Journal of the Egyptian Nat. Cancer Inst., Vol. 15, No. 4, December: 284-292, 2003

Pre-Versus Postoperative Chemoradiation Combined with Total Mesorectal Excision in Locally Advanced Carcinoma of the Low Rectum

AHMAD MORSI, M.D.[1], SOMAIA EZZAT, M.D.[2], AZZA NIAZI, M.D.[2], MOHAMAD REDA HAMZA, M.D.[3] and NADIA MOKHTAR, M.D.[4]

The Dpeartments of Surgery[1], Radiation Oncology & Nuclear Medicine[2], Medical Oncology[3] and Pathology[4], National Cancer Institute, Cairo University.

ABSTRACT

Purpose: Total mesorectal excision (TME) had been established as the standard of care for resection of carcinoma of the rectum, resulting in reduction of the pelvic recurrence rate from 22% to 8.2% [**1**]. The addition of adjuvant chemoradiation further reduces local recurrence rate, yet the impact on the overall survival is not unequivocally demonstrated. The timing of irradiation also, remains as an unanswered question.

Patients and methods: This is a prospective randomized clinical study including patients with locally advanced low rectal cancer treated at the NCI Cairo University, during the period from Dec. 1994 to Jan. 1999. The study included 50 patients with previously untreated low rectal cancer. Patients were randomized into two groups, Group I: subjected to surgery followed by radiation therapy (50Gy/5 weeks, 200 cGy/fraction, 5 days/week) plus chemotherapy and Group II, subjected to preoperative radiotherapy (46Gy/4.5 weeks, 200 cGy/ fraction, 5 days/week) followed by surgery plus chemotherapy.

Results: Locoregional recurrence rate was 4% in group I and 2% in group II. The actuarial 4-year survival in group II was better than group I (81% versus 58%), yet this difference was not statistically significant ($p = 0.49$). Also the 4 year disease free survival in group II was better than grade I (58.2% versus 35.8%), yet this difference was not statistically significant ($p = 0.41$).

Conclusions: This work showed that there is a trend for better results with preoperative chemoradiation, yet it did not reach a statistically significant value. More patients with longer follow up are needed to reach significant values.

Key Words: *Low Rectal cancer - Total mesorectal excision - Adjuvant chemoradiation.*

INTRODUCTION

Local recurrence is a serious problem in the treatment of rectal cancer, since it causes disabling symptoms and it is difficult to treat [**2**]. There is a high incidence of local recurrence (15-45%) after conventional surgery, in which blunt dissection of the rectal fascia often fails to remove all the tissue that may bear tumor [**3**].

The recognition that involvement of the circumferential margin by the tumor cells is associated with high incidence of local recurrence has led to the general use of total mesorectal excision in which the entire mesorectum is enveloped and resected by precise sharp dissection [**4**].

Several clinical trails were conducted to evaluate the impact of adding either pre- or postoperative radiotherapy on local control, overall survival (OS) as well as disease free survival (DFS) in rectal cancer. Friedman [**5**], Ezzat et al., [**6**] and Mohiuddin & Ahmad [**7**]; evaluated the effect of adding high dose preoperative radiation therapy on local control. A dose of 40 Gy/4 weeks was found to improve the incidence of local control. This effect was further significantly intensified by adding chemotherapy during radiation. In addition, the use of postoperative chemotherapy had a positive impact on the OS as well as the DFS [**8**]. The effect of preoperative chemoradiation on improving the local control and survival could be attributed to: better tolerance of chemotherapy, downstaging of the tumor, thereby achieving adequate surgical margins and sterilizing the peripheral and deep margins of the tumor as well as the small satellites which may be present

away from the site of the primary tumor and are usually the cause of local failure [9].

This trial was conducted to compare preoperative Vs. postoperative chemoradiation with standardized total mesorectal excision in patients with locally advanced carcinoma of the low rectum.

PATIENTS AND METHODS

This is a prospective randomized clinical study including patients with locally advanced resectable low rectal cancer treated at the NCI Cairo University, during the period from Dec. 1994 to Jan. 1999. The study included 50 previously untreated patients.

Patient eligibility criteria included, age less than 65 years with histopathologically proven low rectal carcinoma (all tumors were ≤ 7 cm 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 radiologic 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 1992 American Joint Committee of Cancer (AJCC) and the modified Astler-Coller system.

After informed consent had been obtained, we randomly assigned the patients to two groups, Group I: were subjected to surgery followed by radiation therapy plus chemotherapy and Group II, were subjected to preoperative radiotherapy followed by surgery plus chemotherapy.

Treatment protocols:

Surgery: Abdominoperineal resection, posterior pelvic excentration or low anterior resection was performed according to the site and extent of tumor. Total mesorectal excision (TME) was also done in all patients. The technique adopted for TME was that described by Heald et al. [10] (Fig. 1). The plane surrounding the sigmoid colon and the upper rectum is developed sharply. Under direct vision with sharp diathermy or scissor dissection, this plane was extended down into the pelvis around the rectum and the fatty mesorectum as far as the point of emergence of the mesorectum from the levator gutter (Fig. 2). Great effort was made to avoid digital extraction of the tumor on the grounds that this could tear veins or split into tumor planes. In most cases this plane was avascular except where it is crossed by the lateral rectal vessels. The inferior mesenteric artery was ligated 1 cm from the aorta and the vein separately 1 cm from the splenic vein, the proximal lymphatic clearance was thus radical. In patients for whom abdominoperineal resection or posterior pelvic excentration was done. The perineal part was performed and the ano-rectal tube together with the whole mesorectum were removed. In patients for whom low anterior resection was performed, all the mesorectal tissues on the back of the rectal stump is cleared and removed en bloc with the specimen (Fig.3). A 2-3 cm rectal stump was left above the levator, so that most of our anastomoses were 5-6 cm from the anal verge. Loop transverse colostomy was done for all patients and closed after the end of the adjuvant therapy.

Specimen orientation and thorough histopathological examination was done to identify circumferential spread and assure the quality of the total mesorectal excision. Any abnormal bleeding or adhesions in the preoperatively irradiated patients were reported. Postoperative sequalae were reported in both groups.

Radiation therapy:

A 6 MV linear accelerator was used. An isocentric technique is adopted at SAD of 100 cm. All patients were treated in the prone position with a full bladder to displace the small bowel anteriorly and superiorly and to reduce the posteroanterior separation in obese patients. Postoperative irradiation was given in a dose of 50 Gy/5 weeks (200 cGY/fraction, treating 5 days/week). Preoperative irradiation 46 GY/4.5 weeks (200 cGY/fraction, treating 5 days/week). 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:

Chemotherapy was given during the first and last three days of the radiotherapy schedule in both groups of patients. Leucovorin was given as a short term infusion over one hour followed half hour later by 5-flurouracil (FU) administration in a dose 350 mg/m^2 as I.V. infusion over 4-6 hours. Adjuvant postirradiation chemotherapy was given to the preoperative radiotherapy group of patients 4-6 weeks after surgery and to the postoperative radiotherapy group of patients immediately after irradiation. Flurouracil based chemotherapy and leucovorin were given for six months.

Evaluation of patients during treatment:

Patients were evaluated during treatment once a week for assessment of tumor response in case of the preoperatively irradiated patients as well as to score early normal tissue reactions. 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 response.

All patients were followed up monthly for the first 6 months after the end of their treatment, then every 2 to 3 months for at least a period of 2 years, for detection of local failure, distant metastases and/or treatment complications. Evaluation was done by clinical examination, hematological tests to monitor drug toxicities, CEA, periodic X-ray chest, abdomino-pelvic ultrasonography and CT pelvis. Locoregional and/or distant failure were diagnosed clinically and radiologically. Histopathological confirmation of the locoregional failure was done. Survival time was calculated from the first day of diagnosis until the last follow-up or death.

Statistical analysis:

The end points of this study were the time of local recurrence or metastases. Statistical analysis was carried out according to SAS statistical package (JMP version 3). The Kaplan-Meier method was used to construct curves for the overall survival and disease free survival [**11**]. The log-rank statistics was used for the comparison of probability curves. p-value $\leq$ 0.05 was considered significant.

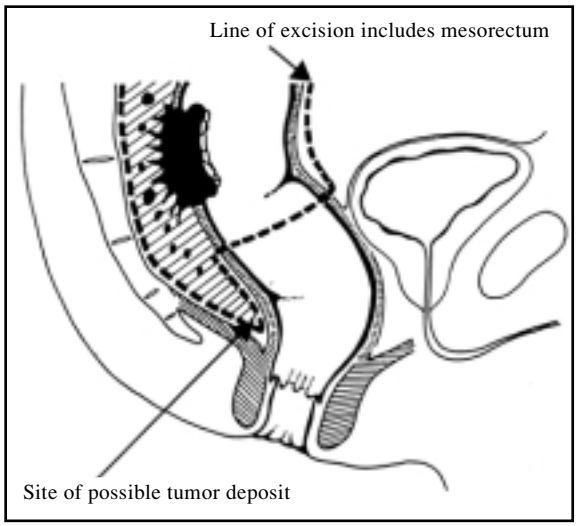

Fig. (1): Diagram showing the mesorectum and possible sites of tumor spread. The plane of excision is shown diagrammatically by the dashed line (10).

Fig. (2): The whole mesorectum is dissected till the level of emergence of the rectum from the levator ani gutter, which appear as the deepest structure in the pelvis.

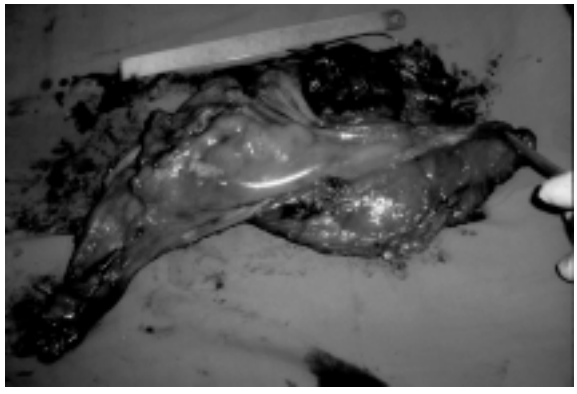

Fig. (3): The extent of the lymph node dissection, from the inferior mesenteric group (Lt) and the stretched mesorectum with its fatty appearance (Rt). The picture also shows a low rectal ulcer and the distal safty margin.

RESULTS

The study included 50 untreated locally advanced low rectal cancer patients. They presented to the National Cancer Institute, Cairo University during the period from December 1994 to January 1999. The patients were randomized into two treatment groups.

Group 1 (G I): Twenty six patients treated by surgery followed by postoperative radiotherapy plus chemotherapy.

Group 2 (G II): Twenty four patients treated by preoperative radiotherapy followed by surgery plus chemotherapy.

Patients' characteristics were shown in Table (1). Sixty two percent of the cases were adenocarcinoma grade II and 32% were grade III, with a minority of 6% were grade I. Moreover, node positive patients constituted 75% of the cases. Seventy percent of the patients were stage III and the rest (30%) were stage II.

Transrectal 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 10 of the evaluated patients who had pathologically negative nodes, CT scan ruled out lymph node involvement in 8 cases and the other 2 cases which showed lymph node enlargement proved to be reactive hyperplasia. For the 32 patients with pathologically positive nodes, the CT scan was able to detect lymph node enlargements in 28 of them, thus giving a positive predictive value of 85% and a negative predictive value of 80%.

In Group I, all the cases were operable. Abdominoperineal resection was done for 17 patients, low anterior resection for 7 cases and posterior pelvic excentration for 2 female patients. Total mesorectal excision was done for all cases. Twenty patients had positive lymph nodes and 6 were negative for lymph node metastases. Median number of the L.N. removed was 14 (range 8-34). In group II, 6 cases were inoperable (fixed posterolateral extension in 4 cases, and extension to the urinary bladder and pelvic wall in two cases) and 18 were operable. Abdominoperineal resection was done for 16 patients, low anterior resection in one patient and posterior pelvic excentration for one female patient. TME was done for all cases. Fourteen patients had positive lymph node metastases and 4 patients had negative lymph nodes. Median number of the lymph nodes removed was 10 (range 6-24). There were no operative mortalities in both groups. In group I patients, wound healing ranged from 11 to 22 days with a median of 14 days. Preoperative irradiation did not cause any significant delay in wound healing where it ranged from 14 to 24 days with a median of 16 days. Perineal wound infection and dehiscence rate was 7.7% in group I and 8.3% in group II. There was no abdominal wound dehiscence. Loop transverse colostomy was done for all the cases of anterior resection in both groups and it was closed after the completion of the adjuvant treatment. Two cases in group I developed acute intestinal obstruction 20 and 22 days after the end of radiotherapy, both were managed conservatively.

Acute cutaneous reactions was the most commonly recorded acute reactions, seen in 44 patients, almost half of them (54%) were grade three toxicity (moist desquamation and ulceration), none had grade four toxicity. This reaction was also the most common cause of treatment interruption (range of 5-14 days). Five out of the 15 patients who experienced treatment gaps were treated using the 4 field box technique to diminish the cutaneous reactions. Radiation induced late rectal reactions occurred in one patient in group I who underwent low anterior resection and developed stenosis of the rectal lumen around the anastomotic line. It was managed by endoscopic dilatation. None of group II patients suffered such a complication.

There were only two cases of isolated locoregional recurrence (4%), both in group I. They were located in the pelvis inside the irradiated field. The first patient was a 35 years old male with signet ring adenocarcinoma, grade III, stage II B. Failure occurred 5 months after surgery and while still under weekly chemotherapy. The second case was 25 years old female with mucoid adenocarcinoma grade III, invading the posterior vaginal wall and 7/11 lymph nodes were positive. Perineal fecal fistula with positive biopsy for recurrence occurred 13 months after

operation. Only one patient (2%) in group II had both locoregional and distant failure, he was a 40 year old male with mucoid adenocarcinoma grade III, 8/12 lymph nodes were positive and positive circumferential surgical margin. The pelvic recurrence occurred 34 months past surgery and was associated with a single focal liver metastasis.

The rate of distant metastasis for the 50 patients was 16% at 4 years, where 75% of these failures occurred within two years. Out of the 8 cases with distant metastasis, 7 were in group I and one in group II (having local recurrence as well). The most commonly affected sites were bone and lung (28.6% each) followed by the liver (14.3%).

The 2-year actuarial survival of the two groups combined (50 patients) amounted to 77.5% and by 4-years 65.8%. The 2-year actuarial survival was 70.8% for group I and 81% for group II. Although the difference increased by 4-years due to a drop in the survival in group I which reached 58% while the survival in group II remained stationary at 81%, yet this difference did not reach a statistically significant level; $p = 0.49$ (Table 2).

The 2-year disease free survival (DFS) for the 50 patients was 60.8% and dropped to 43% at 4 years. Group II patients did better than group I patients with a 4-year DFS of 58.2% for the former and 35.8% for the latter, however, this difference was not statistically significant; $p = 0.41$.

The correlation between the overall survival and the DFS with the various prognostic factors is shown in Tables (3 & 4).

Out of the prognostic factors studied for their effect on overall survival, there was statistically higher 4-year actuarial survival for stage II patients when compared with stage III patients and those who complied to their scheduled systemic therapy. As for the DFS, there was a statistically significant higher 4-year DFS for patients with the lower stage, those who responded to preoperative irradiation as well as those who complied with their systemic therapy.

Table (1): Patient characteristics in the two treatment groups.

Character	Group I (26 patients)	Group II (24 patients)	Total (50 patients)
Mean age	32.8 ± 10	34.6 ± 9.3	33.7 ± 9.3
Male: Female	0.5:1	3:1	1.2:1
Cell type:			
Adenoca	9 (34.6%)	16 (66.7%)	25 (50%)
Mucoid adeno	13 (50%)	5 (20.8%)	18 (36%)
Signet ring	4 (15.4%)	3 (12.5%)	7 (14%)
Grade:			
I	2 (7.7%)	1 (4.2%)	3 (6%)
II	17 (65.3%)	14 (58.3%)	31 (62%)
III	7 (27%)	9 (37.5%)	16 (32%)
Lymph nodes:			
Positive	19 (73%)	14/18 (77%)*	33/44 (75%)
Negative	7 (27%)	4/18 (22%)	11/44 (25%)
Pathological stage:			
II	7 (27%)	8 (33%)	15 (30%)
III	19 (73%)	16 (66%)	35 (70%)

* 6 cases were inoperable.

Table (2): The 2-years and 4-years actuarial survival of patients in each treatment group.

Years	Group I	Group II	*p*-value
2 years actuarial survival	70.8%	81.0%	
4 years actuarial survival	58%	81%	$p = 0.49$

Table (3): Correlation of the 4-year actuarial survival with various parameters.

Tumor grade	Grade II: 75.2%	Grade III: 61.6%		$p = 0.34$
Nodal status	Node +ve: 64.4%	Node -ve: 92.3%		$p = 0.18$
Stage	Stage II: 92.6%	Stage III: 56.8%		$p = 0.0419$*
Clinial response to preoperative radiation	Good responders*: 90%	Partial responders**: 78.6%	Non-responders: 53.7%	$p = 0.06$
Compliance to systemic therapy	Patients finished Chemoth: 71.3%	Patients discontinued Chemoth.: 0.0%		$p < 0.0001$*

* Good responders: This was a clinical evaluation, good responders are cases in which a partially fixed tumor changes 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.

Table (4): Correlation of the 4-year disease free survival with various parameters.

Tumor grade	Grade II: 44%	Grade III: 38%		$p = 0.23$
Nodal status	Node +ve: 44.2%	Node -ve: 83.5%		$p = 0.19$
Pathologic stage	Stage II: 63.2%	Stage III: 34.8%		$p = 0.06$
Clinial response to preoperative radiation	Good responders: 89.5%	Partial responders: 55.2%	Non-responders: 0%	$p = 0.004$*
Compliance to systemic therapy	Patients finished Chemoth: 40.2%	Patients discontinued Chemoth.: 25.6%		$p < 0.0002$*

DISCUSSION

The mainstay of treatment of carcinoma of the rectum is radical surgery, with or without sphincter preservation. While 15-50 per cent of patients will have pelvic relapse after conventional surgery, a recent multicentre trial in which surgery and pathology were standardized, demonstrated that the introduction of TME reduced the pelvic recurrence to 8.2% [**12**]. Total mesorectal excision is not necessary for upper rectal tumors since it is easy to obtain a 5 cm margin of the rectum with its related mesentry below the tumor [**10**]. When abdominoperineal resection is performed for very low lesions not amenable for sphincter preservation, the whole mesorectum is removed en-bloc with the anorectal tube. Care must be taken during dissection of the circumferential margin as there is tendency to get closer to the rectum as you go down in the narrow pelvis. Tumors of the midrectum where a rectal stump can be left for a colorectal anastomsis represent the major risk for leaving mesorectal tissues with residual tumor. Most studies on distal intramural spread have demonstrated that 2 cm margin is satisfactory, however, this is not enough for mesorectum where numerous studies have shown tumor deposits in the mesorectum as far as 4 cm distal to the tumor [**13**]. Accordingly, for tumors of the mid and low rectum the mesorectum as low as the levator ani should be excised sharply off the remaining rectal stump. In the present study where 80 percent of the lesions were ≤ 5 cm from the anal verge, abdminoperineal resection and posterior pelvic excentration with TME was done for 36 patients and low anterior resection with TME was done for 8 patients. The length of the remaining rectal stump was just 1-2 cm above the levator ani (5-6 cm from the anal verge). Loop transverse colostomy was done for these cases as it is recommended by Heald et al. [**10**], for anastomosis below 7 cm from the anal verge.

However, the fact that local recurrence constitutes a principal cause of failure of surgical treatment of rectal cancer specially in locally advanced cases stimulated the application of adjuvant therapy.

The Gastrointestinal tumor study group (GITSG) trial dealing with Dukes B and C showed a local recurrence rate of 11% with combined modality (adjuvant radiation and chemotherapy) versus 20% with postoperative irradiation alone. Furthermore, the overall sur-

vival benefit was statistically significant (p = 0.005) being better for the combined modality (54%) than for the control group (25%) [14]. The same benefit could be confirmed in another trial which reported a significantly lower recurrence rate for the combined modality (14%) when compared to postoperative irradiation alone (25%) (p = 0.036) and an overall 7-year survival of 63% for combined modality versus 48% for the irradiation only group (p = 0.04) [15]. In the light of these results, it seems that the radiotherapy component improves the locoregional control rate while the systemic chemotherapy would reduce the risk of clinical metastases due to the increased frequency of subclinical micrometastases with disease progression.

The relative value of preoperative versus postoperative radiotherapy remains an open question. In North America, adjuvant postoperative radiochemotherapy is a standard treatment for pathologic T3/4 or pathologic N/1/2/3 tumors [15], whereas in Europe, preoperative radiotherapy is preferred. The Swedish Rectal Cancer trial [16], compared preoperative irradiation and postoperative irradiation and reported that preoperative irradiation was associated with statistically significant lower recurrence rate; 12% versus 21% for postoperative irradiation (p = 0.02). However, there was no difference in the overall survival between the two groups. The incidence of late small bowel obstruction was also lower in 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 [17] where all their patients with fixed tumors were rendered resectable after 45 Gy in 5 weeks of preoperative irradiation.

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. This group included patients with low rectal cancer which is 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).

In the present series the patients'age ranged between 15 and 59 years with a mean of 33.7 years with 68% below the age of 40. This differed from the western literature where only 2-6% were under the age of 40. This difference could not be explained on the basis of differences in age structure since the age-specific rates confirmed the higher rate of rectal cancer among young Egyptians [18].

The problem of wound healing has to be considered when surgery is combined with irradiation. Irradiation can inhibit the wound induced proliferative activity of fibroblasts and endothelial cells, which is initiated within the inflammatory phase of wound healing and continued through the proliferative phase [19]. Irradiated fibroblasts cannot produce sufficient collagen which does not also mature quick enough to meet the healing requirements. 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. 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 an average of 14 days for group I and 16 days for group II. The incidence of wound infection in our cases was around 8%, with no difference between the two groups. These results were different from the Uppsala trial who reported 33% wound infection rate in preoperative irradiation group and 18% in the postoperative group [9]. Mohiuddin and Ahmad [7], reported a significantly 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 and low perineal sepsis observed in the present study.

The long-term treatment end results obtained showed that stage II patients had a statistically significant higher 4-year actuarial survival rate when compared to stage III patients (92.6% versus 56.8%; $p = 0.04$). When the depth of invasion through the bowel wall and nodal status were each tested on its own irrespective of clinical stage, a trend for a higher survival rate was noted in node negative patients and in those with tumors not infiltrating beyond muscularis propria. However, the differences did not reach a statistically significant level ($p = 0.18$). As regards treatment modality, preoperative irradiation was associated with a higher 4-year actuarial survival, DFS and a lower incidence of local recurrence (81%, 58.2% and 4.0% respectively) than postoperative irradiation (58%, 35.8% and 8%). These observed differences were not statistically significant ($p = 0.49$, 0.41 and 0.6 respectively). However, the superiority of preoperative irradiation relative to postoperative irradiation as regards distant metastasis was statistically significant, the incidence being 4 and 27% respectively ($p = 0.04$). This superiority of preoperative radiotherapy could be demonstrated in a number of studies. The Swedish rectal Cancer Trial [**16**] showed that preoperative irradiation was associated with statistically significant lower recurrence rate of 12% versus 21% for the postoperative irradiation ($p = 0.02$), but the influence on the risk of distant metastasis was not reported. Mendenhall and colleagues (1992) [**20**] also reported that preoperative irradiation led to significant improvement in local control (93%) and survival (61%) in locally advanced stage B2 and C rectal cancers. An earlier study carried out in the NCI, Cairo University showed that the 3 year DFS rate for the preoperative group was 48% versus 26% in the postoperative group ($p < 0.05$) [**6**]. In the same study an equal incidence of distant metastasis in both groups (29%) was reported, while the local recurrence was lower in the preoperative group; being 23% versus 41% for the postoperative group ($p < 0.06$). The present study differs from the earlier NCI study in various aspects; the concept of the TME during surgery was not established in the old study, the present study involved a higher radiation dose (46 Gy versus 40 Gy), also, in the present study the interval between the end of irradiation and surgery was extended from 2 weeks to 4 weeks, thus allowing more time for tumor regression and downstaging and also allowing time for recovery of endothelial cells and fibroblasts.

In both groups, the influence of compliance to the chemotherapy component was also studied. Compliance proved to be statistically significant factor as regards both the 4-year actuarial survival ($p < 0.0001$) and the 4-year DFS ($p = 0.004$).

Conclusions:

In locally advanced rectal carcinomas, high dose preoperative irradiation produces higher locoregional control rates without any significant increase in acute or late treatment induced reactions. Postoperative adjuvant systemic therapy is of utmost significance for both survival and DFS in high risk patients. Though some of the prognostic factors studied in this work did not reach a statistically significant effect on survival and DFS, yet this is most probably due to the small number of patients and the fact that we were dealing with high risk patients with the worst reported outcome results.

REFERENCES

1- Marijnen C.A. and Velde C.J.: Preoperative radiotherapy for rectal cancer. Br. J. Surg., 2001, 88: 1556-1557.

2- Wiggers T., de Vries M.R. and Veeze-Kuypers B.: Surgery for local recurrence of rectal carcinoma. Dis. Colon. Rectum., 1996, 39: 323-328.

3- Kapiteijn E., Marijnen C. and Colenbrander A.C.: Local recurrence in patients with rectal cancer diagnosed between 1988 and 1992: A population based study in the West Netherlands. Eurp. J. Surg. Oncol., 1998, 24: 528-535.

4- Macfarlane J.K., Ryall R.H. and Heald R.J.: Mesorectal excision for rectal cancer. Lancet; 1993, 341: 457-460.

5- Friedman P., Garb J.L. and Park W.C.: Survival following moderate dose preoperative radiation therapy for carcinoma of the rectum. Cancer; 1985, 55: 967-973.

6- Ezzat S., Abdallah H., El-Naggar M., Zaki A., Zaghloul M., El-Gantiry M. et al.: Preoperative versus postoperative irradiation in locally advanced carcinoma of the rectum. J. Egypt. Nat. Cancer Inst., 1993, 6 (1): 55-62.

7- Mohiuddin M. and Ahmad M: Critical issues in the evolving management of rectal cancer. Semin Oncol., 1997, 24: 732-744.

8- Cohen A.M., Minsky B.D. and Schisky R.L.: Cancer of the rectum, In: Devita V.T., Hellman S., Rosenberg S.A. (eds). Cancer, Principles and Practice of

Oncology. 5th edition Philadelphia, PA; Lippincot Co., 1997, 1197-1233.

9- Pahlman L. and Glimelius B.: The value of adjuvant radio (chemo) therapy for rectal cancer. Eur. J. Cancer; 1995, 31A (7/8): 1347-1350.

10- Heald R.J., Husband E.M. and Ryall R.D.: The mesorectum in rectal cancer surgery-the clue to pelvic recurrence? Br. J. Surg., 1982, Vol. 69: 613-616.

11- Kaplan E.L. and Meier P.: Non-parametric estimation for incomplete observations. J. Am. Stat. Assoc., 1958, 153: 457-481.

12- Kapiteijn E., Marijnen C. and Nategall I: Preoperative radiotherapy combined with total mesorectal excision for Respectable rectal cancer. N. Engl. J. Med., 2001, Vol. 345, No. 9: 638-646.

12- Scott N., Jackopson P., Al-Jabri T. and Finan P.J.: Total mesorectal excision and local recurrence: a study of tumor spread in the mesorectum distal to rectal cancer. Br. J. Surg., 1995, Vol. 82: 1031-1033.

14- Gastrointestinal Tumor Study Group: Prolongation of disease free survival in surgically treated rectal carcinoma. N. Engl. J. Med., 1985, 312: 1465-1472.

15- Krook J.E., Moertel C.G. and Gunderson L.L.: Effective surgical adjuvant therapy for high risk rectal carcinoma. N. Engl. J. Med., 1991, 324: 709-715.

16- Swedish Rectal Cancer Trial: Improved survival with preoperative radiotherapy in respectable rectal cancer. N. Engl. J. Med., 1997, 336: 980-987.

17- Kodner I.J., Shemesh E.I. and Fry R.D.: Preoperative irradiation for rectal cancer: Improved local control and long term survival. Ann. Surg., 1989; 209 (2): 194-199.

18- Soliman A.S., Bondy M.L. and Levin B.: Colorectal cancer in Egyptian patients under 40 years of age. Int J. Cancer, 1997, 71: 26-30.

19- Tibbs K.M.: Wound healing following radiation therapy. A review. Radiother. Oncol., 1997, 42: 99-106.

20- Mendehall W.M., Bland K.I. and Copeland E.M.: Does preoperative radiation therapy enhance the probability of local control and survival in high risk distal rectal cancer? Ann. Surg., 1992, 215 (6): 696-705.