Morbidity and Mortality Following Short Course Preoperative Radiotherapy in Rectal Carcinoma

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Abstract- The aim of this study was to evaluate the morbidity and mortality in patients with operable stage II and III rectal cancers within one or two months after surgery, who has been treated pre-operatively with short course radiotherapy. Twenty-eight patients with rectal adenocarcinoma, consecutively referred to the Cancer Institute of Imam Khomeini Hospital from March 2009 to March 2010, were selected for the study after staging by endorectal ultrasound and CT of abdomen, pelvis, and chest; and if they had inclusion criteria for short course schedule, they were treated with radiotherapy alone at 2500 cGy for 5 sessions, and then they were referred to the surgical service for operation one week later. They were visited there by a surgeon unaware of the research who completed a questionnaire about pre-operative, operative, and post-operative complications. Of 28 patients, 25 patients underwent either APR or LAR surgery with TME. One patient developed transient anal pain grade I and one patient had dysuria grade I; they were improved in subsequent follow-up. Short course schedule can be performed carefully in patients with staged rectal cancer without concerning about serious complications. This shorter treatment schedule is cost-effective and would be more convenient for patients due to fewer trips to the hospital and the main treatment, i.e. operating the patient, will be done with the shortest time the following diagnosis.

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Introduction

Colorectal cancers are the third most common cancer in the world. According to the National Cancer Registry reports in Iran in 2006, colorectal cancer is the fourth and second most common cancer in males and females (8 per 100 000) respectively (1).

Loco-regional tumor control has considerably improved after introduction of total mesorectal excision (TME) such that local recurrence has fallen from 28% to 10% in centers using the TME technique (2). Retrospective analysis of more than 770 patients, operated in the surgery department of Erlangen University in Germany, suggested that local recurrence rate was 14% and the 5-year survival rate was 71.2% after curative surgery without adjuvant radiotherapy (3).

The standard treatment for patients with locally advanced rectal cancer (stage II and III) is surgery and pre- or post-operative chemoradiation, and then chemotherapy.

Potential advantages of preoperative radiotherapy include:

1- Increased probability of down-sizing and the down-staging of tumor; 2- Increased probability of curative surgery (R0); 3- Increased probability of sphincter preservation in low-lying cancers; 4- Increased radiobiological effects of radiation on the tumor due to adequate supply of oxygen to the tissues; 5- Decreased probability of spillage during surgery.

According to this reasons, the neo-adjuvant therapies are preferred for treatment of advanced local rectal cancers (stage II and III).

The standard of preoperative therapy of rectal cancer in North America is 45-50 Gy in 25-28 fractions. But European trials tend to use short course schedule (4).

Preoperative radiotherapy is traditionally 5040 cGy

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in 28 fractions associated with concurrent chemotherapy, and patients are operated 6-8 weeks after radiotherapy, whereas in short course method, patients receive 2500 cGy in 5 fractions over 5 days without concurrent chemotherapy and are operated during the first week after radiation. Thus short course treatment seems more reasonable than a conventional approach in terms of the short treatment period, early surgery, reducing costs, and patients comfort.

Materials and Methods

The present study is a phase II interventional study in which 28 patients with rectal cancer, consecutively referred to the Cancer Institute from March 2009 to March 2010, were included after performing necessary investigations in terms of staging as well as having inclusion criteria, and following informing them and filling the consent form.

Inclusion criteria consisted of stage II and III biopsy proved rectal adenocarcinoma, operable tumors, and age lower than 80, no need for down staging including sphincter preservation, KPS more than 70.

Exclusion criteria were inoperable and fix tumors, other pelvic tumors, previous pelvic radiotherapy, metastatic disease and the most important one, i.e. the need for downstage to any reason including sphincter preservation.

The patients then underwent CT simulation and 3D planning based on the plan developed by physicist such that in each session they were exposed to 500 cGy with cobalt or preferably 18 MV linear accelerator devices through box or 3-field method at a prone position for 5 sessions. After completion of the radiotherapy, they were introduced to the surgery service in which the surgeon selected the operation type. In the surgery department, the patients were visited and examined by a third surgeon who was unaware of the study and completed a questionnaire about pre-operative, operative, and post-operative complications. Finally, the patients were visited during adjuvant chemotherapy (if needed) and 1 and 2 months after treatment and the complications were recorded.

The complications studied in this research included the followings: proctitis, cystitis, dysuria, hematuria, Frequency/urgency, urogenital fistula, anorectal fistula, wound infection, wound dehiscence, anastomotic leakage, intraoperative hemorrhage, skin reaction, proctitis, plexopathy, need for colostomy.

To evaluate the response to treatment, TRG scoring was used as 3 point method which is depicted in Table 1.

Table 1. TRG Scoring

3-point TRG	Description
I	Absence of residual cancer or residual cancer cells scattered through the fibrosis
II	Increase in the number of residual cancer cells, with fibrosis predominant
III	Residual cancer outgrowing fibrosis

Results

In this study, 28 patients including 16 males and 12 females were studied. Their age range was 25-76 years with a mean of 65.5 years. One patient did not consent to surgery, two patients were diagnosed non-operable during surgery due to the extent of the tumor, and 25 patients underwent surgery; 16 patients with LAR and 9 patients with APR, of them 3 patients were margin (+) and the distance of tumor from AV were reported as 15, 6-8, and 7 cm, respectively; of them one underwent APR and 2 LAR surgery. Two patients, who were decided to be operated through APR in the preoperative assessment, had LAR; one of them was operated 12 days and the other 8 days after radiotherapy. One important indicator in this study was the interval between surgery and radiotherapy; such that 7 patients were operated in 10 days or fewer and 20 patients more than 10 days after XRT.

Comparison of clinical and pathological staging showed that 14 (51.8%) patients were down-staged, 8 patients had no change, and 5 patients were up-staged (Tables 2 and 3).

Almost no serious side effects were reported except anal pain grade I in only one patient and dysuria grade I in another, both was improved spontaneously. The patients were visited after surgery to determine the necessity of adjuvant therapy; they were also visited at the end of months 1, and 2 and the complications were recorded. No mortality was reported within one month after surgery, and only one patient died 4 months after surgery due to other reason. A patient had increased

CEA titer one month after surgery with no obvious metastatic site.

TRG scoring findings which were used to evaluate the response to treatment through 3 point method were available only in 18 patients. Short course radiotherapy appeared to cause tumor regression such that TRG I was 45% and TRG II was 55%. However, no significant association existed between the time interval and TRG (*P*=0.5), which may be due to the small number of patients (Table 4). There was also no significant correlation between tumor grade and TRG (*P*=0.7), but increased response to treatment can be seen with better differentiation, such that TRG I was seen in 33% and 45% in well-differentiated and moderately differentiated tumors, respectively (Table 5).

Table 2. T staging in 25 patients treated with short course preop RT

Clinical staging / Pathological staging	CT1	CT2	CT3	CT4
PT0	--	--	1	--
PT1	--	1	1	--
PT2	--	--	7	--
PT3	--	--	13	--
PT4	--	1	1	--

preop RT: preoperative radiotherapy

Table 3. N staging in 25 patients treated with short course preop RT

Clinical N Staging / Pathological N staging	CN0	CN1	CN2
PN0	7	6	4
PN1	1	3	1
PN2	1	2	-

preop RT: preoperative radiotherapy

Table 4. Association of TRG with time interval (between the end of XRT and surgery)

TRG / Days	I	II
≤ 10	1	3
> 10	7	7

Table 5. Association of TRG with tumor differentiation

Differentiation / TRG	Well differentiation	Moderate differentiation	Poorly differentiation
I	2	5	1
II	4	6	0

Discussion

This pilot phase II study was conducted to assess the frequency of acute complications after short course radiotherapy in patients with stage II and III rectal cancer.

A phase III EORTC trial to compare preoperative therapy of 34.5 Gy in 15 fractions with surgery alone showed that this type of treatment improves local control without survival improvement (5).

In some important trials, Swedish researchers have studied the impact of short course treatment of 5 sessions. The first trial was conducted to study the short course method in Stockholm and patients were randomly

divided into two groups of surgery alone and 25 Gy into 5 sessions and surgery after a week. The results showed the improvement of disease free survival and reduction of local recurrence (6).

In the next trial by the Swedish Cancer Society, preoperative short-course treatment with 25.5 Gy in 5 fractions was compared with postoperative treatment with 60 Gy in 30 sessions (7). In this study, patients with Duke B or C stages were included. Significant improvement was observed in the local failure rate with short-course preoperative treatment (13% vs 22%), while the overall survival rate, disease-free survival, and morbidity showed no significant difference between the two groups, and the morbidity rate was not increased in short-course preoperative therapy in 5-10 years follow-up as well.

The design of Stockholm II trial was similar to Stockholm I, but the multi-field technique limited to the pelvis was used. This trial showed that local recurrence decreased in short-course preoperative treatment, and the overall survival was improved in a subgroup of patients who have undergone curative surgery. Furthermore, postoperative mortality was not increased (8).

In the largest Swedish trial, in which short-course preoperative therapy with a dose of 25 Gy in 5 fractions has been compared with surgery alone, more patients were included (1168 patients). The findings showed that in a 13-year follow-up, the overall survival had improved (38% versus 30%), and local recurrence had reduced (9).

In a study by Medical Research Council (MRC) in England, the 3-year follow-up showed a reduction in local recurrence (4.4% vs 10.6%) and improved disease-free survival (77.5% vs 71.5%) in short-course preoperative radiotherapy compared with chemoradiation after surgery (10).

Hartly *et al*., studied acute toxicity retrospectively in 177 patients and reported the mortality rate as 6% after 30 days of treatment. One or more complications occurred in 38% of patients and it was concluded that surgery performed a week after short course radiotherapy improved preoperative staging of the patients and use of appropriate techniques of radiotherapy reduced acute complications (11).

In a study conducted in Greek, 85 patients with advanced rectal cancer (locally advanced) were randomly divided into two groups of surgery alone and surgery followed by short-course preoperative radiotherapy. The objective of this study was to investigate the complications immediately after surgery. No postoperative mortality was reported in the two groups, and bleeding, wound infection, delayed ileus, and acute urinary tract infection was equal in both groups. Researchers have concluded that short-course preoperative radiotherapy is a safe and reliable method for advanced rectal cancer (12).

According to literature review for comparison of short course and conventional methods, although it is believed that neoadjuvant chemoradiation is preferred when sphincter preservation is necessary, there is no significant difference between these two methods in terms of other end points; and even some studies defended the priority of short course method, such as the study of Bujko *et al*., who compared 312 patients in two groups in a randomized trial. The first group received 25 Gy in 5 fractions and was operated the next week and the second group received 50.4 Gy in 28 fractions and concurrently received bolus 5FU and leucovorin chemotherapy, and then was operated 4-6 weeks later. The results of this study are as follows: disease free survival was 58.4% and 55.6% for short course and conventional radiotherapy, respectively, (P=0.820), local recurrence was 9% and 14.2%, respectively, (P=0.170) severe late toxicity was 10.1% and 7.1%, respectively, (P=0.360), and early radiation toxicity was 3.1% and 18.2%, respectively. Although this study is relatively small, it shows the importance of short course radiotherapy (13).

Marijnen *et al*., studied the acute complications after short-course preoperative radiotherapy in 1530 patients and based on their results, acute complications after radiotherapy and then TME were very rare and only bleeding during surgery was 100 ml more in a few patients and perineal complications was higher in patients who had APR. Thus no difference was observed in the mortality of patients (14).

The problem with the Swedish studies is that they have not used TME surgery. In a trial similar to Swedish design performed by Dutch researchers (Dutch TME Trial), TME surgery was applied and no difference was found in overall survival, while 5-6% absolute benefit was reported in local recurrence rate (15). There is always concern about increased complications in techniques using high-dose radiation in each session. The 5-year follow-up in Dutch studies showed that intestinal dysfunction such as fecal incontinence and blood and mucus excretion was more in treated patients than patients treated with TME surgery only (16), while in Australian study (Trans-Tasman), the long-term complications was the same in both groups of short-course preoperative radiotherapy and preoperative chemo-radiation (17).

In the present study, although the number of the patients is fewer than the above-mentioned studies, the results are fully consistent with that results, and of 28 patients, only 7.1% (2 patients) showed grade I complications (anal pain and dysuria) who recovered spontaneously and 14 patients were down staged.

As mentioned earlier, TRG scoring was used to evaluate the response to treatment. According to previous studies, TRG can predict the rate of local recurrence and overall survival, and a better TRG means better disease-free survival (18).

In a study to evaluate the correlation of TRG with time interval between short course radiotherapy and surgery, Veenhof AA *et al*., reported that the number of TRG1 and TRG2 cases in a group operated 6-8 weeks later was more than the group operated within two weeks but this tumor regression did not lead to better radical surgery or improved local control or overall survival (19).

In a study conducted to examine the association between TRG with radiotherapy, Vironen *et al*., reported that tumor regression is higher in conventional method than short course radiotherapy, while T-stage down-staging was similar in both groups (20).

In the present study, TRG I 45% and TRG II 55% was observed following short course radiotherapy, indicating tumor regression, but the correlation between TRG with tumor differentiation and time interval was not significant due to the low number of patients.

Therefore, regarding what was discussed, and given that the treatment of cancer is time-consuming and costly for medical staff and patients, and due to shortening of the treatment time in the shorter treatment schedule and limitations in our country, it may be concluded that with accurate evaluations before treatment, the patients can be easily treated and good treatment results will be achieved.

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