



Local recurrence after surgery of locally advanced rectal cancer treated with or without preoperative chemoradiotherapy

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SUMMARY

Introduction: The „gold standard” for patients with locally advanced rectal cancer is neoadjuvant chemoradiotherapy followed by surgery. **Aim:** Evaluation of local recurrence after surgery for locally advanced rectal cancer. **Methods and patients:** Retrospective study included 189 patients, who were operated at Oncology Institute of Vojvodina from January 1st 2012 until December 31st 2017. Patients were divided into two groups. In the first group 73 patients who received chemoradiotherapy were included, while 116 patients without neoadjuvant treatment were in the second group. All patients were diagnosed with locally advanced rectal cancer. The existence of operable metastases in the liver and/or lungs did not exclude patients from the study. Patients who had undergone resection of the rectum by Miles, Hartmann or local tumor excision were excluded from the study. **Results:** The median follow-up period was 48 months (range 13-84). In total, 23 (12.2%) patients developed local recurrence. In the chemoradiotherapy group, 15.1% (11 of 73 patients) had a local recurrence, as compared with 10.3% (12 of 116 patients) in the group without neoadjuvant treatment. In both groups, there were no correlation between rate of local recurrence with other clinical and pathological parameters such as gender, tumor location, T and N stage, histological differentiation, or lympho-vascular and perineural invasion ($p > 0.05$). We confirmed significant association between circumferential resection margin with local recurrence in patients who were treated by preoperative chemoradiation ($p = 0.014$). **Conclusion:** This study has not shown reduced risk of local recurrence after neoadjuvant therapy most likely due to small number of patients. Despite our results, neoadjuvant treatment followed by surgery remains the best treatment protocol for patients with locally advanced rectal cancer.

Key words: Rectal cancer, Total mesorectal excision, Recurrence

INTRODUCTION

Neoadjuvant radiotherapy or chemoradiotherapy (CRT) followed by surgery (total mesorectal excision, TME) is optimal treatment for patients with stage II/III of rectal cancer (1).

Improved surgical techniques and use of preoperative hypofractionated radiotherapy or chemoradiotherapy treatments have reduced local recurrence rates from 30% to 10% (2).

As a result of neoadjuvant chemoradiotherapy (nCRT) reduction in relapse rates and tumor downsize can be achieved leading to increase of number of tumor resections and sphincter-saving procedures (3).

Imaging modalities, including magnetic resonance imaging (MRI), endoscopic ultrasound, positron emission tomography-computed tomography (PET-CT) are indispensable tools for preoperative patient's estimation and selection for nCRT (4).

Some clinical features such as in depth tumor invasion, lymphonodal involvement, and affection of mesorectal fascia are important factors for assessment of the local recurrence rate. The multidisciplinary approach in preoperative therapy of rectal cancer is important to avoid patient overtreatment (5).

The response to nCRT in stage II/III of rectal cancer varies. About 40% of patients experience a partial response (downstaging/downsizing), while in 8%-20% of cases viable tumor cells were not found at microscopic findings of the resected specimen (6,7).

The aim of this study was to evaluate rate of local recurrences in patients with locally advanced rectal cancer treated with or without preoperative CRT and sphincter preserving surgical treatment.

METHODS AND PATIENTS

This retrospective study included 189 patients (108 male and 81 female) who underwent sphincter-saving surgery with TME at Oncology Institute of Vojvodina in the period from 1st January 2012 until 31st December 2017, either with or without preoperative CRT.

After digital rectal examination and colonoscopy with biopsy histological diagnosis of rectal adenocarcinoma was established in all patients. Patients with proximal tumor border located no more than 15cm from the anal margin were included in evaluation.

Pelvic MRI was mandatory for initial staging and restaging after neoadjuvant CRT. Follow up period was until 1st January 2019 year with the median follow-up of 48 months (range 13-84).

Among 189 patients, 73 (38.6%) received neoadjuvant chemoradiation. The operation was performed 6-8 weeks after completing neoadjuvant radiotherapy.

A negative circumferential resection margin (CRM) was defined as the presence of microscopic foci of adenocarcinoma more than 1 mm from CRM.

The number of harvested lymph nodes and the number of involving lymph nodes were recorded. The lymph node ratio (LNR) was calculated as the number of lymph nodes with secondary deposits divided by the number of lymph nodes retrieved. Patients were categorized into 4 groups: LNR 1 (<7%), LNR2 (8-25%), LNR3 (26-50%) and LNR4 (>50%).

The existence of liver and/or lung metastases had not excluded patients from the study.

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Patients who had undergone abdominoperineal rectal resection, Hartmann procedure or local tumor excision were excluded from the study.

Patients were separated in two groups. In the first, CRT group 73 (38.6 %) patients received neoadjuvant CRT, while in second noCRT group 116 (61.4%) patients did not receive neoadjuvant CRT-these (due to technical issues or patient's decision to be operated immediately).

Patients were checked every 3-4 months during the first 18 months or up to 4 years. After that patients were checked annually. Check-up protocol consisted of digital rectal examination, colonoscopy (with biopsy), and measurements of carcinoembryogenic antigen (CEA), CA 19-9, MRI of pelvis and abdomen, and chest CT.

Local recurrence was considered as relapse disease in pelvis, and described based on clinical, radiologic or pathologic evidence of recurrent cancer.

STATISTICAL ANALYSIS

Statistical analysis was performed using Statistical Package for the Social Sciences (SPSS, IBM; Version16). Fischer's exact test and χ^2 tests were used to compare the data between the groups. Values were considered as statistically significant when $p < 0.05$.

RESULTS

The CRT group was divided into following stages according to postoperative histopathological findings: 27.4% (20) of patients were in stage I, 37% (27) in stage II, 27.4% (20) in stage III and 8.2% (6) were in the stage IV. The same was done for the noCRT group: 37.9% (44) of patients were in stage II, 51.7% (60) in stage III, and 10.4% (12) in stage IV.

In the CRT group, 41.7% (5 of 12) patients who had positive CRM developed a local recurrence, as compared to 6.3 percent (1 of 16) in the noCRT group.

Clinicopathological characteristics of patients were summarized in Table 1 and Table 2.

Regarding to extent of primary tumor, 52% and 1.4% of patients from CRT group, and 88.8% and 4.3% of patients from noCRT group were diagnosed with T3 and T4 stage rectal cancer, respectively.

In the Table 3 association between postoperative stage disease and rate of local recurrence was presented.

Twenty-three (12.2%) patients developed a local recurrence. In the CRT group, 15.1% (11 of 73 patients) had a local recurrence, as compared to 10.3% (12 of 116 patients) in the noCRT group (Table 3).

The mean time to local recurrence was 14.5 months (range 3-33) for patients with preoperative CRT, and 17.6 months (range 4-30) for patients without preoperative CRT (Figure 1).

Patients with mid rectal cancer (distant to anal verge 6-10 cm) had a higher local recurrence rate than those with lower and upper rectal cancer, while the difference was not significant ($p=0.115$).

The number of harvested lymph nodes was significantly lower in the group treated with preoperative CRT *i.e.* 10.43 (range 0-28) compared to 17.39 (range 7-39) in patients without nCRT ($p < 0.05$).

We have found a higher local recurrence rate in patients with N0 stage and LNR < 25%, independent from nCRT.

Risk of local recurrence was almost the same between two groups by LNR (Table 3).

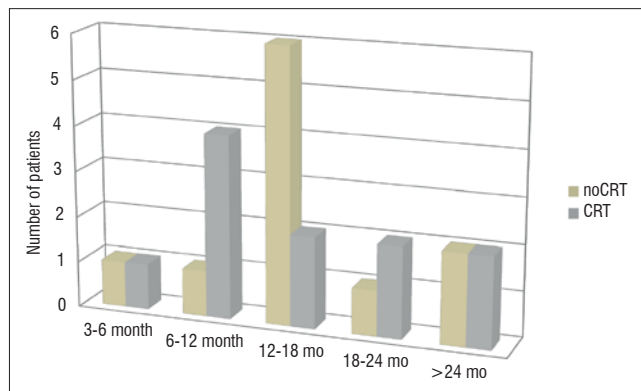


Figure 1. Local recurrence in CRT and noCRT groups during 24 months follow-up after surgery

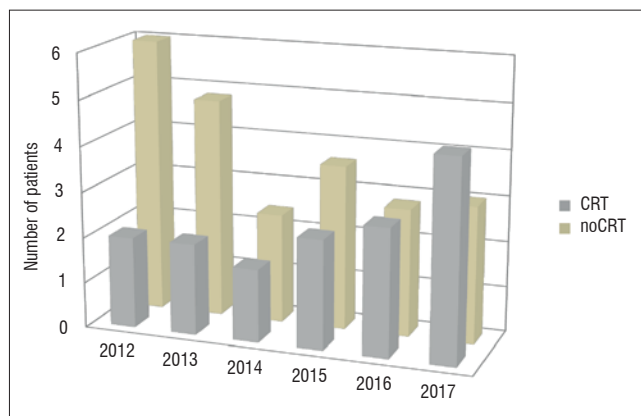


Figure 2. Distribution of CRT and noCRT patients engaged in study

	Without local recurrence (n=62)	With local recurrence (n=11)	p value
Gender			
Male	31 (50%)	6 (54.5%)	1.0
Female	31 (50%)	5 (45.5%)	
Age			
65	47 (75.8%)	8 (72.7%)	0.56
≥65	15 (24.2%)	3 (27.3%)	
Tumor location			
Low	31 (50%)	5 (45.4%)	0.688
Middle	28 (45.1%)	6 (54.6%)	
Upper	3 (4.9%)	0 (0%)	
T stage			
T0	6 (9.6%)	3 (27.3%)	0.131
T1	2 (3.2%)	0 (0%)	
T2	21 (33.8%)	1 (9.1%)	
T3	32 (51.7%)	7 (63.6%)	
T4	1 (1.7%)	0 (0%)	
N stage			
N0	42 (67.7%)	6 (54.5%)	0.665
N1	17 (27.4%)	4 (36.4%)	
N2	3 (4.9%)	1 (9.1%)	
LVI			
yes	27 (43.5%)	8 (72.7%)	0.072
no	35 (56.5%)	3 (27.3%)	
PNI			
yes	20 (32.2%)	5 (45.4%)	0.301
no	42 (67.8%)	6 (54.6%)	
CRM			
positive	7 (11.3%)	5 (45.4%)	0.014
negative	55 (88.7%)	6 (54.6%)	

Table 1: Clinicopathological characteristics and local recurrence of CRT patients

	Without local recurrence (n=104)	With local recurrence (n=12)	p value
Gender			
Male	62 (59.6%)	9 (75%)	0.239
Female	42 (40.4%)	3 (25%)	
Age			
65	59 (56.7%)	8 (66.6%)	0.362
≥65	45 (43.3%)	4 (33.4%)	
Tumor location			
Low	28 (26.9%)	3 (25%)	0.579
Middle	58 (55.7%)	7 (58.3%)	
Upper	18 (17.4%)	2 (16.7%)	
T stage			
T2	8 (7.7%)	0 (0%)	0.058
T3	93 (89.4%)	10 (83.3%)	
T4	3 (2.9%)	2 (16.7%)	
N stage			
N0	42 (40.4%)	5 (41.6%)	0.872
N1	33 (31.7%)	3 (25%)	
N2	29 (27.9%)	4 (33.4%)	
LVI			
yes	57 (54.8%)	8 (66.6%)	0.321
no	47 (45.2%)	4 (33.4%)	
PNI			
yes	33 (31.7%)	4 (33.4%)	0.592
no	71 (68.3%)	8 (66.6%)	
CRM			
positive	15 (14.4%)	1 (8.4%)	0.408
negative	89 (85.6%)	11 (91.6%)	

Table 2: Clinicopathological characteristics and local recurrence of noCRT patients

	CRT		noCRT	
	LR-	LR+	LR-	LR+
Stage 0	6 (9%)	3 (27.2%)	0 (0%)	0 (0%)
Stage I	19 (30.6%)	1 (9%)	0 (0%)	0 (0%)
Stage II	16 (25.8%)	2 (18.8%)	40 (38.5%)	4 (33.7%)
Stage III	15 (24.2%)	5 (45%)	52 (50%)	8 (66.3%)
Stage IV	6 (10.4%)	0 (0%)	12 (11.5%)	0 (0%)
Total	62 (100%)	11 (100%)	104 (100%)	12 (100%)
LR - patients without local recurrence				
LR+ patients with local recurrence				

Table 3: Association between postoperative stage and local recurrence rate

In both groups, there was no correlation of recurrence with other clinical and pathological parameters such as: gender, tumor location, T and N stage, histological differentiation, lymphovascular or perineural invasion ($p > 0.05$).

We confirmed the significant association between CRM involvement with occurred local disease relapse in patients who received preoperative chemoradiation ($p = 0.014$).

However, the recurrence in patients with clear CRM, who didn't receive nCRT was higher, but was not significant ($p = 0.408$).

Histopathological examination of specimens after sphincter saving surgery showed that 9 out of 189 (4.8%) patients, who underwent preoperative chemoradiation, had pathological complete response (pCR).

CRT			0.175
LNR1 (< 7%)	44 (71%)	6 (54.5%)	
LNR (7-25%)	5 (8%)	2 (18.2%)	
LNR3 (25-50%)	6 (9.7%)	3 (27.3%)	
LNR4 (>50%)	7 (11.3%)	0 (0%)	
noCRT			0.057
LNR 1 (< 7%)	58 (56.3%)	5 (41.7%)	
LNR2 (7-25%)	18 (17.5%)	6 (50%)	
LNR3 (25-50%)	16 (15.5%)	1 (8.3%)	
LNR4 (>50%)	11 (10.7%)	0 (0%)	

Table 4: Local recurrence according to LNR

DISCUSSION

Surgical resection is the most important component of treating patients with rectal cancer, but tumor relapse after surgery and neoadjuvant or adjuvant therapy is in connection with a severe morbidity and high risk of death (8,9).

The advantage of neoadjuvant in comparison to adjuvant CRT was demonstrated by the German Rectal Cancer Trial in 2004 reporting that the neoadjuvant therapy approach resulted in decrease of locoregional recurrence rate from 13% to 6% and less toxicity (10).

The Dutch study from 2011 showed that addition of short-course neoadjuvant radiotherapy followed by optimal surgery (total mesorectal excision, TME) reduced the relapse rate of disease in 2-year follow up, from 8.2% in the surgery alone group to 2.4% ($p < 0.0001$). In the same study, preoperative radiotherapy (5x5 Gy) could not prevent local recurrence in patients with involved resection margin (11).

The clinical trials FFCD 92-03 and EORTC 22921 compared neoadjuvant radiotherapy vs preoperative CRT and similar results were presented. Chemotherapy increased the rate of pCR (11.4% vs. 5.3%) and significantly reduced local recurrence from 17% without CRT to 8% with preoperative CRT (12,13).

In our study, patients who received nCRT had a higher percentage of local recurrent rectal cancer than the patients who did not receive nCRT (15.1% vs. 10.3%).

The Swedish study analyzed the impact of limfovascular invasion (LVI) and perineural invasion (PNI) on occurred local recurrence in 2649 patients with stage II rectal cancer. The detection rate of LVI was significantly lower in patients treated with nCRT followed by surgery versus surgery alone (8.1% vs. 20.6%, $p < 0.001$), while no difference in PNI was found (28.3% vs. 29.1%, $p = 0.786$). In patients who were candidates for adjuvant chemotherapy, three-year local recurrence risk was 25% versus 24% for tumors with and without LVI ($p = 0.836$) and 47% vs. 20% ($p < 0.001$) for tumors with and without PNI (14). Korean randomized phase 3 trial showed similar results (15).

Our study showed that patients with LVI and without PNI had a higher rate of local recurrence in both groups, but this was not statistically significant ($p > 0.05$).

Nodal involvement in patients with advanced rectal cancer constitutes the primary prognostic determinant. Cienfuegos et al. demonstrated that LNR is a better prognosis predictor than number of positive nodes (16). The high ratio of positive to total nodes retrieved was shown to be related to poor survival and high relapse rate of disease (17). Peng et al. found connection between LNR, OS and local recurrence in patients with rectal cancer. They demonstrated increased risk of local relapse among patients with LNR >0.34 compared to patients with LNR ≤0.34 (18). Huh et al. investigated the utility of LNR in 514 rectal cancer patients. Patients were grouped as LNR ≤0.9, LNR 0.9-0.18, LNR 0.19-0.33 and LNR >0.34. As the LNR increased, the 5-year survival rate significantly decreased ($p < 0.05$) (19). In our study, there was no difference in the rate of local recurrence between patients with a lymph node metastases compared to those with NO stage. While probability of recurrence increased as the LNR decreased in both groups, this was not significant ($p = 0.762$). These results could be explained with small number of patients included in this study. Despite the importance of extensive surgery with clear margins, local recurrence may be related to metastases in the lymph nodes outside the mesorectal plane, and on the pelvic side-wall, which are not removed during the standard surgery (20).

Involvement of CRM in rectal cancer is strong predictive factor for local recurrence and metastatic disease (4). Wheeler et al. analyzed patients who underwent curative resection following neoadjuvant CRT. They found that 54% of patients with positive CRM after curative resection following nCRT, developed local recurrence, compared to 6% of patients with R0 resection (21). In our study, the local relapse rate in patients with positive CRM was lower in the CRT group (41.6%).

Quirke suggests that patients with CRM >1 mm were associated with a 50% the relapse rate of disease after neoadjuvant chemoradiation. A margin of 1 mm and 2 mm or more were related to a 27.6% and 3% of local relapse, respectively (22).

The results of our study showed significant difference in the rate of local recurrence between the patients with a positive CRM compared to those with negative CRM (≥ 2 mm) in the group that underwent nCRT (41.7% vs. 9.83%; $p < 0.014$).

The Brazilian study by Habr-Gama and colleagues reported that 5-year local recurrence rate of the patients who achieved complete response through preoperative CRT was recorded in 21% cases (23). The available results from the other studies showed higher survival rates in patients who achieved pCR compared to patients with incomplete histopathological regression (24). In the study from Petrović et al. that included patients with locally advanced rectal cancer who received preoperative chemoradiotherapy, complete histopathological response was achieved in 10.7%, while local relapses were detected in 12.5% cases (25). In our study, similar results were obtained, i.e. complete histopathological regression was detected in 12.3% cases, while 15.1% patients developed a local recurrence after preoperative chemotherapy.

Mass and colleagues have published oncological outcomes for patients with and without complete pathological response. After follow-up of 5-year, local recurrence rate was 2.8% versus 9.7% for incomplete responders (26).

In our study local recurrence was recorded in 3 (33%) patients with pCR after nCRT, with median time to detection of 12 months.

In conclusion, this study has not shown reduced risk of local recurrence after neoadjuvant CRT most likely due to small number of patients. Despite our results, nCRT followed by surgery, remains the best way of treating patients with local advanced rectal cancer.

Declaration of Interests

Authors declare no conflicts of interest.

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