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The results of postoperative chemoradiotherapy in rectal cancer

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ABSTRACT

The aim of this study was to investigate the treatment results of postoperative chemoradiotherapy (CRT) and the prognostic factors of locally advanced rectal cancer. Sixty nine patients with rectal cancer treated with postoperative CRT were analyzed. Irradiation was given with a total dose of 50.4 Gy in 28 fractions. They all received concurrent 5- fluorouracil and leucovorin chemotherapy regimens during radiotherapy. Clinical, pathologic and treatment characteristics were analyzed using univariate and multivariate Cox models. There were thirty-nine male and thirty female patients; their median age was 58. Thirty patients received 1 to 2 cycles of chemotherapy before concurrent CRT, while 39 has started with CRT simultaneously. The median follow-up was 25 months. Late intestinal toxicity appeared in 7 patients and 5 of them had required intestinal resections. Univariate analysis showed that number of involved lymph nodes, AP-PA field technique and having chemotherapy before CRT had significant impact on overall survival (OAS). In multivariate analysis, high number of involved nodes (p=0.004, HR: 1.09) and AP-PA technique (p=0.017, HR: 4.48) were independent poor prognostic factors for OAS. High number of involved nodes and AP-PA technique were independent poor prognostic factors for survival in patients with rectal carcinoma treated with surgery and postoperative CRT. Our results show that appropriate radiotherapy technique should be utilized for rectal cancer patients in order to improve survival. [Turk J Cancer 2008;38(1):5-11]

KEY WORDS:

Chemoradiotherapy, rectal cancer, survival

INTRODUCTION

Surgery is the primary treatment in rectal carcinoma. But the cure rate by surgery alone is poor in patients with locally advanced rectal carcinoma (1). Pre- or postoperative adjuvant treatment strategies have been needed to decrease local recurrence and improve survival. Postoperative chemoradiotherapy (CRT) is the only adjuvant therapy to reduce local recurrence and improve survival in patients undergoing definitive surgery with stage II or III rectal carcinoma (2-6). But the most important problem of the combined modality treatment is acute or delayed toxicity from chemotherapy or radiotherapy. For example; gastrointestinal toxicity is the most common cause of morbidity and mortality after pelvic irradiation for rectal carcinoma. There is a relationship between the volume of irradiated small bowel and the degree of bowel toxicity in patients treated with pelvic radiotherapy. As radiation technique has an important role to reduce the irradiated volume, the use of multiple field technique may have an advantage of reducing the small bowel volume and the probability of complications from pelvic radiotherapy as compared to two-field technique (7).

In this study, treatment results of patients who underwent radical surgery and received postoperative CRT were evaluated and prognostic factors on the outcome were investigated.

MATERIALS AND METHODS

The records of all consecutively treated patients with resected rectal carcinoma treated with adjuvant radiotherapy in our institution between 1999 and 2004 were retrospectively evaluated. Patients were irradiated either with linear accelerator (80%) or 60Co unit. They all received concurrent 5-fluorouracil and leucovorin chemotherapy regimens during radiotherapy. Standard Mayo regimen (5-FU bolus 425 mg/m^2/day+FA 20 mg/m^2/day×5 days every 4 weeks), was employed before and after the radiotherapy administration (8). 5-FU, during radiotherapy was continued as weekly bolus, with appropriate dose reduction.

All patients were placed in the supine position during the radiotherapy. Either four-field technique (anterior-posterior and two laterals) or parallel opposed (AP-PA) two fields technique was used for the radiation treatment. The lateral borders of the anterior-posterior radiation field were 1.5-2 cm lateral to the widest body margin of the true pelvis walls; the superior margin was at the L5-S1 interspace; inferior border included the perineum in patients with abdominoperineal resection (APR) and at the ischial tuberosities with low anterior resection (LAR). The anterior border of the lateral fields was at the anterior edge of the symphysis pubis and posterior border was placed at the posterior aspect of the sacrum. Irradiation was given with a single daily fraction of 1.8 Gy to a total median dose of 50.4 Gy.

Statistical analysis

Univariate tests and multivariate Cox models were used to determine any significant association between survival and patient characteristics, including age, sex, clinical stage, operative method, tumor differentiation, number of removed and involved lymph nodes, AP-PA or box treatment designs, administration of chemotherapy before radiotherapy and development of late toxicity.

RESULTS

There were thirty-nine male and thirty female patients; their median age was 58 (24-83). All patients had undergone primary radical surgery with LAR in 39 patients and APR in 30. Histopathological examination demonstrated adenocarcinoma in all cases. Patients were staged pathologically as follows: IIa 39%, IIb 4.3%, IIIa 5.8%, IIIb 31.9 and IIIc 18.8%. The median number of removed and involved lymph nodes were 12 and 2, respectively. Patient characteristics are given in Table 1.

Thirty patients received 1 to 2 cycles of chemotherapy before concurrent CRT, while 39 has started with CRT simultaneously. Additional 2-4 cycles of chemotherapy were continued after the end of chemoradiation in all patients. A total of 64 patients received radiotherapy with the box technique and 5 with the AP-PA technique. The median interval between surgery and onset of radiotherapy was 58 days and radiotherapy was completed in median 42 (30-73) days.

The median duration of follow-up was 25 (5.5-65) months. Late severe intestinal toxicity appeared in 7 out of 69 patients (10%) and 5 of them had required intestinal resections, the others had occlusive crises responded to medical treatments. Three (4.3%) patients died as a result of treatment toxicity from CRT, within 6 months after the end of radiotherapy. One of them was treated with AP-PA and the others with the box technique.

Local recurrence and distant metastasis were detected in 5 (7.2%) and 7 (10.1%) patients, respectively. Median progression-free and overall survivals (OAS) were 55 and 58 months. Univariate analysis showed that number of involved lymph nodes, AP-PA field technique, and having 1 to 2 course of chemotherapy before CRT had significant impact on OAS. Similarly, disease-free survival was superior in patients treated with four field box technique. In multivariate analysis, high number of involved lymph nodes (p=0.004, HR=1.09) and AP-PA field technique (p=0.017, HR=4.48) were independent poor prognostic factors for OAS. Refer to table 2 for the results of Cox regression anal-

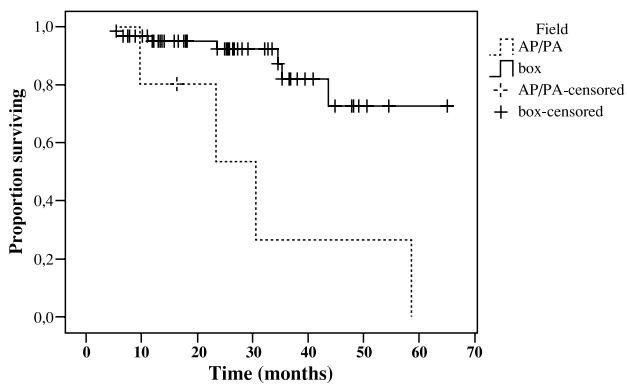

Fig 1. Overall survival with respect to the radiotherapy technique used

Table 1
Patient characteristics

Patient characteristics	n (%)	Median/Mean	Range
Total	69 (100.0)		
Age		58/57	24-83
Gender			
Female	30 (43.5)		
Male	39 (56.5)		
Histologic grade			
Well differentiated	16 (23.2)		
Moderately differentiated	44 (63.8)		
Poorly differentiated	9 (13.0)		
Operation			
APR	30 (43.5)		
LAR	39 (56.5)		
Stage			
II	30 (43.5)		
III	39 (56.5)		
Number of resected lymph nodes		12/13	1-49
Number of involved lymph nodes		2/4.2	1-49
Treatment unit			
60Co	14 (20.3)		
Linac	55 (79.7)		
Radiation technique			
Four field (box) technique	64 (92.8)		
AP / PA technique	5 (7.2)		
Radiation dose		5040/4917.2	3060-5400
Time from operation to radiotherapy		58/65	24-210
Duration of radiotherapy		42/42.8	30-73
Chemotherapy before radiotherapy			
Yes	30 (43.5)		
No	39 (56.5)		

ysis and figure 1 for the survival curves for patients receiving AP-PA field and four field techniques.

DISCUSSION

Our study demonstrates that AP-PA field technique and high number of involved lymph nodes are detrimental on OAS in patients having adjuvant CRT for rectal cancer. In alignment with this finding, previous reports show significant mortality rates and increased toxicity with AP-PA field technique (9,10). However to the best of our knowledge a direct comparison between AP-PA and box technique in the adjuvant setting has not been published prior to this study.

The most frequent complication of pelvic radiotherapy is gastrointestinal toxicity from the effect of radiation on the small bowel. In general the incidence of grade 3+ acute toxicity of postoperative radiotherapy in rectal carcinoma is 20%-35% (11-13). In particular, the most important acute gastrointestinal complications are diarrhea, abdominal cramping, increasing bowel frequency, proctitis, tenesmus and bloody or mucus discharge (14). However, long term complications probably occur 6-18 months after radiotherapy but longer latency period is also reported. In an

Table 2
Factors associated with overall survival

	Univariate p value	Multivariate p value	
General patient / tumor characteristics			
Gender (male vs. female)	0.878		
Age	0.834		
Grade	0.518		
Stage	0.421		
Number of lymph nodes involved	0.001		0.004
		(HR = 1.09)	
Treatment characteristics			
Type of operation (APR versus LAR)	0.824		
Number of lymph nodes removed	0.183		
Radiotherapy unit (60Co vs. Linac 25MV)	0.565		
Radiotherapy technique (AP-PA vs. Box)	0.044		0.017
		(HR = 4.48)	
Chemotherapy use before radiotherapy (present vs. absent)	0.022		0.059
		(HR = 0.35)	
Chronic radiation toxicity (present vs. absent)	0.376		
Time from operation to onset of radiotherapy	0.607		
Duration of radiotherapy	0.341		

HR: Hazard Ratio

analysis of 304 patients treated with adjuvant radiotherapy from Mayo Clinic between 1981 and 1990, the probability of treatment-induced bowel injury at 5 years was 19% (15). Persistent diarrhea, increasing bowel frequency, proctitis, small bowel obstruction, urinary incontinence, bladder atrophy and bleeding may develop as a late complication. Luckily, the incidence of small bowel adhesion and obstruction requiring surgical intervention after postoperative radiotherapy is about 5% (16). In the Mayo/North Central Cancer Treatment Group (NCCTG) trial 79-47-51 (4), four field box technique were used and the rate of small bowel obstruction requiring surgery was 6.7%. Similarly, in the current study, surgical resection has been needed because of the gastrointestinal complications in 5 (7.2%) patients.

In general, the mortality rates of postoperative radiotherapy without chemotherapy range from 0 to 5% (3, 17-19). In specific, the Uppsala trial has the mortality rate of 5% after adjuvant radiotherapy which was applied with three portals in prone position. High median age and total dose were the main risk factors defined in this study (19). Treatment related death risk increase when chemotherapy is combined with radiotherapy. The rate ranges increase to 0.3% - 18% in patients treated with postoperative CRT (12,20,21). The main causes of mortality were intestinal obstruction, sepsis and peritonitis (22). In our study, radiotherapy was applied postoperatively and treatment related mortality rate was 4.3%. Only five patients were irradiated with two field technique and one of them had died related to radiation toxicity on small bowel. These results with the AP-PA technique are not different from the previous series.

Can the mortality from adjuvant/neoadjuvant CRT or radiotherapy be reduced? In some trials, when radiotherapy is given in the neoadjuvant setting, mortality rates were higher among patients treated with anterior posterior portals than treated with three or four field techniques (9,10). In Swedish rectal cancer trial, 25 Gy external beam radiotherapy were delivered in 5 fractions preoperatively. The postoperative mortality rates were 15% versus 3% in patients

treated with two field and three or four field techniques, respectively (10). In Copenhagen trial three patients died as a direct consequence of the adjuvant treatment and this study closed after 17 patients had been treated with adjuvant CRT (21). This high morbidity was probably associated with the use of methotrexate concomitantly and the two-field radiotherapy technique. In the Stockholm Rectal Cancer Study Group Trial I, radiotherapy was applied with using AP-PA technique to a large volume and high fraction doses from 60Co unit (9,23). Postoperative complication was 26% in the radiotherapy group compared to 19% in the surgery alone group ($p<0.01$). This results; however, had been obtained from patients treated with radiotherapy preoperatively, thus may not directly apply to the adjuvant setting. In addition, gastrointestinal complications and side effects are seen more commonly in patients treated with postoperative radiotherapy, because of the volume of small bowel in the pelvis is to be greater after radical surgery (24,25). We think new studies are needed in order to delineate better the associates of treatment mortality in patients receiving adjuvant CRT after radically resected rectal carcinoma.

There is a strong correlation between the development of small bowel toxicity and volume of the irradiated bowel (14,26,27). Several methods had been defined to minimize the radiation related small bowel toxicity (28,29). Concerning the pelvis, four-field box technique is considered the standard treatment design. Two-field irradiation technique is out of date in pelvic radiotherapy because of the inhomogeneous dose distribution and high small bowel toxicity. The use of multiple field technique has an advantage of reducing the small bowel volume and the chance of complication from pelvic radiotherapy as opposed to two-field technique (5). The homogenous dose distribution in the target volume and minimum dose to the small bowel are obtained by using the combination of multiple field technique and high energy photons. In this situation, treatment of the patient with the four field technique may be helpful to exclude most of the small bowel volume from the radiation field. Computerized treatment planning also should be done by using high energy photon beams in linear accelerators. The recent, three dimensional conformal (3D-CRT) and intensity-modulated radiotherapy (IMRT) techniques give opportunity to decrease the volume of bowel irradiated (14, 30-32). Such newer radiotherapy techniques may enable delivery of more effective and less toxic radiation treatment, perhaps leading to better patient survival. This hypothesis needs testing in randomized clinical trials.

In the literature, it has been well demonstrated that the number of lymph nodes with metastasis has the most important prognostic variable on outcome in patients with rectal carcinoma (33,34). Additionally in staging of rectal carcinoma, nodal staging is dependent on the number of lymph nodes with metastases. It provides important prognostic information and facilitates decision-making with regards to adjuvant therapy. Similarly, in our cohort it represents the most powerful prognosticator.

High number of involved lymph nodes and AP-PA radiotherapy technique were independent poor prognostic factors for survival in patients with rectal carcinoma treated with surgery and postoperative CRT. Our results show that appropriate radiotherapy technique should be utilized for rectal cancer patients in order to improve survival.

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