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ORIGINAL ARTICLE

Neoadjuvant Chemoradiation in Patient with Localy Advanced Rectal Cancer

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Summary.
Introduction. Neoadjuvant (preoperative) concomitant chemoradiotherapy (CRT) has become a standard treatment of locally advanced rectal adenocarcinoma.
Aim of the study is to analyze efficacy of neoadjuvant CRT and survival rates in patients with locally advanced rectal cancer.
Materials and methods. Retrospective study of 60 locally advanced rectal cancer patients who underwent neoadjuvant radiotherapy with or without addition of neoadjuvant chemotherapy in Clinic of Oncology of Pauls Stradiņš Clinical University Hospital from 2007 to 2012 was done.
Results. Long-course radiotherapy (45-50.4 Gy) received 52 patients. Median time from diagnosis to radiotherapy was 35.8 days. Median time to surgery was 47.7 days. Pathological complete remission (pCR) of the primary rectal cancer was not observed. Distribution by pathologic staging was as follows: 28.8% Stage I (7.7% T1N0M0), 32.7% Stage II and 38.5% Stage III. Downstaging occurred in 93.7% in concomitant chemoradiation with Ftorafur, 61.9% in combination with 5FU/LV, and 53.3% in radiation without chemotherapy. Median PFS and OS were not met. In median follow up of 22.6 month overall survival was 90.3%, and PFS – 88%.
Conclusions. Addition of chemotherapy to neoadjuvant radiotherapy is increasing tumor downstaging rate. Ftorafur in concomitant neoadjuvant chemoradiation showed increased downstaging compared to standard 5FU therapy. Response to preoperative therapy improves survival in patient with locally advanced rectal cancer.
Key words: Rectal cancer, neoadjuvant chemoradiotherapy, tumor downstaging, survival.

INTRODUCTION

Rectal cancer is one of the most common cancers. About 450 patients (20 per 100.000 inhabitants) are diagnosed in Latvia every year, 55% of patients are considered locally advanced disease (stage II-III)(5).

Preoperative radiotherapy with conventional protracted fractionation (45-50.4 Gy in daily fractions of 1.8 – 2 Gy during 5-6 weeks) with concurrent venous 5-fluorouracil (5-FU) followed by surgery at 4-8 weeks is a standard treatment of locally advanced rectal cancer in the last 10 years. Neoadjuvant chemoradiation(CRT) reduces tumor volume, increases complete R0 resection, improves local control and overall survival in advanced rectal cancer patients.Neoadjuvant CRT is more effective than adjuvant therapy in reducing local recurrence and in minimizing toxicity (10). Still there are situations in daily practice when patient's treatment is started with urgent surgery due to bowel obstruction or perforation. In these cases there are place for postoperative adjuvant CRT.

The most frequently used chemotherapy agent is venous 5-FU in continuous or short infusions. Oral fluoropyrimidines (Ftorafur, Capecitabine) have been developed as a therapeutic alternative of 5-FU, and have been shown similar efficacy and tolerability in the combined preoperative treatment (2,4).

The status of down staged pathologic stage after neoadjuvant chemoradiation is an important factor for oncologic outcomes.

Modern neoadjuvant concurrent CRT regimens have consistently demonstrated pathological complete remission (pCR) in 10% to 20% (7). Pathologic stage is the most reliable predictor of survival in patients undergoing neoadjuvant CRT and surgery. The degree of tumor regression and downstaging has been correlated to long-term survival outcomes. The pCR is associated with a very favorable prognosis (6,8,9).

AIM OF THE STUDY

The aim of study is to characterize downstaging of tumor and survival data in patients with locally advanced rectal cancer after neoadjuvant radiotherapy with or without addition of chemotherapy.

MATERIALS AND METHODS

Between January 2007 and December 2012 167 patients received adjuvant, neoadjuvant or palliative radiotherapy for rectal cancer at the Pauls Stradiņš Clinical University Hospital.

A retrospective review included 60 patients with histologically confirmed locally advanced rectal cancer who received neoadjuvant radiotherapy with or without addition of fluoropyrimidines based chemotherapy. Patients who were not considered for surgical treatment at the end of radiotherapy were excluded.8 patients (13.3%) received short-course (5 x 5Gy) neoadjuvant radiotherapy – 1 patient in 2011, 1 patient in 2010 and 6 patients in 2007. These patients were excluded from further analysis.

Data were retrieved from each patient's medical records, and included radiotherapy and chemotherapy information, clinical and pathological TNM stage, long-term outcome – progression free survival (PFS) and overall survival (OS).

Overall survival and progression free survival rates were estimated by the Kaplan-Meier method. The log-rank test was used to calculate any significant difference between the subgroups by univariate analysis. Significance levels were set at $p< 0.05$. All statistical analyses were performed by MedCalc.

RESULTS

Long-course radiotherapy (45-50.4 Gy) received 52 patients, 37 patients (71.2%) received combined chemoradiation – 16 patients (43.2%) Ftorafur p/o 400-1200 mg/d (daily during radiotherapy) and 21 patients (56.8%) short infusions with 5FU/LV (5FU 425 mg/m^2 and leucovorin 20 mg/m2 bolus d1-5 two cycles during radiotherapy).

Patients included 25 females and 27 males with a median age at diagnosis of 62.7 years (range, 34-82 years).

Median time from diagnosis to radiotherapy was 35.8 days (95% CI 23.3-46.9 days)

Median time from the end of radiotherapy to operation was 47.3 days (95% CI 38.0-49.9 days).

Local treatment response assessment. Clinical and pathological TNM data were available for all 52 patients. Pathological complete remission (pCR) of the primary rectal cancer was not observed in this study.

Patient distribution by clinical and pathological staging is shown in Table 1.

Downstaging occurred in category T or N, or both in 36 patients (69.2%), in category T – 21 patients (40.4%), but in category N – 27 patients (51.9%). Tumor AJCC stage downstaging occurred in 27 patients (51.9%) ($p<0.0001$). (Table 1)

37 patients received combined chemoradiation – 21patients received venous 5-FU/LV, 16 patients – Ftorafur per oral treatment. Downstaging occurred in 75.7% patients, compared to 53.3% in patients received neoadjuvant radiotherapy without chemotherapy. Subgroup analysis reviewed a 93.7% downstaging in patients received Ftorafur and 61.9% in patients received 5FU combined treatment (Table 2).

In 33 patient (63.5%) time from the end of radiotherapy to surgery was >42 days (6 weeks). In this group total downstaging rate were 66.7%, compared to 63.1% in patient group with early surgery (<42 days) (p=ns).

Outcomes. Survival data for all 52 patients were available.

With a median follow up of 22.6 months (3-60 months), 9 cancer relapses were identified (17.3% of all patients) – only local relapse in one patient, distant metastases in 5 patients and both local relapse and metastases in 3 patients. The median for disease-free survival and overall survival had not been reached yet.

In all patient group progression free survival (PFS) at median follow-up of 22.6 months was 88%, but overall survival (OS) was 90.3%. The median PFS and OS were not met. (Fig.1 and Fig.2)

There was seen improvement in PFS in patients with downstaging in T category –no progression was observed at median follow up 22.6 months (PFS at 22.6 months 100%). In patients without T category improvement, actuarial PFS at 22.6 months was 76.2%. (p=0.0409) (Fig.3).

Similarly, the addition of chemotherapy improve overall survival – 3 year overall survival in chemoradiotherapy group was 83.8%, but in radiotherapy only group - 67.2% (p=ns) (Fig.4)

In node positive ($pT_{any}N1$-2) stage III patients PFS at median follow-up of 22.6 months (was 72.9% (mPFS 36 months), but in stage I (T1-2N0) patients – 100% (Fig.5, Fig.6).

In patients without cancer downstaging after neoadjuvant treatment (downstaging in T or N, or both categories) PFS at median follow up of 22.6 months was 73.3% (mPFS 35 months), but in patients with observed cancer downstaging - 92.2% (Fig.7)

DISCUSSION

In this retrospective study we demonstrated our experience in rectal cancer neoadjuvant treatment.

Fluoropyrimidines based(venous 5FU, Capecitabine, Ftorafur) neoadjuvant chemoradiation is widely used in clinical practice in patient with locally advanced rectal cancer. The main priority is to achieve maximum tumor regression without increased toxicity. The most frequently used fluoropyrimidines in CRT settings are venous 5FU. However, infusional regimens are time-consuming, inconvenient and uncomfortable for the patient, and require regular hospital visits and sometimes hospitalization. They are also often associated with venous access-related

complications such as infection, sepsis, thrombosis and blockage. Therefore, efforts have been made to identify alternative strategies to 5FU in this setting. The use of oral fluoropyrimidines such as Ftorafur has the potential to represent an appealing alternative. Ftorafur alone and combined with radiotherapy has not been sufficiently developed as a neoadjuvant treatment of rectal cancer, and our study provides important information of this setting. Preliminary results have been described previously in clinical case-control studies revealed low toxicity and high downstaging rates (2,3,4).

In preoperative radiotherapy without chemotherapy and delayed surgery downstaging rates of 18% have been reported (1). However, preoperative CRT achieves downstaging rates of 65% (2,11). In our study, downstaging (T or N, or both) was observed in 75.7% of the patients received 5FU containing CRT and in 93.7% of patients received Ftorafur containing CRT , which compares favorably with the best results of preoperative CRT with venous 5FU.

28.8% of patients achieved the earliest stage (Stage I), but complete pathological remission was not achieved in this study.

We found that survival outcomes after preoperative chemoradiotherapy for locally advanced rectal cancer are correlated with treatment response. Final pathologic

stage is an early response indicator for long-term outcomes that provides better prognostication than does the clinical stage. Patients who achieve pathological stage I have excellent prognosis with low risk for local or distant recurrence.

The inclusion of different multimodal treatments into the surgical oncologic concept,adapted to the tumor location and stage and to an individual patient's risk factors, is mandatory. In the future, clinicopathological and molecular features as well as accurate preoperative imagingwill take an important and integrative part in multimodality treatment of rectal cancer.

CONCLUSIONS

1. Addition of chemotherapy to neoadjuvant radiotherapy is increasing tumor downstaging rate.
2. Ftorafur in concomitant neoadjuvant chemoradiotherapy showed increased downstaging compared to standard venous 5FU/LV therapy.
3. Response to preoperative therapy (pathological stage) improves survival in patient with locally advanced rectal cancer.

Conflict of interest: None

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Table 1. Patient distribution by clinical and pathological stage

		Clinical stage, (%)	Pathological stage, (%)	T-test
All patients	Stage I	2 (3.9%)	15 (28.8%)	
	Stage II	6 (11.5%)	17 (32.7%)	p<0.0001
	Stage III	44 (84.6%)	20 (38.5%)	

Table 2. Downstaging in T category and N category in chemoradiation group versus radiotherapy alone (n=52)

Down-staging	Radio-therapy (15 patient) No (%)	Radio-therapy + 5FU/LV short infusion (21 patient); No (%)	Radio-therapy + Ftorafur (16 patients); No (%)	
T or N	8 (53.3)	13 (61.9)	15 (93.7)	p=0.03
T	6 (40)	6 (28.6)	9 (56.2)	p=ns
N	5 (33.3)	11 (52.4)	11 (68.7)	p=ns

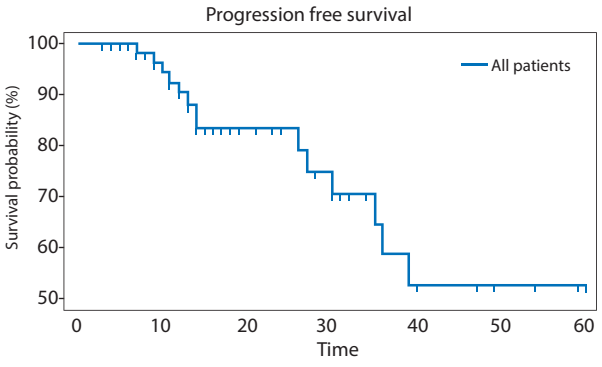

Fig. 1. Progression free survival. Median PFS: not met. At median follow-up of 22.6 months PFS 88% (n=52)

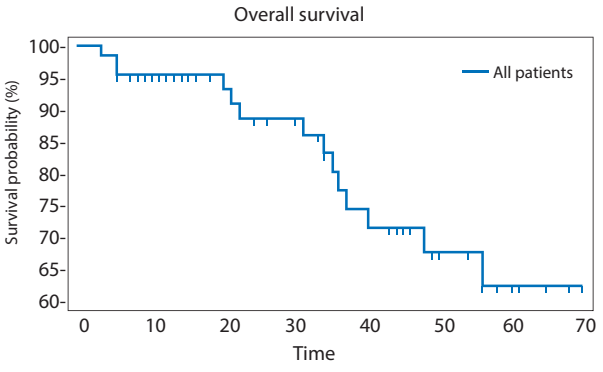

Fig. 2. Overall survival. Median OS: not met. At median follow-up 22.6 months OS 90.3% (n=52)

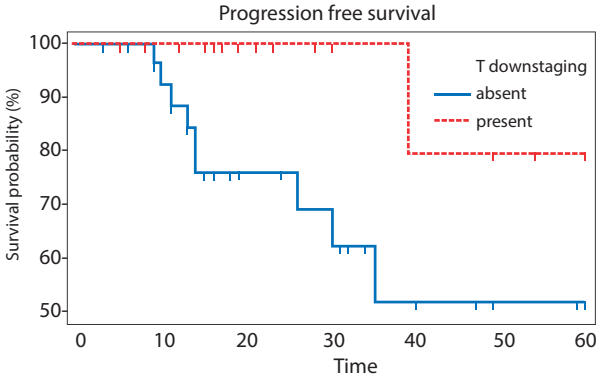

Fig. 3. Progression free survival, according to T downstaging. (p=0.0409; HR 3.73; 95% CI 1.0558-13.2318 (n=52))

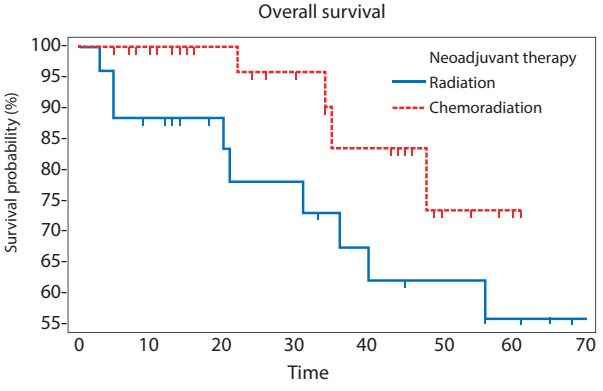

Fig. 4. Overall survival, according to addition of chemotherapy to radiotherapy; 3yOS 83.8% in chemoradiotherapy group, 3yOS 67.2% in radiotherapy only group; p=0.09, HR 2.57, 95%CI 0.84-7.85 (n=52)

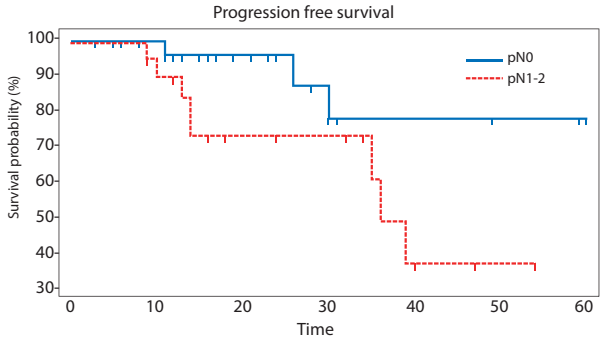

Fig. 5. PFS according to pathological node status. Median PFS in pN1-2 patients - 36 month. PFS at median follow-up 22.6 months in node positive patients 72.9%, but in node negative patients 96.2%. (p=0.048; HR 0.29; 95%CI 0.09-0.98)

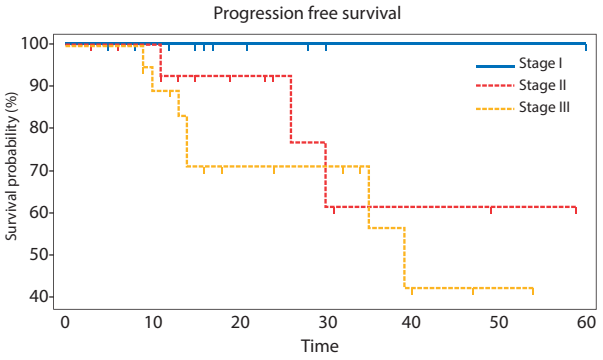

Fig. 6. PFS according to pathological stage. In Stage III patients (n=20): median PFS 36 months

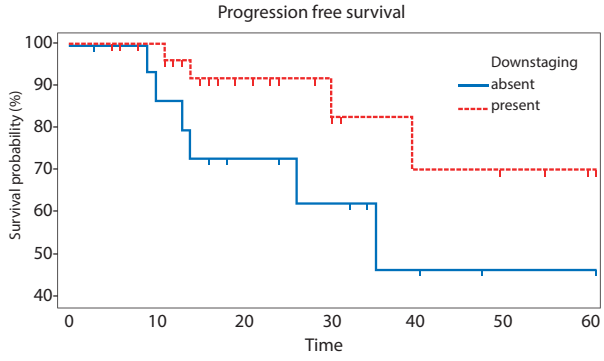

Fig. 7. PFS according to cancer downstaging in T or N, or both categories. In patients without cancer downstaging after neoadjuvant treatment PFS at median follow up of 22.6 months was 73.3% (mPFS 35 months), but in patients with cancer downstaging 92.2%. (p=0.08; HR 3.11; 95%CI 0.84-11.53)