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A Comparison of Early Side-Effects of Short-Course and Long-Course Radiotherapy in Rectal Cancer

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Abstract

Background: The variety of neoadjuvant treatments concerning rectal cancer has led to acute complications. The present study aimed to evaluate and compare the acute complications of short-course (SC) and long-course (LC) radiotherapy.

Method: We studied 100 patients suffering from rectal cancer, who referred to Nemazee Hospital before their surgery, in this cross-sectional study. The patients were divided into two categories: SC (25 grays radiotherapy at 5 fractions in 5 days) and LC (chemoradiotherapy with a dose of 45-50.4 grays in 25- 28 fraction in 5-6 weeks with concurrent Capecitabine (825 mg / m^2) twice daily and five days a week). Subsequently, we evaluated them for acute complications in the SC group 10-14 days after the end of the treatment and in the LC group at intervals of the treatment, the end of it and 2 weeks afterwards.

Results: In the LC group compared to the SC group, the percentage of patients with grade 1 diarrhea, grade 2 colitis and grade 1 cystitis at the end of the treatment was statistically different (P<0.001, P=0.046, P=0.036). In addition, the total number of the patients with grade 1 and 2 dermatitis was higher in the LC group compared with that in the SC group (P=0.046). We observed no significant differences between the two groups concerning the severe acute complications (P>0.05).

Conclusion: This study implied that there were no significant differences regarding severe acute complication between the two groups.

Keywords: Radiotherapy, Rectal nesoplasms, Side-effects

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Introduction

Despite the recent decrease in colorectal cancer incidence, these cancers are still considered as the most common and the most fatal human cancers. It has been estimated

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that over 4% of people are involved by colorectal cancer throughout life. About one third of the colorectal cancers originate from rectum.[1] Local recurrence is a major problem in rectal cancer whose treatment is rather difficult.[2]

Previously, the chosen treatment was surgery, but radiotherapy (RT) has been shown to be effective on increasing the survival rate. Preoperative RT has been found to be of better outcomes and tumor control rather than surgery alone or preoperative RT. Moreover, the toxicity of preoperative RT and chemoradiothetapy (CRT) seems to be better than that of postoperative RT. Even though only one trial compared preoperative and postoperative RT in rectal cancer, neoadjuvant short-course (SC) or long-course (LC) RT is the standard of care.[2, 3]

Despite the difference in dose of RT and chemotherapy administration, SC and LC RT schedules seem to have similar effects. Studies have shown that outcomes and late toxicities are similar, so patients' desire and preference is of great importance in choosing a schedule. Side-effects are also determining in choosing a schedule.[4]

Methods and Materials

This is a prospective cross-sectional study carried out in Nemazee Hospital, Shiraz University of Medical Sciences between June 2017 to September 2018. We conducted the present research to compare the side-effects associated with SC and LC RT in patients with rectal cancer. Our participants had biopsy proven rectal cancer whose tumors were located up to 12 cm of anal verge. All were medically fit, without systemic disease, between 18-70 years old and they all signed written consent. We did tumor staging and metastatic work-up ahead of the treatment, on top of pelvic magnetic resonance imaging, abdominal and chest computed tomography scan. Liver and kidney function tests and complete blood count was done for all of the subjects before the treatment. We randomly divided the patients to two groups, each receiving RT for 5 or 25 days. The SC group received 2500 cGy in 5 fractions and the other group, LC group, received 4400 cGy in 22 fractions, 5 fractions per week. Our RT machine was Oncor, Simens, with 6, 9, 12, and 18 MV photons. The LC group also received concurrent chemotherapy with capecitabine, 825mg/m^2, twice a day, 5 days a week. Our patients were evaluated on a weekly basis for the side-effects during RT. Those patients in LC group were also visited 2 weeks after RT. Skin, genitourinary, and gastrointestinal toxicities were scored according to CTCAE. The side-effects were registered after the SC RT and in the LC group on the 3rd week, following the RT treatment and 2 weeks after RT.

Results

100 patients entered the study, among whom 2 in the LC group refused to cooperate for regular examinations and exited the study. We had 98 patients who completed the study. The mean ages in the SC group and in the LC one were 65.4 (±10.11) and 62.21(±11.49) years, respectively. Most of the patients in both groups were men (72% and 66.6%, respectively in the SC and LC groups) (Table 1).

The most prevalent side-effect associated with the treatment of RT was anemia that occurred in 72.7% and 68% of the patients in the LC and SC groups, respectively. Two patients in the LC and one patient in the SC one developed grade 3-4 anemia and required treatment. Meanwhile, 26% and 7% of the patients in the SC group had grade 1 and 2 anemia, and 21% and 13% of them in the LC group had anemia with grade 1 and 2.

Only five subjects in the LC and no patients in the SC group developed neutropenia, which was not severe in any of them. Thrombocytopenia was also not seen in the SC group; whereas, only 6.25% of the patients in the LC group had grade 1 thrombocytopenia. Hematologic complications were not statistically significant in neither of the groups. Two weeks after the treatment was finished, we did not observe thrombocytopenia or neutropenia, while 58% of the patients in the LC group had grade 1-2 anemia.

The patients showed low gastrointestinal bleeding in both groups, yet they represented a different result concerning diarrhea and colitis.

Table 1. Age and sex distribution in short-course and long-course groups

	Long-course CRT group (n=48)	Short-course RT group (n=50)	*P*-value
Age(year)	62.21 (SD11.49)	65.4 (SD 10.11)	0.72
Sex			
Male	32 (66.6%)	36 (72%)	0.99
Female	16 (33.3%)	14 (28%)	

RT: Radiotherapy; CRT: Chemoradiotherapy

One patient had grade 3 diarrhea after the SC RT, and no other patients had grade 3-4 diarrhea in none of the groups. We observed grade 1 diarrhea in 22% of the patients with the SC treatment and in 41.7% of those with the LC treatment.

As shown in table 2, after the treatment was finished, grade 1 diarrhea and grade 2 colitis were significantly more common in the LC group.

Aseptic cystitis was another side-effect that was measured. No patients were found to have grade 4-5 cystitis, whereas one patient in each group had grade 3 cystitis. Grade 1 cystitis was more common in the LC group (33.3% versus 16%); this difference was statistically significant. After 2 weeks, 10.4% of our patients still had cystitis.

Grade 1-2 dermatitis was statistically significant in the LC group. 56% of the participants in the SC group had grade 1-2 dermatitis, while 75 % of those who received the LC treatment had dermatitis. Only one patient had grade 3 dermatitis, and no patient had grade 4-5 dermatitis. Interestingly, 2 weeks after RT, only one patient had grade 1 dermatitis.

Discussion

We treated 100 patients in the current study. Mild toxicities were more frequently seen in the LC group. Except for one patient with grade 3 diarrhea in the SC group, other grade 3-4 toxicities were more common in the LC one. Regarding early toxicity, it seems that SC is more efficient than LC radiotherapy. The main drawback of our study was the small size of our patients.

In rectal cancer, preoperative RT is preferred over post-operative. There are two preoperative RT regimens widely employed for patients with rectal cancer; the SC RT, in which 5 Gy RT is administered during 5 days, and the LC treatment, in which during 28 days, 1.8 Gy RT is administered. In the LC treatment, concurrent chemotherapy is usually administered.[5]

Regarding the effectiveness, SC and LC RT in locally advanced rectal cancer has been compared in randomized trials. In a study on 326 patients after a median of 5.9 years F/U, the survival time of 5 years was similar in both groups. They also compared late side-effects that were also similar in both groups.[4] Furthermore, another study also compared the survival rate and late toxicity of SC and LC RT. 312 random patients received SC or LC treatment. After a median of 2 years F/U, local control, survival and late side-effects were still similar.[3]

RT by itself has some side-effects. In a study in 2005, the side-effects of RT were evaluated. In this study, 1147 patients with rectal cancer received RT before the surgery, or surgery alone. Certain complications such as infection, bowel obstruction, abdominal pain, and nausea were evaluated. Gastrointestinal complications leading to admission of the patients in the hospital were more frequent in the RT group compared with those treated only with surgery. The most important complication was more frequently observed in the RT group rather than the surgery group.[6] In this study, chemotherapy was not administered and post-surgery side-effects were evaluated.

Chemotherapy increases the RT complications. A study by Bosset et al. reported that the addition of 5FU-LV chemotherapy to conventional RT prior to surgery increases the acute toxicity. The most common side -effect was diarrhea and then dermatitis. Other side-effects were vomiting,

Table 2. Early side effects of RT and CRT in patients

	Long-course group (N=48)			Short-course group (N=50)	*P*-value
	At the middle of treatment	At the end of treatment	2 weeks after RT		
Diarrhea					
Grade 1	10 (20.8%)	20 (41.66%)	1 (2.08%)	11 (22%)	0.036
Grade 2	8 (16.66%)	9 (18.75%)	0 (0%)	6 (12%)	0.66
Grade 3	0 (0%)	0 (0%)	0 (0%)	1 (2%)	0.2
Grade 4	0 (0%)	0 (0%)	0 (0%)	0 (0%)	-
Grade 5	0 (0%)	0 (0%)	0 (0%)	0 (0%)	-
Ginger bleeding					
Grade 1	1 (2.08%)	4 (8.33%)	0 (0%)	2 (4%)	0.65
Grade 2	0 (0%)	0 (0%)	0 (0%)	1 (2%)	0.19
Grade 3	0 (0%)	0 (0%)	0 (0%)	0 (0%)	-
Grade 4	0 (0%)	0 (0%)	0 (0%)	0 (0%)	-
Grade 5	0 (0%)	0 (0%)	0 (0%)	0 (0%)	-
Colitis					
Grade 1	24 (50%)	28 (58.33%)	11 (22.91%)	24 (48%)	0.89
Grade 2	16 (33.33%)	35 (72.91%)	2 (4.16%)	15 (30%)	<0.001
Grade 3	0 (0%)	1 (2.08%)	0 (0%)	1 (2%)	0.99
Grade 4	0 (0%)	0 (0%)	0 (0%)	0 (0%)	-
Grade 5	0 (0%)	0 (0%)	0 (0%)	0 (0%)	-
Aseptic cystitis					
Grade 1	7 (14.58%)	16 (33.33%)	4 (8.33%)	8 (16%)	0.046
Grade 2	1 (2.08%)	5 (10.41%)	1 (2.08%)	5 (10%)	0.95
Grade 3	0 (0%)	1 (2.08%)	0 (0%)	1 (2%)	0.93
Grade 4	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0.88
Grade 5	0 (0%)	0 (0%)	0 (0%)	0 (0%)	-
Dermatitis					
Grade 1	6 (12.5%)	21 (43.75%)	1 (2.08%)	18 (36%)	0.2
Grade 2	1 (2.08%)	15 (31.25%)	0 (0%)	10 (20%)	0.09
Grade 3	0 (0%)	1 (2.08%)	0 (0%)	0 (0%)	0.85
Grade 4	0 (0%)	0 (0%)	0 (0%)	0 (0%)	-
Grade 5	0 (0%)	0 (0%)	0 (0%)	0 (0%)	-
Thrombocytopenia					
Grade 1	1 (2.08%)	3 (6.25%)	0 (0%)	0 (0%)	0.07
Grade 2	0 (0%)	0 (0%)	0 (0%)	0 (0%)	-
Grade 3	0 (0%)	0 (0%)	0 (0%)	0 (0%)	-
Grade 4	0 (0%)	0 (0%)	0 (0%)	0 (0%)	-
Neutropenia					
Grade 1	2 (4.16%)	3 (6.25%)	0 (0%)	0 (0%)	0.07
Grade 2	1 (2.08%)	2 (4.16%)	0 (0%)	0 (0%)	0.11
Grade 3	0 (0%)	0 (0%)	0 (0%)	0 (0%)	-
Grade 4	0 (0%)	0 (0%)	0 (0%)	0 (0%)	-
Febrile neutropenia					
Grade 3	0 (0%)	0 (0%)	0 (0%)	0 (0%)	-
Grade 4	0 (0%)	0 (0%)	0 (0%)	0 (0%)	-
Grade 5	0 (0%)	0 (0%)	0 (0%)	0 (0%)	-
Anemia					
Grade 1	17 (35.41%)	21 (43.75%)	19 (39.58%)	26 (52%)	0.22
Grade 2	11 (22.91%)	13 (27.08%)	9 (18.75%)	7 (14%)	0.09
Grade 3	1 (2.08%)	1 (2.08%)	0 (0%)	1 (2%)	0.88
Grade 4	1 (2.08%)	0 (0%)	0 (0%)	0 (0%)	0.7
Grade 5	0 (0%)	0 (0%)	0 (0%)	0 (0%)	-

RT: Radiotherapy; CRT: Chemoradiotherapy

neutropenia and cystitis, stomatitis, thrombocytopenia, and infection. The side-effects associated with CRT lead to treatment interruption (5 versus 12) or treatment stop (1 versus 9). In the above-mentioned study, preoperative acute toxicity was compared in RT and in CRT. The second degree toxicities were measured. 150 patients from the total 398 patients (37.7%) in group 1 and 3, and 217 patients from 400 patients (54.3%) had high levels of toxicity in RT and CRT groups, which was mainly diarrhea. Compared to RT alone, CRT significantly increases toxicities.[7] In our study, the side-effects seen in the patients in the LC group were more severe. This might be due to the concurrent chemotherapy.

Bujko et al., in a randomized study, compared the early side-effects and outcomes of SC and LC schedules. Grades 3-4 side-effects were statistically significant in the LC treatment. Only 3.2 % of their patients in the SC group had severe reactions; whereas, 18.2% of those in the LC group had such issues.[3] Our obtained findings similarly demonstrated more toxicity in the LC treatment.

Ansari compared the side-effects of RT to LC RTs.

In their study, the applied SC treatment was 5 Gy daily irradiation during one week and early surgery on the other hand. The other treatment course was a LC treatment with 28 fractions of radiation and totally, 50.4 Gy radiation was administered concurrently with chemotherapy (5-fu infusion). 7% of their patients in the LC treatment were not able to complete the treatment course, but in the SC treatment, all of them finished the treatment successfully. Nearly all the participants in the LC group had at least mild (grade 1 or 2) side-effects, while 72% of the patients in the SC treatment, had grade 1 or 2 side-effects. Regarding grade 3 or 4 side-effects, only 1.3% of the patients in the SC treatment, had diarrhea and no other serious side-effects were observed. Grade 3 or 4 side-effects, including radiation dermatitis (5.6%), proctitis (3.7%), nausea (3.1%), fatigue (3.7%), and diarrhea (14.2%) were significantly more common among the LC treated subjects. We had no grade 3 or 4 complications among our patients in any of the groups. In our study, only grade 2 colitis was significantly more prevalent among the patients with the LC treatment rather than the SC treated patients.[8]

In a study on 305 patients, Bujka et al. compared post-operation complications in SC to those in LC RT. 27% and 21% of their subjects, respectively in the SC and LC treatment schedule developed one type of complication. This difference was not statistically significant. The most common complication was wound healing process and infection. 29% and 21% of the patients, respectively in the SC and LC groups developed wound complications, none of which was severe enough to undergo a surgery. In this study, three deaths occurred, one in the LC and two in the SC group. Wound healing process, anastomosis leakage, and post operation hospital stay were similar in both groups. They also compared the complications after the operation between the two groups and severe complications requiring an operation were statistically equal in both groups. In the SC group, 15 patients and in the LC groups, 16 patients required reoperation due to severe complications. This difference was not significant. There were two cases of death in the SC and one in the LC groups.[5]

Conclusion

SC RT was found to be more efficient than the LC one. As other studies have also reported similar effectiveness, it seems that SC is the preferred RT regimen. However, further research is of great necessity, and long-term survival must be kept in mind.

Conflict of Interest

None declared.

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