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NEOADJUVANT CHEMORADIOTHERAPY IN THE DOWNSTAGING OF LOCALLY ADVANCED RECTAL CANCER AND ITS IMPACT ON PROGRESSION–FREE SURVIVAL

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Summary
Introduction. The standard treatment for locally advanced rectal cancer (LARC) is neoadjuvant chemoradiotherapy (NACRT) followed by radical surgery, which allows to reduce local recurrence, downsize the tumor and facilitate its R0 resection.
Aim of the study. The aim of this study was to evaluate the downstaging of LARC after NACRT and to assess the impact of downstaging on progression–free survival (PFS).
Materials and methods. 65 patients diagnosed with LARC from 2012 to 2018, who received NACRT with subsequent radical surgery were identified in the Pauls Stradins Clinical University Hospital in Riga and included in this retrospective study. Average follow–up period was 31 months. Data were analysed with SPSS Statistics 22.0, Wilcoxon signed–rank test and Kaplan–Meier survival analysis were performed.
Results. Overall, 66.7% (n=40) of patients experienced a downstaging in response to NACRT, of which 37.5% (n=24, p=0.004) had a downstaging of T and 63.3% (n=38, p=0.0001) of N.
12–month PFS was 87.8%, 24–month PFS – 66.1% and 3–year PFS – 62.7%, median PFS (mPFS) was not met. 3–year PFS of those patients treated with intravenous 5FU/LV boluses was significantly higher (76.5%) than those who received oral tegafur (45.6%, mPFS 32 months), p=0.038. 3–year PFS of patients with downstaged T was 85.9%, compared to 52.1% without it; mPFS not met, p=0.04. Similarly, 3–year PFS of patients with downstaged N was 71.5%, compared to 43.3% without it (mPFS 24 months), p=0.112. Lymphatic and vascular invasion were associated with significantly lower PFS compared to the patients with absent lymphatic and vascular invasion (p=0.0001 and p=0.014, respectively), while perineural invasion did not show any impact on PFS. Age at diagnosis, tumor location, type of surgery and adjuvant chemotherapy did not have a significant impact on PFS.
Conclusions. Results confirm the efficacy of NACRT in LARC in the downstaging of T and N. Downstaging of LARC, intravenous chemotherapy and absence of lymphovascular invasion are associated with significantly increased PFS.
Keywords: locally advanced rectal cancer, neoadjuvant chemoradiotherapy, downstaging

INTRODUCTION

The incidence of rectal cancer in the European Union is 12–25 cases per 100 000 population, i.e. 12 500 new cases every year on average. (4) In Latvia, the number of new cases is around 400 per year. (13) Nearly half of the patients diagnosed with rectal cancer are at stage 2 or 3, known as locally advanced rectal cancer (LARC). (9)

The mainstay of treatment for rectal cancer is the resection, however maintenance of clear resection lines (R0) is not always possible in case of stage 2 or 3 cancer due to the extensive spread of the tumour. Therefore surgical management bears risk for local recurrence, as well as resection of the rectal sphincter in case of distal localization of the tumour. To tackle these risks neoadjuvant chemoradiotherapy (NACRT) had been developed, which allows for the reduction of the tumour size, sphincter sparing surgery in case of distal rectal cancer, increased R0 resection rates, as well as decreased rates of intraoperative dissemination and local recurrence. NACRT consists of 5–6 weeks of radiotherapy delivered in 25–28 fractions of 1,8–2 Gy each with concomitant administration of chemotherapy, mostly fluoropyrimidines, e.g. 5–FU or capecitabine. The resection of the tumour then follows after 8–10 weeks on average.

The desired outcome of the NACRT is downstaging, defined as either the decrease in the tumour size and the involvement of regional lymph nodes or pathological complete remission (pCR). Downstaging is evaluated preoperatively by MRI and postoperatively in the resected specimen. Response to NACRT is an important prognostic tool for local recurrence risk and survival.

AIM OF THE STUDY

The aim of this study was to compare the TNM stage of LARC before and after NACRT and subsequent surgery and to assess the impact of treatment on progression–free survival (PFS).

MATERIALS AND METHODS

This research is a retrospective analysis of patients treated in Pauls Stradins Clinical University Hospital Clinic of Oncology from January 2012 to December 2018 with histologically approved rectal cancer (code C20 in ICD–10). The ambulatory history records were revised and patients with locally advanced disease who had received course of neoadjuvant chemoradiation with following resection of rectum were included. Patients with incomplete course of chemoradiation and/or those who did not receive further surgical treatment were excluded. The inclusion criteria were met in 65 patients. Average follow–up period was 31 months.

Using the ambulatory card records the following data were obtained: sex, age at the diagnosis, the date of the diagnosis, cTNM, the localization of the tumour according to radiological data (according to the distance between lower pole of the tumour and the anus, tumors were divided into high (11–15 cm), middle (6–10 cm) and low (≤5 cm)), the dates of the start and the end of the chemoradiation, the mode of chemotherapy (drug used and route of administration), the date of surgery, the type of surgery (low anterior resection, abdominoperineal resection or local excision), pTNM, lymphatic, vascular and perineural invasion, the status of resection lines, pCR, adjuvant chemotherapy, progression (including the date and mode of remission (local or metastatic)), and the date of the last visit. The data of mesorectal fascia (MRF) invasion and preoperative MRI could not be obtained due to the lack of thereof.

The data were gathered in Microsoft Excel 2007. The following parameters were calculated: time from the diagnosis to the start of NACRT, time from the completion of NACRT to surgery, time to progression. Time to progression was calculated using the dates of last visits and the dates of investigations proving progression. The time to progression was used in calculations of progression–free survival (PFS). Only the data available were used in calculations, thus incomplete information about certain parameters led to decrease in total number of patients in whom the parameter was analyzed (valid percent).

The statistical analysis was carried out using IBM SPSS Statistics 22.0, descriptive statistics, Wilcoxon signed–rank test and Kaplan–Meier survival analysis were obtained. A p–value of less than 0.05 was deemed as statistically significant.

RESULTS

Descriptive statistics. 65 patients were included in the statistical analysis, of which 33 (50.8%) were males and 32 (49.2%) were females. Mean age at diagnosis was 64. In the majority of patients tumor was localized in the lower third of the rectum (n=33, 57.9%), while the rest of the patients had middle (n=16, 28.1%) and high (n=8, 14.0%) tumor localization. The mean time from diagnosis to treatment was 39 days and the mean time from the completion of NACRT to surgery 12 was weeks. Most patients (n=44; 68.8%) were treated with low anterior resection (LAR), while 28,1% (n=18) underwent abdominoperineal resection (APR). Local excision was feasible only in two patients (3.1%). R1 rates were 10.8% (n=7). Pathological complete response (pCR) to NACRT was observed in 2 (3.1%) cases. Adjuvant chemotherapy was indicated and administered to 35 (53.8%) patients. 16 (24.6%) patients experienced a progression of the disease during the follow–up time, of which 5 (7.7%) had local recurrence and 11 (16.9%) had distant metastases.

Patients were divided into 4 groups according to the neoadjuvant chemotherapy regimen:

1) *Mayo clinic* regimen or 5–fluorouracil and leucovorin bolus on the first and the last week of radiation (5FU/LV) was administered to 29 (45.3%) patients;
2) 22 patients (34.4%) received oral tegafur;
3) Continuous 5FU infusion was given to 12 (18.8%) patients;
4) Only one (1.6%) patient received oral capecitabine and was excluded from further analysis.

Downstaging. 40 (66.7%) patients experienced a downstaging in response to NACRT with statistically significant difference between clinical and pathological TNM stage (p=0.0001). (Fig. 1) Similarly, 24 (37.5%) patients experienced a downstaging of T stage with a significant difference between clinical T (cT) and pathological T (pT) (p=0.004). (Fig. 2) Lymph node status downstaged in 38 (63.3%) patients with a significant difference between clinical N (cN) and pathological N (pN) (p=0.0001). Most patients (n=51, 80.9%) had positive lymph node status (N1–N2) before the NACRT. 46 (75.4%) were pathologically N0 (pN0) on posttreatment evaluation. (Fig. 3)

Kaplan–Meier progression–free survival analysis. Median progression–free survival (mPFS) was not met. 12–month PFS was 87.8%, 24–month PFS – 66.1% and 3–year PFS – 62.7%.

When analyzing the impact of neoadjuvant chemotherapy regimen on PFS, oral capecitabine group was excluded from the analysis due to small number of patients (one patient without the progression during the follow–up). Median PFS in oral tegafur group was 32 months, 12–month PFS 79.0%, 24–month PFS 53.2% and 3–year PFS – 45.6%. In the 5FU/LV group mPFS was not met, 12–month was PFS 92.8%, 24 and 3–year PFS – 76.5%. Continuous 5FU group did not meet mPFS as well, with only one registered progression during the follow–up and 12–month PFS of 90.0%. The 3–year PFS in oral tegafur group was lower than in 5FU/LV with statistically significant difference between the groups (p=0.038). (Fig. 4)

The 12–month PFS of patients who experienced a downstaging of T after NACRT was 95.5%, while 24–month and 3–year PFS was 85.9%. By contrast, the 12–month PFS of patients with no downstaging was significantly lower, with 12–month PFS of 86.1%, 24–month PFS 57.9% and 3–year PFS – 52.1% (p=0.04) (Fig. 5)

Similarly, 12–month PFS of patients who experienced a downstaging of lymph node status after NACRT was 88.5%, while 24–month and 3–year PFS was 76.3% and 71.5%, respectively. Conversely, patients who did not exhibit the downstaging of N status had lower 12–month PFS (83.3%), while 24–month and 3–year PFS was only 43.3%, reaching a mPFS at 24 months. Comparing the 3–year PFS of the patients with downstaged lymph node status to those without the evidence of downstaging, the threshold of statistical significance was not reached (p=0.112). (Fig. 6)

In patients who responded to NACRT with a TNM stage decrease, 12–month and 24–month PFS was higher (82.8% and 47.4%, respectively), compared to non–responders with 12–month PFS of 88.6%, 24–month PFS – 75.9% and 3–year PFS 70.8% (p=0.152).

Analyzing the impact of pathological T stage on PFS, a correlation between the higher T stage and lower PFS was noted, but significant difference was only observed between the impact of pathological T2 (pT2) and pathological T4 (pT4) on PFS (p=0.032). (Fig. 7)

Analyzing the impact of pathological TNM stage on PFS, patients with stage I had 12–month and 24–month PFS of 90.0%; stage II – 12–month PFS was 84.0%, 24–month PFS – 62.4% and 3–year PFS – 53.5%; stage III patients had 12–month PFS of 85.1%, 24–month and 3–year PFS – 48.6%. When pathological stages compared, 3–year PFS of patients with pathological TNM stage I was significantly higher than stage II (p=0.026), and stage III (p=0.029), with no significant differences between stages II and III.

Lymphovascular invasion was associated with significantly lower PFS compared to the patients with absent lymphovascular invasion. Patients with lymphatic invasion had significantly lower 12–month and 24–month PFS (65.6% and 49.2%, respectively) compared to the patients with no proven lymphatic invasion (12–month and 24–month PFS of 100% and 83.3%, respectively, p=0.0001). Median PFS in patients with lymphatic invasion was 16 months only. (Fig. 8)

Patients with vascular invasion had significantly lower 12–month and 24–month PFS (55.6%) compared to the patients without vascular invasion (12–month and 24–month PFS of 92.4% and 77.0%, respectively, p=0.014). Median PFS in patients with vascular invasion was not met. (Fig. 9) Perineural invasion did not show any impact on PFS.

Patients with positive resection margins experienced lower PFS (12–month and 24 month PFS – 71.4% and 35.7%, respectively) with mPFS of 22 months compared to R0 patients with 12–month and 24 month PFS of 87.9% and 85.4%, respectively (p=0.096).

Age at diagnosis, tumor location, type of surgery and the administration of adjuvant chemotherapy did not show a significant impact on PFS.

DISCUSSION

Some of the clinically relevant data regarding LARC could not be analyzed due to lack of thereof, i.e. MRI findings after the NACRT and involvement of mesorectal fascia on primary staging. Moreover, data from pathology reports were often incomplete and lacked details about lymphovascular and perineural invasion, and, as it is regarded as important prognostic factor for PFS (7), the shortage of data had an impact on the accuracy of the results of the study.

The proportion of LAR (68.8%) and APR (28.1%) as a surgical treatment modality in our study was similar to the results in other studies, where LAR is performed in 70% of LARC patients on average. (6) Our study showed low pCR rate (3.1%) compared to 20–25% in other studies, which might be explained by relatively small patient group available for analysis. (4, 6) R1 rates in our study were 10,8% compared to 4% in Sirohi, B. et al (2014) and 13.3 % (elective 10.4%; emergency 23.6%) in Khan, M.A.S et al (2015). (12, 5) Positive resection lines in turn have effect on the local and distant (metastatic) progression rates, which in our study were 7.7% and 16.9% respectively, while in a study of Farhat, W. et al (2019) 5–year recurrence rate was 44.6% (without a distinction between local and distant recurrences) and a 5–year recurrence rates reported by meta–analysis by Pahlman were between 23% and 41% with a mean of 27%. (3, 8) These differences could be partly explained by the short average follow–up time in our study (31 months).

The use of tegafur is not common worldwide for treatment of LARC. Tegafur is mostly used in Eastern Asia countries (China, Japan, Taiwan, etc.) as well as particular European countries including Latvia. In Latvian clinics oral tegafur is more commonly used than oral capecitabine, and, although both being prodrugs of 5FU, their metabolism is different, therefore they cannot be regarded as equal when comparing studies. Wide use of tegafur in our study (34.4%) can be explained by cost–effectiveness and convenient use (oral over intravenous), which leads to high compliance. (14) Despite being a first–choice regimen, continuous 5FU infusion was used only in 18.8%, while 5FU/LV boluses were administered in 45.3%. However, there is a tendency to choose continuous infusion over the 5FU–LV regimen over the last years.

Downstaging of T was observed in 37.5% in our study (equally in both oral tegafur and 5FU/LV bolus groups) compared to 46–53% in a study of Calvo, F.A et al (2001) where oral tegafur was associated with higher rates of T downstaging than 5FU/LV bolus regimen. (2) Downstaging of lymph node status in our study was observed in 63.3%, whereas in a study of Calvo, F.A et al (2006) only in 42%, using 5FU/LV bolus as NACRT regimen. (1) The discrepancy can be explained by chemotherapy regimens used in NACRT (we analyzed three modalities compared to one in Calvo, F.A. et al), as well as differences in cN staging on radiographical imaging in two different countries and time periods. According to Quah, H. M. et al (2008) and Rödel, C. et al (2005), pTNM and the presence of downstaging in response to NACRT are the best prognostic factors for PFS in LARC. (10, 11) Similarly, our study proves

the association between lower pTNM, pT and a downstaging of T with longer PFS rates.

CONCLUSIONS

1. Neoadjuvant chemoradiotherapy decreases the stage of locally advanced rectal cancer in majority of patients. Notable decrease in tumour mass and regional lymph node involvement supports the efficacy of and the need for NCRT in treatment of LARC. However, some patients do not benefit form NCRT and there are no predictive tools to identify these individuals before initiation of the therapy to avoid overtreatment.
2. Response to NCRT (decrease in pTNM, pT and T) is associated with increased progression–free survival.
3. Lymphovascular invasion is associated with significantly lower PFS.
4. Use of oral tegafur is associated with significantly lower PFS compared to intravenous 5FU, therefore more research evaluating the effectiveness of tegafur is warranted. Continuous 5FU infusion with concurrent radiotherapy should be used as the first–line therapy in patients without contraindications as per guidelines.

Conflict of interest: None

	Clinical stage		Pathological stage	
	n	%	n	%
0			2	3,3
1	1	1,6	17	27,9
2	11	17,5	27	44,3
3	51	81,0	15	24,6
p value	p=0.0001			

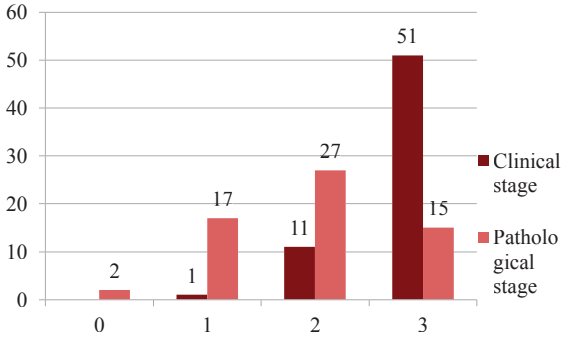

Fig. 1. TNM stage before and after NACRT (downstaging of TNM), ***Wilcoxon signed–rank test***

	cT		pT	
	n	%	n	%
0			2	3,1
1			3	4,7
2	9	13,8	20	31,3
3	48	73,8	31	48,3
4	8	12,3	8	12,5
p value	p=0.004			

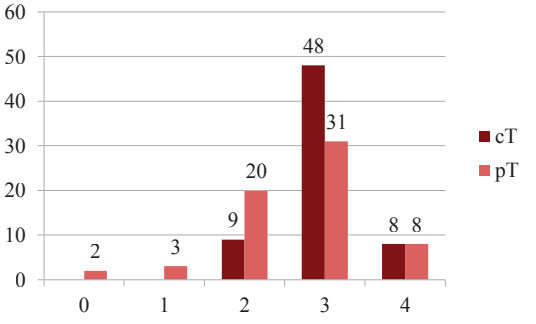

Fig. 2. T stage before and after NACRT (downstaging of T), ***Wilcoxon signed–rank test***

	cN		pN	
	n	%	n	%
0	12	19,0	46	75,4
1	38	60,3	14	23,0
2	13	20,6	1	1,6
p value	p=0.0001			

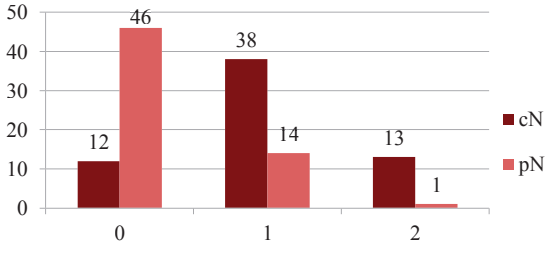

Fig. 3. N stage before and after NACRT (downstaging of N), ***Wilcoxon signed–rank test***

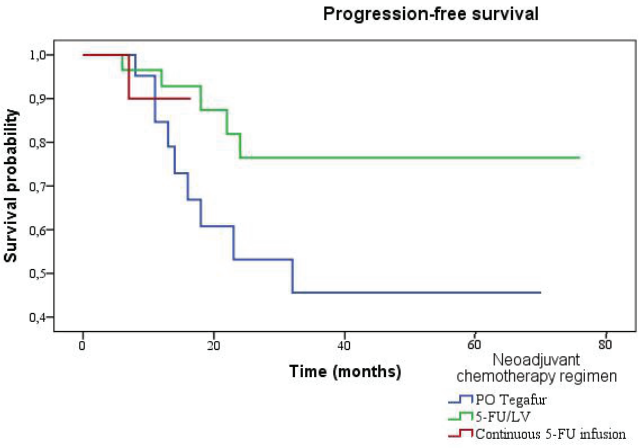

Fig. 4. PFS according to the neoadjuvant chemotherapy regimen, *Kaplan–Meier* survival curve

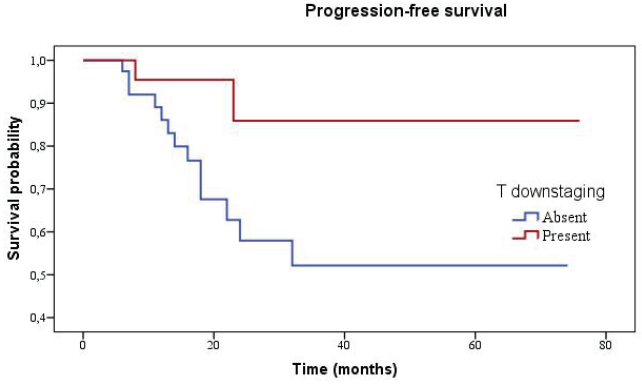

Fig. 5. PFS according to the presence of the downstaging of T, *Kaplan–Meier* survival curve

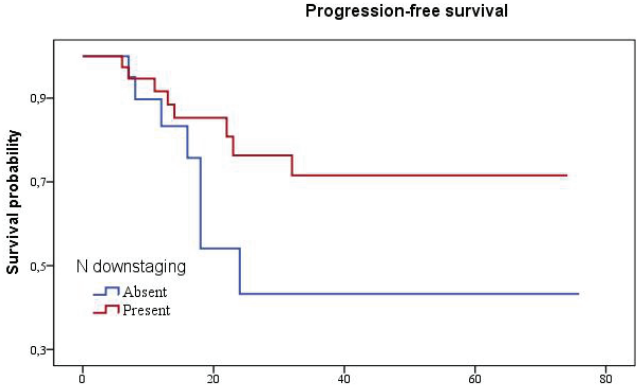

Fig. 6. PFS according to the presence of the downstaging of N, *Kaplan–Meier* survival curve

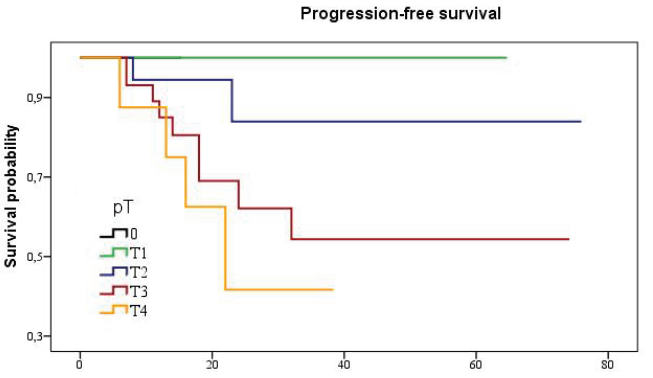

Fig. 7. PFS according to the presence of pathological T stage, *Kaplan–Meier* survival curve

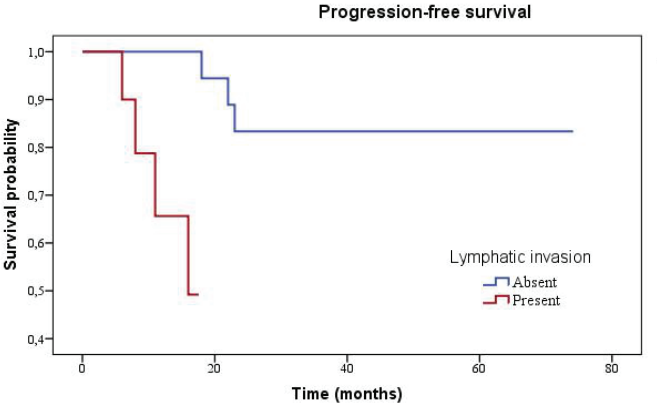

Fig. 8. PFS according to the lymphatic invasion, *Kaplan–Meier* survival curve

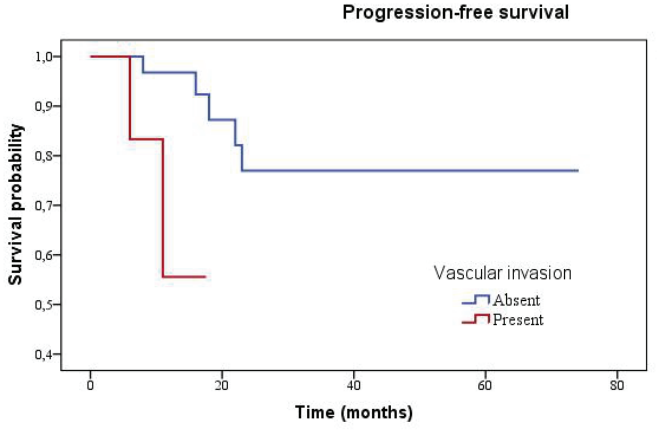

Fig. 9. PFS according to the vascular invasion, *Kaplan–Meier* survival curve

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