</td>
<td>0.10</td>
</tr>
<tr>
<td>Negative</td>
<td>7 (26.9)</td>
<td>9/16 (56.3)</td>
<td></td>
</tr>
<tr>
<td>Ploidy**:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diploid</td>
<td>2/20 (10)</td>
<td>3/20 (15)</td>
<td>0.322</td>
</tr>
<tr>
<td>Aneuploid</td>
<td>18/20 (90)</td>
<td>17/20 (85)</td>
<td></td>
</tr>
</tbody>
</table>

* 8 patients in group II were inoperable. ** 10 patients ploidy not done.
# p-values ≤ 0.05 are considered significant.
Table (2): Correlation of 10 years Survival Rates with patients and tumor-related prognostic factors.

<table>
<thead>
<tr>
<th>Factor (No.)</th>
<th>OS</th>
<th>p-value</th>
<th>DFS</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Whole group:</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Postoperative (26)</td>
<td>67±7%</td>
<td></td>
<td>62±8%</td>
<td></td>
</tr>
<tr>
<td>Preoperative (24)</td>
<td>63±10%</td>
<td>p=0.698</td>
<td>62±10%</td>
<td>p=0.816</td>
</tr>
<tr>
<td>Gender:</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male (27)</td>
<td>70±10</td>
<td>0.343</td>
<td>71±10</td>
<td>0.463</td>
</tr>
<tr>
<td>Female (23)</td>
<td>50±14</td>
<td></td>
<td>61±10</td>
<td></td>
</tr>
<tr>
<td>Lesion mobility:</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Limited mobility (27)</td>
<td>50±18</td>
<td>0.222</td>
<td>67±8</td>
<td>0.732</td>
</tr>
<tr>
<td>Mobile (23)</td>
<td>65±9</td>
<td></td>
<td>63±16</td>
<td></td>
</tr>
<tr>
<td>Grade:</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>I-II (39)</td>
<td>91±9</td>
<td>0.114</td>
<td>69±8</td>
<td>0.698</td>
</tr>
<tr>
<td>III (11)</td>
<td>55±9</td>
<td></td>
<td>73±13</td>
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</tr>
<tr>
<td>Pathological cell type:</td>
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<td></td>
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<td></td>
</tr>
<tr>
<td>Adenocarcinoma (26)</td>
<td>86±11</td>
<td>0.065*</td>
<td>65±10</td>
<td>0.797</td>
</tr>
<tr>
<td>Mucinous (18)</td>
<td>67±12</td>
<td></td>
<td>69±12</td>
<td></td>
</tr>
<tr>
<td>Signet ring (6)</td>
<td>33±19</td>
<td></td>
<td>55±25</td>
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<tr>
<td>Lymph node:</td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Positive (26)</td>
<td>60±10</td>
<td>0.221</td>
<td>65±10</td>
<td>0.201</td>
</tr>
<tr>
<td>Negative (16)</td>
<td>69±17</td>
<td></td>
<td>87±9</td>
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<tr>
<td>Diploidy:</td>
<td></td>
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<tr>
<td>Anepolid (35)</td>
<td>60±10</td>
<td>0.952</td>
<td>72±8</td>
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<td>Diploid (5)</td>
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<td>40±22</td>
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<td></td>
<td></td>
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</tr>
<tr>
<td>B (13)</td>
<td>77±15</td>
<td>0.077*</td>
<td>92±7</td>
<td>0.027*</td>
</tr>
<tr>
<td>C (37)</td>
<td>57±9</td>
<td></td>
<td>55±9</td>
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</tr>
<tr>
<td>Response to radiotherapy:</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CR (8) + Partial (6)</td>
<td>85±18</td>
<td>0.194</td>
<td>78±9</td>
<td>0.04*</td>
</tr>
<tr>
<td>No (10)</td>
<td>51±19</td>
<td></td>
<td>38±16</td>
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</tr>
<tr>
<td>Compliance to chemotherapy:</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes (38)</td>
<td>67±9</td>
<td>0.009*</td>
<td>72±8</td>
<td>0.019*</td>
</tr>
<tr>
<td>No (12)</td>
<td>47±15</td>
<td></td>
<td>50±14</td>
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* p-values ≤ 0.05 are considered significant.

Table (3): Treatment complications.

<table>
<thead>
<tr>
<th>Variables</th>
<th>Group I Post-operative N=26</th>
<th>Group II Pre-operative N=24</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Early complication:</td>
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<td>0.768</td>
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<tr>
<td>Wound healing time:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean (±SD)</td>
<td>25.8±13.2</td>
<td>24.6±13</td>
<td></td>
</tr>
<tr>
<td>≥ Grade 3 radiation reactions:</td>
<td></td>
<td></td>
<td>0.039*</td>
</tr>
<tr>
<td>Yes</td>
<td>9 (34.6%)</td>
<td>2 (8.3%)</td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>17 (65.4%)</td>
<td>22 (91.7%)</td>
<td></td>
</tr>
<tr>
<td>Radiation interruption (days):</td>
<td></td>
<td></td>
<td>0.681</td>
</tr>
<tr>
<td>Median</td>
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<td>9.5</td>
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</tr>
<tr>
<td>Range</td>
<td>4-13</td>
<td>2-14</td>
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* p-values ≤ 0.05 are considered significant.
DISCUSSION

The mainstay of treatment of carcinoma of the rectum is radical surgery, with or without sphincter preservation. In the randomized trials including a surgery-alone group, local recurrence rates exceeded 20% (average 28%), after a follow-up mostly more than five years, using standard rectal cancer surgery [14]. The 5-year survival rates for Dukes stage B and C rectal cancer range from 25% to 45% [15]. Locoregional recurrence causes pain, bleeding, soiling, ulceration, fistulation and profoundly deteriorates the quality of life. This fact led to several trials investigating the role of adjuvant radiotherapy, with or without chemotherapy.

The role of radiotherapy in addition to surgery for rectal carcinoma has been, and still is, a controversial issue despite the positive results of several large clinical trials. In a systematic overview of the effect of radiotherapy in rectal carcinoma, the Swedish Council of Technology Assessment in Health Care (SBU) analyzed data from a total of 131 scientific articles involving 25,351 patients. They included 3 meta-analyses, 42 randomized trials, 36 prospective studies, 7 retrospective studies and 17 other articles [14]. To evaluate the effect of preoperative radiotherapy versus postoperative radiotherapy, only randomized trials were included. Altogether, 27 trials comparing RT Vs no RT have been identified and analyzed, 19 of them

<table>
<thead>
<tr>
<th>Toxicity</th>
<th>Grade</th>
<th>Group I Post-operative (N=26)</th>
<th>Group II Pre-operative (N=16)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>I- Non hematological toxicities</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1- Gastrointestinal toxicities</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Oral mucositis</td>
<td>1</td>
<td>6 (23%)</td>
<td>4 (25%)</td>
<td>0.768</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>4 (15%)</td>
<td>2 (12.5%)</td>
<td></td>
</tr>
<tr>
<td>Diarrhea</td>
<td>1</td>
<td>4 (15%)</td>
<td>3 (19%)</td>
<td>0.8</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>1 (4%)</td>
<td>1 (6%)</td>
<td></td>
</tr>
<tr>
<td>Nausea and vomiting</td>
<td>1</td>
<td>5 (19%)</td>
<td>4 (25%)</td>
<td>0.9</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>5 (19%)</td>
<td>3 (19%)</td>
<td></td>
</tr>
<tr>
<td>2- Cutaneous</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Palmar plantar erythrodysesthesia</td>
<td>1</td>
<td>0</td>
<td>1 (6%)</td>
<td>0.09</td>
</tr>
<tr>
<td>II- Hematological toxicity:</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Neutropenia</td>
<td>1</td>
<td>3 (11%)</td>
<td>1 (6%)</td>
<td>0.9</td>
</tr>
<tr>
<td>Anemia</td>
<td>2</td>
<td>2 (8%)</td>
<td>1 (6%)</td>
<td>0.8</td>
</tr>
</tbody>
</table>

Fig. (1): 10-year overall survival for the whole group.

Fig. (2): 10-year disease free survival for the whole group.
for preoperative radiotherapy and 8 for postoperative radiotherapy. In addition, one trial, only, directly compared preoperative and postoperative radiotherapy [16].

Statistically significant lower local recurrence rates have been seen in most trials comparing preoperative radiotherapy (followed by surgery) versus surgery alone, and in some of the trials comparing surgery Vs surgery with postoperative radiotherapy [14,17]. The radiotherapy trials included in the meta-analyses have used different radiation schedules with different fraction sizes. In the preoperative radiotherapy trials, the schedules used ranged from 5 Gy x 1-5 fractions to 2 Gy x 20 fractions. In the postoperative radiotherapy trials, only conventional fractionation (1.8-2.0 Gy) was used. In order to compare doses, the trials were ranked according to biological effective dose (BED) values calculated by the linear quadratic time model. The preoperative radiotherapy trials were arbitrarily divided into three groups with BED <20 Gy, 20-30 Gy, and >30 Gy (maximum 37.5). All postoperative radiotherapy trials fell in the >30 Gy group (range 35.4-43.8 Gy). A dose-dependent influence on local failure rates was seen in the preoperative trials and preoperative radiotherapy proved to be more dose-efficient than postoperative. The latter statement was confirmed in the only trial having directly compared pre- and postoperative radiotherapy [16]. The latter study proved that preoperative irradiation was associated with statistically significant lower recurrence rate; 12% versus 21% for postoperative irradiation (p=0.02), and the 5-year OS was 42% Vs. 38% in favor of the preoperative arm. The incidence of late small bowel obstruction was also lower in the preoperative irradiation group (5 versus 11%) (p<0.01) [16]. The possibility that preoperative irradiation can downstage tumors and render fixed tumors resectable was supported by Kodner and colleagues [18], where all their patients with fixed tumors were rendered resectable after 45 Gy in 5 weeks of preoperative irradiation.

Preoperative radiotherapy at biological effective doses above 30 Gy decreases the relative risk of a local failure by more than half (50-70%), while postoperative radiotherapy decreases the risk by 30-40% at doses that are generally higher than those used preoperatively. There is strong evidence that preoperative radiotherapy improves survival (by about 10%), whereas postoperative radiotherapy does not improve survival except when postoperative radiotherapy is combined with concomitant chemotherapy [14,19]. In light of these results, it seems that the radiotherapy component improves the locoregional control rate while the systemic chemotherapy would reduce the risk of metastasis due to the increased frequency of subclinical micrometastases with disease progression.

In the present study, the long-term treatment end results obtained showed that both groups had almost similar 10-year overall survival rates of 60±10% Vs 63±14% for preoperative and postoperative radiotherapy, respectively (p=0.698). The preoperative group had higher 10-year disease free survival of 88±8% Vs 72±10% for the postoperative group, though the difference did not reach a significant value (p=0.168). In the present study, preoperative radiotherapy (without concomitant chemotherapy) was at least equivalent to concomitant postoperative chemoradiation. The superiority of preoperative radiotherapy had been demonstrated in an earlier study carried out at the NCI, Cairo University. In that study, the 3-year DFS rate for the preoperative group was 48% versus 26% in the postoperative group (p<0.05) with a lower local recurrence in the preoperative group; being 23% versus 41% for the postoperative group (p<0.06) [6]. However, the incidence of distant metastasis was equal in both groups (29%). In the present study, the dose increased to 46 Gy compared to 40 Gy in the previous study. The radiotherapy-surgery interval weeks increased to 4 weeks versus 2 weeks in the previous study, thus allowing more time for tumor regression and downstaging, and also allowing time for recovery of endothelial cells and fibroblasts. Moreover, the postoperative arm in the previous study did not include any adjuvant chemotherapy which resulted a lower survival rate (26%) in the postoperative arm [6].

Preoperative radiotherapy studies suggest that after preoperative doses of 40 Gy/4 weeks, the endothelial cells and fibroblasts may be able to repair potentially lethal damage after an interval of 3 to 4 weeks [20]. However, for smaller doses in the order of 20-25 Gy, the interval may be shortened to less than a week. On the other hand, the proliferative phase of
wound healing ends 4 weeks after wound incision. Postoperative irradiation after such interval is not therefore expected to interfere with sound wound healing. In the present study, the time interval between preoperative or postoperative radiotherapy and surgery was 4 weeks. This choice was based on the above-mentioned biologic considerations. The two therapeutic groups had an almost similar wound healing time with a mean of 25.8±13.2 days for group I and 24.6±13 days for group II, p=0.768. Moreover, the rate of grade 3 acute reactions (mainly cutaneous) were much lower in the preoperative group being 8.3% Vs. 34.6% in the postoperative group (p=0.039) and there was no difference in the mean time of treatment interruptions due to these reactions. As regard serious (≥ grade 3) late radiation reaction, there was also only 1 case of grade 3 late radiation reaction in group I as opposed to none in group 2. The same findings are supported by the meta-analysis studies [14,21], where postoperative morbidity was reported to be reduced in the preoperative arm [21]. Mohiuddin and Ahmad [3] reported a lower incidence of complications with high dose preoperative irradiation (4%) in comparison to postoperative irradiation (13%). The adoption of a conventional fractionation preoperative radiotherapy regimen and an ample interval between radiation and surgery may have contributed to the improved healing observed in the present study. Preoperative radiotherapy at adequate doses (similar to postoperative radiotherapy) can be given with low acute toxicity. Higher and unacceptable acute toxicity seen in some preoperative radiotherapy trials was explained by using suboptimal techniques [14].

The role of chemotherapy in locally advanced rectal carcinoma is also a topic of debate. In the adjuvant setting, chemotherapy proved to increase both local control as well as survival rates when combined with postoperative radiotherapy [16,21]. Although it had a positive effect when combined with preoperative radiation [22-24], yet there is still a need to identify the optimal chemotherapy dose, optimal chemotherapeutic combination of drugs and the best administration schedule for 5FU. The dose and infusion rate for 5FU when given concomitantly has been tested in the bolus and 24 hours continuous IV infusion [25]. Survival benefit was shown with the continuous infusion of 5-FU compared to the bolus administration [25]. In this study, the tolerance and efficacy of a 6-hour infusion 5FU concomitant with radiotherapy were evaluated to allow treatment on an out-patient basis. It was well tolerated, with minimum toxicity. However, further comparative trial of concomitant 5FU 24-hour infusion Vs 4-6 hour infusion is further warranted. In view of the promising results with concomitant chemoradiation, another study has been conducted at our institute for the past 3 years with 2 arms; arm I: Conventional high dose preoperative irradiation with concurrent daily cisplatinum as radio-sensitizer (6mg/m²/day, with max. of 10mg/day and max. total dose of 200mg) arm II: Same preoperative schedule with administration of 5-FU (375mg/m²) during the first and last 3 days of irradiation. Postoperative chemotherapy is administered to all patients using the Mayo Clinic regimen [26]. Results are not available yet.

In the present study, compliance to chemotherapy proved to be a statistically significant factor as regards both the 10-year overall survival (p<0.009) and the 10-year DFS (p=0.019) regardless of the treatment arm, thus highlighting the previous results of large randomized trials showing DFS benefit and OS benefit with adjuvant chemotherapy [16,21].

In the present study, we have selected a subset of patients who had a combination of high-risk prognostic factors for locoregional and distant failure and whose expected overall and disease-free survival rates were low, as identified by Stevens [27]. This group included patients with rectal cancer, which was locally advanced (partially fixed or circumferential tumors and/or with nodal involvement), high grade or bad pathological cell subtype (mucoid adenocarcinoma and signet ring cell carcinoma). Most tumors were in the mid and lower portion of the rectum with penetration through the bowel wall. However, the 10-years OS and DFS rates were comparable to the published results in such high risk patients. In the present study, although it is of a randomized nature, we had noticed a bias in the patients’ characteristics, with more high risk patients in the preoperative arm (Table 1). In spite of this, the DFS and OS rates were similar in the 2 arms, despite the fact that we did not administer any preoperative chemotherapy.
The present study was conducted in the era of conventional surgical techniques. The outcome of surgery depends largely on achieving adequate proximal, distal and lateral safety margins with complete regional lymphadenectomy. The lateral safety margin is considered a problem in low rectal lesions as there is no barrier between the tumor and lateral wall. This accounts for the wide variation in the reported locoregional and survival rates. In the trials included in the meta-analyses [14], surgery was not standardized. During the past decade, however, it has been repeatedly claimed that surgery has not been optimal in the trials generally recruiting patients during the 1980s, and that fewer local recurrences can be obtained if surgery is improved. Lower figures were also reported from institutions with dedicated and well-trained surgeons [28]. Improved lateral clearance after careful dissection in the plane outside the fascia surrounding the mesorectum “total mesorectal excision” is likely responsible for the markedly lower local recurrence rates. There are also several reports pointing to the importance of the surgeon for the outcome [29,30].

Conclusion: In locally advanced rectal carcinomas, high dose preoperative irradiation did not cause any significant increase in acute or late radiation induced reactions, delay in wound healing or increased postoperative morbidity when compared to postoperative adjuvant radiochemotherapy. Duke’s stage and response to preoperative irradiation proved to be of significance regarding DFS, while compliance to systemic therapy was of significance regarding both OS and DFS.

REFERENCES


