

Re-irradiation in recurrent rectal cancer: single institution experience

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Purpose: To determine the rates of acute and late toxicity, the efficacy to relieve symptoms, progression free survival, and over all survival in rectal cancer patients treated with re-irradiation.

Patients and methods: Between June 2009 and December 2012, 32 patients with recurrent rectal cancer previously treated with pelvic irradiation, were treated with 180 cGy/fraction, with a total dose 39 Gy if the treatment interval ≥ 1 year, and 30 Gy if interval < 1 year. The dose was delivered to planning target volume (PTV) including gross target volume plus 2-3 cm margin. Concurrent chemotherapy was administrated in first five days of radiotherapy. Patients were evaluated during and after completion of treatment for acute, late toxicity, and response.

Results: Re-irradiation was well tolerated, no grade 4 toxicity was recorded, most toxicities were mild (grade 1-2), only 6.2% developed grade 3 acute gastrointestinal and 6.2% developed grade 3 late skin toxicity. Symptoms were effectively palliated, bleeding was relieved in 100%, and 80% recovered of pain symptoms. Two years rates of progression free survival and overall survival were 21% and 38% respectively. Interval to re-irradiation, previous radiation dose, and total radiation dose showed significant relation with overall survival.

Conclusions: Re-irradiation in recurrent rectal cancer was well tolerated with mild rates of acute and late toxicities. Bleeding and pain were well controlled.

Keywords: Rectal cancer; re-irradiation; local recurrence

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Introduction

Over the last years there has been marked evolution in the management of rectal cancer, resulting in great reduction in local recurrence (1,2). The combination of irradiation (adjuvant or neoadjuvant) and anatomic mesorectal dissection significantly lowered the incidence of local recurrence from 20-40% to 4-8% (3). However, about 5-20% of patients treated with surgery and radiotherapy can have a local recurrence (4-6).

This combination has led to the appearance of a new problem: the treatment of local recurrence in patients who have been irradiated to the pelvis (7,8), especially it has been proved that surgical resection is the main therapy for patients with locally recurrent rectal cancer and preoperative chemo-radiation has been shown to greatly

increase the surgeon's ability to perform resection (9).

Re-irradiation has been discouraged because it is thought to be associated with high incidence of late normal tissue complications, so patients with local recurrence and previously received pelvic irradiation were only given palliative care (10,11). However, many series reported safety and efficacy of re-irradiation for recurrent rectal cancer (12-15). In addition, it is found that re-irradiation could potentially improve local control in patients with recurrent rectal cancer previously treated with radiation therapy (15,16).

The aim of this study is to determine the rates of acute and late toxicity, efficacy of re-irradiation to relief symptoms, freedom from local progression, and overall survival in patients treated with re-irradiation for recurrent

rectal cancer, and furthermore factors affecting overall survival.

Patients and methods

Prospective study was conducted in the Clinical Oncology and Nuclear medicine department, Mansoura University Hospital on 32 patients with recurrent rectal adenocarcinoma and a history of pelvic radiotherapy, between June 2009 and December 2012.

Eligibility

Patients were eligible if they presented with histologically confirmed local recurrent adenocarcinoma of the rectum, disease limited to pelvis and received previous pelvic irradiation as adjuvant treatment and were aged more than 18 years with an Eastern Cooperative Oncology Group performance status of 2 or below, adequate hematological, liver and renal function and no evidence of distant metastatic spread. Patients who fulfilled the above eligibility criteria were made aware of the purpose and the design of the study and required to sign the informed consent.

Pretreatment evaluation

Patients were assessed at baseline by digital examination when possible, abdomen and pelvic computed tomography (CT) scan and/or MRI, chest X-ray, barium enema, and tumor markers (CEA, CA 19-9) were also assessed.

Treatment

All patients were planned via conformal three-dimensional radiotherapy. Patients were stimulated in a prone position with full bladder to exclude as much as possible of the bladder and small intestine from the treated portal. Re-irradiation was delivered to planning target volume (PTV), which included gross tumor volume with a 2 to 3 cm margin. Radiation therapy was delivered using 6- to 15-MV photons. Multiple field techniques were used, fields were arranged taking into account doses delivered to normal tissues during radiotherapy for primary tumor. However, no specific dose-volume constraints were indicated by the treatment protocol. The dose was referred to a normalization point inside the PTV to obtain a homogeneity ranging between $\pm 5\%$ to the prescribed dose. Re-irradiation was given at a total of 39 Gy (n=23

patients) in 22 fractions with 1.8 Gy/fraction if the retreatment interval was ≥ 1 year or at a total dose of 30 Gy (n=9 patients) in 17 fractions if the retreatment interval was < 1 year.

Concurrent chemotherapy was administered in the first five days of re-irradiation in the form of folinic acid 20 mg/m² i.v. (bolus) days 1-5 and 5-fluorouracil 425 mg/m² i.v. (bolus) days 1-5.

Subsequent treatment

Second line chemotherapy was used in the case of progressive disease with consideration for previous chemotherapy and general condition of the patients.

Follow-up

During concomitant chemo-radiation treatment patients were evaluated weekly with physical examination and complete blood count. Acute radiation related toxicities were graded according to the Radiation Morbidity Scoring Criteria of the Radiation Therapy Oncology Group (RTOG); late toxicity was graded according to European organization for Research and Treatment of Cancer (EORTC)/RTOG criteria. Six to eight weeks after the completion of concomitant treatment; all patients underwent a physical examination, complete blood count, chest X-ray, and abdominal-pelvic CT scan or MRI for response. Follow-up was performed with physical examination monthly, then every 3-4 months in the first two years and then every six months (by physical examination), by complete blood count, CEA, CA 19-9 levels, and liver ultrasound (were also performed) at each evaluation; chest X-ray was performed every two follow-ups and pelvic CT scan yearly, unless symptoms appeared. The median follow up interval was 18 months (ranging from 6-38 months).

Statistical analysis

Data was analyzed using Statistical Package for Social Sciences (SPSS) version 15. Qualitative data was presented as number and percent. Chi-square test was used for comparison between groups. Non-parametric data was presented as min-max and median. Mann-Whitney test was used for comparison between groups. Kaplan-Meier survival curve was used to estimate survival. Confidence intervals (CIs) were calculated using Cox's proportional hazard model. P value is considered significant if it is < 0.05 .

Table 1 Patient's characteristics

Characteristic	Number of patients, n=32 (%)
Gender	
Male	23 (71.9)
Female	9 (28.1)
Age (years)	
Range	37-68
Median	55
ECOG	
1	19 (59.4)
2	13 (40.6)
Symptoms at diagnosis	
Bleeding	7 (21.8)
Pain	18 (56.3)
Initial stage	
II	6 (18.7)
III	26 (81.3)
Previous surgery	
Low anterior resection	10 (31.3)
Abdomino-perineal resection	22 (68.8)
Previous radiation dose (Gy)	
Median	40
Range	28-45
Interval to re-irradiation (months)	
Median	18
Range	6-38
Previous chemotherapy	
Yes	23 (71.9)
No	9 (28.1)

ECOG, Eastern Cooperative Oncology Group; Gy, gray.

Results

Patient characteristics

From June 2009 to December 2012, 32 patients were enrolled in this study. Their characteristics are reported in *Table 1*. They included 23 male and 9 female with a median age of 55 years (range, 37-68 years). Most of the patients had performance status ECOG 1 (59.4%). Eighteen patients (56.3%) presented with pain; however (and) seven patients (21.8%) presented with bleeding. Twenty six patients (81.3%) had initial stage III. Most of the patients underwent abdominoperineal resection (68.8%). Previous

radiation doses to the pelvis ranged from 28-45 Gy with a median of 40 Gy. Interval from initial radiation treatment to time of re-irradiation ranged from 6 to 38 months with a median time of 18 months. Twenty three patients (71.9%) received chemotherapy.

Efficacy of re-irradiation for relief of symptoms

Re-irradiation was very effective in palliation of symptoms. Symptomatic response was evaluated six weeks after the end of chemo-radiation. Bleeding was palliated in 100% of patients who presented with bleeding (seven patients) and remained controlled in five patients (70%) until death with a median of nine months.

Pain was also palliated effectively. Fifteen of 18 patients with pain before treatment had symptomatic response (80%) with median duration of six months.

Response

All patients were evaluable for response using CT scans or MRI after six to eight weeks of chemo-radiation.

Clinical complete response was observed in one patient (3.1%).

Clinical partial response was achieved in 21 patients (65.6%). Nine patients (28.2%) had stable disease. Only one patient (3.1%) developed progression of the disease at the first evaluation after chemo-radiation.

Twenty one patients (65.5%) who achieved clinical partial response had surgical consultation for possibility of resection of recurrent tumor. Surgical resection was not performed in all cases because of technically unresectable disease in 7/21 patients due to pelvic side wall involvement and 14/21 patients advised for pelvic exenteration and all the patients refused.

Acute and late toxicity

The acute toxicity grades during chemo-radiation are listed in *Table 2*. Neither grade 4 toxicities nor treatment related deaths were recorded. Only two patients (6.2%) had grade 3 acute gastrointestinal toxicity. Most of adverse events were mild to moderate (grade 1 to 2) in intensity and all of them recovered spontaneously with supportive management. Late toxicity is shown in *Table 3*. Late toxicity was infrequent and generally mild. Only two patients (6.2%) had G3 skin toxicity.

Survival

The median overall and median progression free survival

Table 2 Acute toxicity					
Toxicity	G0	G1	G2	G3	G4
Hematologic (%)	28 (87.5)	4 (12.5)	0 (0.0)	0 (0.0)	0 (0.0)
Skin (%)	0 (0.0)	27 (84.4)	5 (15.6)	0 (0.0)	0 (0.0)
Gastrointestinal (%)	8 (25.0)	15 (46.9)	7 (21.9)	2 (6.2)	0 (0.0)
Urologic (%)	23 (71.9)	7 (21.9)	2 (6.2)	0 (0.0)	0 (0.0)
G0, grade 0 (no toxicity); G1, grade 1 (mild); G2, grade 2 (moderate); G3, grade 3 (severe); G4, grade 4 (life threatening).					

Table 3 Late toxicity					
Toxicity	G0	G1	G2	G3	G4
Skin (%)	10 (31.3)	15 (46.9)	5 (15.6)	2 (6.2)	0 (0.0)
Intestine (%)	9 (28.1)	15 (46.9)	8 (25.0)	0 (0.0)	0 (0.0)
Bladder (%)	10 (31.3)	16 (50.0)	6 (18.7)	0 (0.0)	0 (0.0)
G0, grade 0 (no toxicity); G1, grade 1 (mild); G2, grade 2 (moderate); G3, grade 3 (severe); G4, grade 4 (life threatening).					

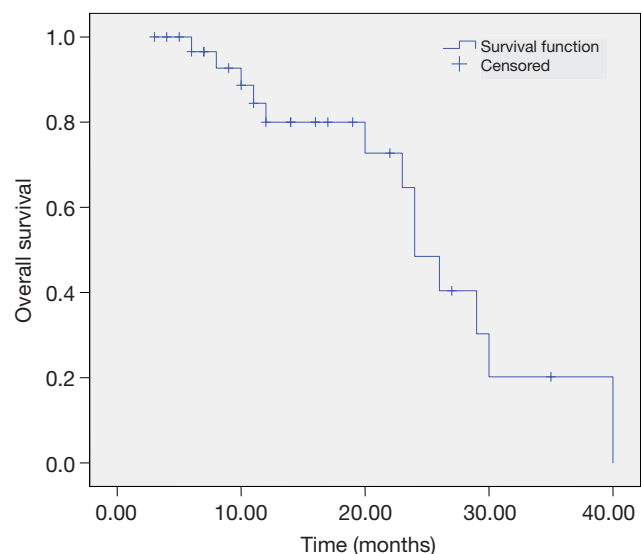


Figure 1 Kaplan-Meier estimates of overall survival in patients with re-irradiated recurrent rectal cancer.

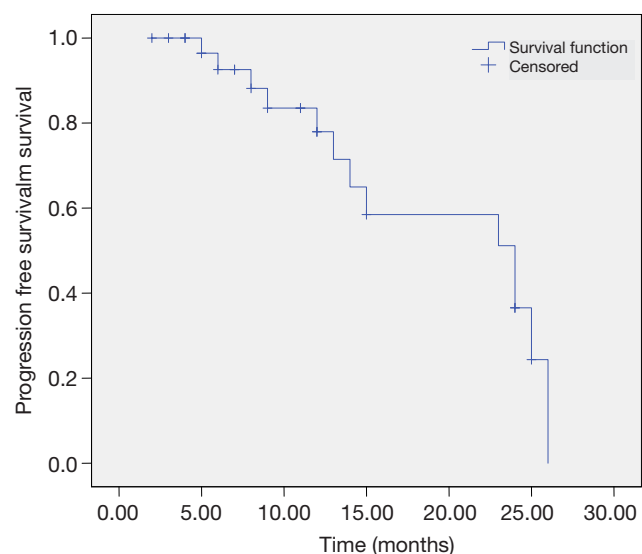


Figure 2 Kaplan-Meier estimates of progression free survival in patients with re-irradiated recurrent rectal cancer.

times were 14 and 11 months respectively. The 2-year overall survival and progression free survival rates were 38% and 21% respectively (*Figures 1,2*). Factors affecting survival are shown in *Table 4*. Interval to reirradiation, reirradiation dose and total radiation dose improved survival. Age, performance status and initial stage didn't appear to influence survival. Multivariate analysis confirmed that the re-irradiation dose was the only predictor factor for survival (*Table 5*).

Discussion

Local recurrence represents a frequent relapse of disease after conventional treatment of rectal carcinoma. Re-irradiation appears possible for short term symptom relief and potentially for cure if surgical resectability is complete, recent data suggest that limited doses of 30 Gy re-irradiation are likely to be safe even with chemotherapy (8,17).

In this current study we assess the toxicity after re-irradiation in recurrent rectal cancer. There were no grade

4 acute or late toxicity, only two patients (6.2%) developed grade 3 acute toxicity of gastro-intestinal nature. Also, two patients developed grade 3 late skin toxicity. Many studies reported results comparable to ours, no grade 4 toxicity and low rate of grade 3 (15,16,18,19). Whereas, Mohiuddin *et al.*, who studied the long-term results of re-irradiation for patients with recurrent rectal carcinoma, reported grade 4 diarrhea in six patients and high rate grade 3 (21%) (14). The difference between the two studies may have been due to larger field size or higher total dose used by Mohiuddin.

As regard late toxicity, we had minor late complications regarding other studies, this is because patients in this study did not underwent surgical resection, while in patients underwent extensive surgical procedures such as pelvic exenteration and multivisceral resection were associated with higher rate of late toxicity than who did not undergo

surgery (16,20), and may also related to higher prior radiotherapy dose ≥ 54 Gy (12,16).

It is proven that the addition of chemotherapy as a radiation sensitizer has improved the efficacy of radiation treatments more than the radiation or chemotherapy alone in the management of primary rectal cancer (21-23). No data are available on the optimum choice of chemotherapeutic agents to be used when treating recurrent rectal cancer in conjunction with radiation, often it is 5-fluorouracil-based regimen (24), so we used concurrent chemotherapy administered in the first five days of re-irradiation in the form of folinic acid 20 mg/m² i.v. (bolus) days 1-5 and 5-fluorouracil 425 mg/m² i.v. (bolus) days 1-5.

Patients with previously irradiated locally recurrent rectal cancer have not only a poor survival but may also suffer of disabling symptoms that significantly affect the quality of life (25), and since most symptoms in recurrent rectal cancer are due to tumor growth within the pelvis, the concepts of cure and symptoms palliation are almost identical aiming both at achieving long-term tumor control without prohibitive toxicity (23,26).

In the current study bleeding was palliated in 100% of patients and remained control in 70% until death, also pain palliated in 80% complete response and complete response was observed in 30%.

As regard palliation of pain and bleeding our results coincide with that reported by Mohiuddin *et al.* (14) and Valentini *et al.* (15), but Mohiuddin reported higher rate of complete response (55%) this may be attributed to using hyper fractionation of irradiation and or using boost after single fractionation of 1.8 Gy/fraction.

The median overall survival was 14 months, with 2 years survival rate 38%. This result similar to results obtained by Mohiuddin *et al.*, in patients who did not undergo surgery, while in patients who underwent surgical resection after reirradiation the median and two years rate were 44 months and 80% respectively (14). Our results also coincide with the result of Das *et al.*, (16 months and 38%) for who not performed surgical resection, with higher results in patients performed surgical resection (16). Other study proved better overall survival in patients treated with surgery after

Table 4 Univariate analysis of factors affecting survival

Factor	P value
Age (year)	0.586
<60	
≥ 60	
Performance status	0.514
ECOG 1	
ECOG 2	
Initial stage	0.359
Stage II	
Stage III	
Interval to reirradiation (month)	0.017
<24	
≥ 24	
Reirradiation dose (Gy)	0.000
<30.6	
≥ 30.6	
Total radiation dose (Gy)	0.000
<74	
≥ 74	

ECOG, Eastern Cooperative Oncology Group; Gy, gray.

Table 5 Multivariate analysis for factors affecting survival

Variable	B	SE	Sig	Exp (B)
Interval to re-irradiation	0.824	0.732	0.261	2.280
Re-irradiation dose	3.071	0.792	0.000	21.554
Total radiation dose	-0.268	0.611	0.661	0.765

chemo-radiation treatment, but was not significant (27).

We concluded that the most factors affecting survival were interval to re-irradiation, total radiation dose, and re-irradiation dose. In the studies which used surgical resection after re-irradiation proved that surgery is a main prognostic factor on survival in recurrent rectal cancer (14-16). However, retreatment interval >2 years was significantly associated with better survival in Das study (16), this may be explained by that the interval between the two courses of radiotherapy likely serves as a surrogate for tumor biology, with earlier recurrences portending worse prognosis, hence the time from prior course of radiotherapy could potentially be used to select patients who are most likely to benefit from re-irradiation. Re-irradiation dose was associated with better survival in Mohiuddin study (14).

Conclusions

Re-irradiation combined with chemotherapy for patients developing recurrent rectal cancer after previous pelvic irradiation is feasible and provides high chances for palliation. Acute and late toxicity are not prohibitive if proper attention is paid to radiation dose and technique.

Future studies should investigate methods to further improve local control, like escalation of radiotherapy dose or use new chemotherapeutic agents.

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