

Preoperative Radiochemotherapy in Locally Advanced Rectal Cancer

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ABSTRACT

Combined modality has proven efficacy in many malignant tumors (head and neck, cervix) with the advantage of organ preservation. Therefore we studied 15 patients with locally advanced rectal cancer (T3-4, Nx, M0). Patients received 45-50 Gy whole pelvic irradiation concomitant with 20 mg/m² leucovorin (30 minute IV infusion) and 5-fluorouracil 370 mg/m² (1 hour IV infusion) days 1-5 and repeated days 29-34 through the course of radiotherapy (RT). Surgery performed 4-6 weeks from the end of RT. Ten out of fifteen patients showed clinical downstaging. There was no enhancement of the toxicity and all the patients had unremarkable postoperative course. In conclusion radiochemotherapy is feasible, safe and effective with good downstaging in locally advanced rectal cancer.

Key Words: *Rectal cancer - Preoperative - Radiochemotherapy - Downstaging.*

INTRODUCTION

Surgery alone has been the standard treatment for patients with adenocarcinoma of the rectum. Despite advances in surgical technique, local recurrence is still a considerable problem.

At the time of initial presentation, approximately 15% of the patients diagnosed with rectal cancer have locally advanced unresectable disease [2,15]. Many studies showed that cases that were preoperatively assessed as being surgically unresectable became fully resectable after preoperative irradiation in about 64-85% of cases [7,10].

There are many potential advantages of preoperative radiotherapy for rectal carcinoma, these include biologic effects (decreased tumor seeding at the time of surgery) as well as functional effects increasing the ability to change the operation from an abdominoperineal resection to a sphincter preserving low anterior re-

section [16]. The European Organization for Research and Treatment of Cancer has shown a significant reduction in the local recurrence rate with preoperative radiotherapy in these cases [9].

The addition of chemotherapy to preoperative radiotherapy may help in the improvement of survival of those patients. Many studies showed that this combination leads to enhanced resectability rates and tumor downstaging [12,20]. Also, synergy between 5-FU and radiotherapy may have an important role in preventing postoperative distant metastasis [12].

This study was conducted to assess the effect of preoperative radiochemotherapy in the management of locally advanced rectal carcinoma increasing the chance for downstaging, complete surgical excision and sphincter preservation.

PATIENTS AND METHODS

Fifteen patients with advanced histologically proven rectal carcinoma (T3-4 Nx Mo) were included in this study. All patients presented to the Clinical Oncology Department and the Unit of Colorectal Surgery, Faculty of Medicine, Alexandria University between February 1999 and March 2000. There were 11 males and 4 females. Their age ranged between 28 and 65 years with a median age of 49.5 years.

Eligibility and pretreatment evaluation:

All patients had to have ECOG performance status of < 2 and a written consent. In addition to complete physical examination, barium enema, procto sigmoidoscopy and/or colonoscopy, endorectal sonography (TUS) and C.T scan were performed.

Preoperative radiochemotherapy:

Preoperative radiotherapy (RT) with a daily fraction of 1.8 Gy to a total dose of 45-50 Gy over 5-5.5 Wks concomitantly with chemotherapy (CT); Leucovorin 20 mg/m² given as 30 minutes intravenous infusion followed by 5-fluorouracil (5-FU) 370 mg/m² as one hour infusion given on day (1-5) and repeated day (29-34) through the course of RT. No antiemetics was used prior to chemotherapy and patients were instructed to use ice chips by mouth starting 5 minutes before 5-FU and continuing during its infusion to diminish the incidence of mucositis.

Radiotherapy (RT) was given through four portals (10 patients); anteroposterior, postroanterior and two laterals, or three portals (5 patients); one postroanterior and two laterals with wedges. Simulation was done for every patient with contrast enema. All patients were treated in the prone position and were instructed to have distended bladder during the time of irradiation to keep as much of small bowel as possible outside the irradiation field. All the patients were treated with 10 Mev linear accelerator, 1.8 Gy/Fr to a total dose of 45 Gy/5 Wk. Patients with T4 tumors received 50 Gy/5.5 Wks.

Evaluation of therapy effects was done 2-5 weeks after the end of therapy regarding symptom control and tumor downstaging using clinical examination according to TNM staging system (AJC 1997). C.T scan and transrectal U/S. Treatment toxicity were reported according to NCI common toxicity criteria [6].

Patients were prepared for surgery within 4-6 weeks from the end of therapy.

Histopathological staging of the resected specimens and operative data for unresected tumors were compared with the pre-therapy stage to evaluate downstaging.

RESULTS

As shown in (Table 1) the most frequent presenting symptoms in our cases was change in bowel habits (diarrhea-constipation). In 13 cases (86.6%) the tumor was located in the middle and lower thirds of the rectum. In seven cases (46.6%) the tumor involved 75% of the rectal circumference. Seven cases had fixed tumors while in 8 cases the tumor showed limited

mobility. Histopathological examination of the biopsy specimens revealed 6 cases (40%) to be well differentiated adenocarcinoma and 60% had moderately and poorly differentiated adenocarcinoma.

C.T scan (performed in all cases) showed rectal tumor with thickening of the rectal wall and invasion of the surrounding structures in 7 cases (4 cases anteriorly, 2 cases laterally and one case posteriorly). Obliteration of the surrounding fat planes without invasion of nearby structures was found in 8 cases (53.3%). Perirectal lymph nodes invasion was suggested in 3 cases.

Transrectal ultrasound (TUS) was performed only in 9 cases. Pain and narrowing prevented the procedure in the rest of cases. Invasion of the adjacent structures was confirmed in 4 cases while obliteration of the surrounding fat planes was detected in 5 cases. Suggestion of lymph node involvement was found in 2 cases. The results of C.T scan and TUS (when it was performed) were nearly similar.

Pretreatment staging of the patients was performed using TNM staging system (AJCC 1997) (with exclusion of lymph node status) according to the results of clinical examination, C.T. and TUS (Table 3).

Post-treatment symptom control:

Detectable control of some symptoms was observed. The change in the bowel habits disappeared in 8/13 (61.5%) and the bleeding per rectum stopped in 6/12 patients (50%). However, some treatment related toxicity developed (Tables 4,5). Prior to surgery almost all the patients recovered from toxicity.

Post treatment clinical examination, C.T scan and TUS performed 2-5 weeks after therapy, showed partial tumor regression in 10 cases whereas 4 cases had no change and only one case showed progressive course with increase in the tumor size following radiochemotherapy (Table 3).

Surgery was performed 4-6 weeks after therapy. Abdominoperineal resections were performed in 5 patients and anterior resection with colo-anal anastomosis in 7 patients. Three patients (20%) were found to be surgically irresectable, so proximal colostomy (permanent) was performed for them and they were subject-

ed to additional doses of radiochemotherapy. It was noticed that radiochemotherapy did not add any difficulty to the surgical procedures.

Evaluation of the depth of tumor invasion using the same preoperative tools together with the operative findings and histopathological examination of the resected specimens showed invasion of the proper muscle layer (T2) in 8 cases, invasion of pre rectal (T3) in 4 cases (26.6%) whereas invasion of the nearby structures (T4) was found in 3 cases (20%) (Table 3).

Clinical downstaging was detected in 10 patients (66.6%); the tumor became confined to the bowel wall in 8 cases (53.3%). Four patients (26.6%) did not show any effect to radiochemotherapy while one case showed tumor progression and upstaging of the depth of tumor invasion.

Four out of the ten cases showing downstaging were poorly differentiated adenocarcinoma (4/5), three cases were well differentiated (3/6) and another 3 cases (3/4) were moderately differentiated adenocarcinoma.

Treatment toxicity:

Diarrhea was the most prominent toxicity; 11 patients (73%) had either grade I (9) or II (2) diarrhea during the radiation course, while at the end of therapy 4 patients had grad III diarrhea both irradiation and chemotherapy contrib-

uted to this toxicity. As expected toxicity after the second cycle of chemotherapy was more frequent than after the first one. None of the patients required discontinuation of treatment because of toxicity.

Ten patients had dry desquamation at the end of irradiation, three progressed to wet desquamation that completely healed 3 weeks later. Five patients developed proctitis that was well responding to corticosteroid enema. Dysuria occurred in five patients with spontaneous recovery, Three patients complained of anal pain at the end of preoperative treatment with good response to analgesics.

Short term follow-up:

The postoperative course was uneventful in all patients except one patient who suffered from anastomotic leakage for which a covering stoma was established. This stoma was closed 2 months later. Three patients (20%) suffered from wound infection that was managed conservatively.

The period of follow-up ranged between 5-13 months (median 8 months). One of the three patients who were unresectable died 9 months after the operation from disseminated disease, the other two patients were lost to follow-up.

During this short follow-up period no evidence of local recurrence or distant metastasis were detected in the rest of patients.

Table (1): The main presenting symptoms and effect of preoperative therapy.

Pretreatment			Posttreatment		
Symptom	No.	%	Symptom	No.	%
Bleeding per rectum	12	80	Bleeding per rectum	6	40
Diarrhea	7	46.6	Diarrhea	8	53
Constipation	6	40	Constipation	2	13.3
Mucous per rectum	5	33.3	Mucous per rectum	10	66.6
Anal pain	4	26.6	Anal pain	3	20
Tenesmus	4	26.6	Tenesmus	6	40
Abdominal pain	2	13.3	Frquency of micturition	2	13.3
			Nausea-vomiting	2	13.3
			Dysurea	5	33.3
			Incontinence	1	6.6

Table (2): Tumor location, extent and degree of differentiation.

Tumor location	No.	%	Extent			Mobility			Degree of different		
			50% of circumf	75% of circumf	Whole circumf	Mobile	Limited mobility	Fixed	Well diff.	Mod. diff.	Poory diff.
Lower third	5	33.3	2	2	1	-	2	3	1	2	2
Middle third	8	53.3	2	4	2	-	4	4	3	2	3
Upper third	2	13.3	1	1	-	-	2	-	2	-	-
Total	15	100	5	7	3	-	8	7	6	4	5

Table (3): Pretreatment evaluation of the depth of tumor (T) invasion and the effect of radiochemotherapy.

	Pre treatment		Post treatment					
	No.	%	T ₂		T ₃		T ₄	
			No.	%	No.	%	No.	%
T ₂	0	0						
T ₃	8	53.4	5	33.3	2*	13.3	1**	6.6
T ₄	7	46.6	3	20	2	13.3	2*	13.3
Total	15	100	8	53.3	4	26.6	3	19.9

T₂ = Invasion of the proper muscle layer.T₃ = Invasion of the prerectal fat.T₄ = Invasion of nearby organs.

* No change.

** Tumor progression.

Table (4): Chemotherapy related toxicity.

Toxicity	After first cycle			Over al the treatment course		
	Grade I	Grade II	Grade III	Grade I	Grade II	Grade III
Diarrhea	4	3	1	3	10	4
Mucositis	4	2	-	4	2	-
Leucopenia	3	1	-	5	2	1
Thrombocytopenia	2	-	-	2	4	-
Hand foot syndrome	-	-	-	3	-	-
Nausea and vomiting	5	-	-	7	5	-

According to NCI common toxicity criteria [6].

DISCUSSION

The proper management of locally advanced rectal carcinoma is not standardized. The beneficial effect of preoperative pelvic irradiation as an adjuvant treatment has been confirmed in several studies [5,22,25]. Pahlman and Glimelins showed the superiority of preoperative radiotherapy over postoperative one [22]. Many studies claimed a better local control and improvement of resectability after preoperative radiotherapy [5,10,25].

Table (5): Radiation related toxicity.

Symptom	Grade I	Grade II	Grade III
Skin desquamation	3	4	3
Proctitis	2	3	-
Dysurea	1	3	-
Pain	2	1	-

The addition of chemotherapy to radiotherapy was found to help in the improvement of survival of these patients. Early effects such as downstaging and symptom control noticed with the application of preoperative radiochemotherapy may imply improvement of local recurrence and survival rates [20]. This combination provides systemic treatment that may be of value for the management of subclinical tumor implants in addition to enhancement of the radiation effect on the local lesion [20,21].

Many studies reported that combining conventional dose preoperative radiotherapy with 5-FU was safe, tolerable, increased surgical downstaging, improved loco-regional control and may contribute to enhanced survival [3,17].

Regarding downstaging and resectability rate following radiochemotherapy, Chan et al. [3] treated 46 patients with fixed or tethered cancer rectum using preoperative irradiation (40 Gy) plus Mitomycin C, 5-FU and leucovorin, reported downstaging in 89% of patients while Landry et al. [12] and Minsky et al. [16] reported high resectability rates of 100% and 90% respectively while Sherif et al. [24] reported 71%. On the other hand Videtic et al. [26] reported a lower resectability rate of 62% using preoperative conventional dose radiation ranging between 48-60 Gy together with 5-FU at a rate of 225 mg/m²/24h/7 days a week continuously during radiotherapy.

The effect of RT on pathological characteristics and consequently on the occurrence of downstaging in rectal cancer, depends on total dose, fractionation size and the interval between the start of RT and the day of surgery, i.e. the overall treatment time (OTT) [13]. Marijnen et al., analyzed 1321 patients who received preoperative RT followed by surgery within less than 10 days; although there was decrease in tumor size and the number of recovered lymph nodes, there was no change in the tumor staging. They concluded that this short-term interval was not enough for downstaging to occur despite the fact of better local control of preoperative RT [13].

In contrast the Lyon randomized trial reported lower tumor stage after long term interval LI (6-8 Wk) from preoperative RT to surgery than after short-term interval SI (< 2 Wk) $p = 0.007$. They also reported less or few residual tumor cells after the long interval [8]. This is consis-

tent with our finding since we elect 4-6 Wk interval, between preoperative irradiation and surgery.

Downstaging was also reported in the MD Anderson study; with preoperative radiochemotherapy 45 Gy/25 Fr concomitant with 5-FU continuous infusion 300 mg/m²/day then surgery 6 Wk after completion of RT. Out of 117 patients mostly (96%) T3, N0-1, there was 62% tumor downstaging with 27% of cases had complete pathologic response. Sphincter sparing procedure was possible in 59% of the patients and abdominoperineal resection (APR) was required in 41%. The authors concluded that preoperative radiochemotherapy allowed sphincter sparing surgery in over 40% of patients who would have required permanent colostomy [11].

Although almost all trials of preoperative RT reported better local control, there was lack of downstaging in trials with short-term interval to surgery. This can be explained by the fact that downstaging is not the mechanism by which the reduction in local recurrence is achieved [7,9,10,11-13].

In our study clinical downstaging was detected in 66.6% (10/15) and resection was achieved in 80% of cases. Downstaging was demonstrated in all grades of adenocarcinoma but the poorly differentiated type seemed to have a better response (4/5 showed downstaging) than the well-differentiated adenocarcinoma (3/6 showed downstaging). Histopathological examination of operative specimens showed that 53.3% (8/15) had the tumor confined to the bowel wall. In four patients (26.6%) the tumor was not confined to the rectal wall and so they received postoperative adjuvant chemotherapy with 4 courses of 5-FU and leucovorin for adverse pathological features such as positive margins, nodal positivity and evidence of persistent involvement of adjacent structures. These results are comparable with other similar studies [5,3,24] and also with the results of Videtic et al. [26] who found that 41% of their cases had the tumor confined to the bowel wall and 24% (7/29) of cases received postoperative adjuvant chemotherapy.

Although predictive factors were not done in our study; pretreatment proliferative assays e.g. proliferating cell nuclear antigen (PCNA) and mitotic activity are good predictors for response to preoperative RT; Willett et al. [27] reported

marked tumor regression in smaller tumors with high PCNA/mitotic activity. In addition Adell et al. [1] reported that patients (from the Swedish trial) with P53 negative tumors had significant reduction of local failure on receiving preoperative RT compared with P53 negative patients who didn't receive RT ($p = 0.0008$). On the other hand P53 positive patients showed no benefit from preoperative RT. These findings may predict the likelihood of response to irradiation, which may aid in formulating a policy for patients with rectal cancer.

Many authors reported cases of complete tumor regression after preoperative combined radiochemotherapy; Minsky et al. [16] reported 72% rate of pathologically complete response, Landry et al. [12], 20%, Videtic et al. [26], 13% Chan et al. [3] while reported a lower incidence of complete regression in 4% of cases. However, non-of our cases showed this response may be because our patients had higher a tumor stage than those reported in these studies also the small number of patients in our study.

Sphincter preservation was possible in 58.3% of our cases. In three cases the tumor was found to be still unresectable and was managed by premanent colostomy plus additional doses of radio chemotherapy. Surgical resection was not associated with any extra difficulty and this agrees with many other studies, which demonstrated that no surgical difficulties were encountered during rectal resection after radiochemotherapy [4,16].

Postoperative complications included small bowel adhesive obstruction, delayed wound healing and anastomotic breakdown in 3.6%, 2.7% and 1.4% respectively in the study of Mohiuddin et al. [19]. Also, Minsky et al. [18] reported anastomotic leak in 6%, small bowel obstruction in 4% and rectal stricture of 2%, while Sherif and Habashy [24] reported wound infection in 29%, pelvic abscess and rectal stricture in 5.9%. In the present study anastomotic leakage occurred in one patient (1/12) and wound infection in 20% of cases.

If radiotherapy is given with curative intent usually we use the conventional dose per fraction (1.8-2 Gy). In the current study we used 1.8 Gy/Fr. it is possible that higher doses per fraction may increase radiation toxicity. This was well demonstrated in the Swedish trial [25]

5 Gy/Fr was used and high rate of complication was reported.

Complication of preoperative RT were minimal in our study (Table 5) skin desquamation and diarrhea were the prominent toxicities. Similar results were reported by Marks et al. [14] who reported mild diarrhea in 5/20 patients after 45 Gy preoperative RT with one patient developing perineal radiation dermatitis.

Rau et al. [23] reported in a study of 55 patients with locally advanced or recurrent rectal cancer treated with preoperative RT concomitant with continuous infusion 5-FU and regional hyperthermia, there was no enhancement of the preoperative radiochemotherapy toxicity.

Furthermore, Minsky et al. [18] reported less grade III and IV toxicity in patients receiving adjuvant preoperative radiochemotherapy than those who received the same treatment postoperative by ($p = 0.02$).

As regards local recurrence, different reports describe rates of 0-25%. Mohiuddin et al. [19] after a median follow-up of 37 months reported local recurrence rate of 23% and local recurrence with distant metastasis in 7% of cases, in a group of medically inoperable patients who received 45 Gy preoperative irradiation followed by local excision. Another study [26] reported a local recurrence rate of 10% and crude survival rate of 70% for a median follow-up of 34 months. In the study of Thomas Jefferson University [4], the local recurrence rate was 3% and local recurrence associated with distant metastasis was 13%. In our study, because of the short follow-up period, firm conclusion on recurrence rate and long term survival cannot be given. During this short period of follow-up, no evidence of local or distant metastasis was detected in the twelve patients in whom the tumor was resected.

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