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ORIGINAL ARTICLE

The potential benefit of adjuvant chemotherapy in locally advanced rectal cancer treated with neoadjuvant chemoradiotherapy is not predicted by tumor regression grade

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Abstract

Introduction Recommended treatment for locally advanced rectal cancer (LARC) is neoadjuvant chemoradiotherapy (NACRT) followed by surgery and total mesorectal excision (TME). The role of adjuvant chemotherapy (ACT) in this regimen is still debated. Assessment of Dworak's tumor regression grade (TRG) after NACRT could potentially select patients who might benefit from ACT.

Materials and methods Data for patients who underwent NACRT and TME for LARC between 2007 and 2014 were retrieved from the Bordet Institute database. Overall survival (OS) and disease-free survival (DFS) were calculated for the whole population, according to whether or not they received ACT, and according to TRG.

Results We included 74 patients (38 males) with a median age of 62.7 years (33–84 years). AJCC stage cIIIb disease was the most frequent (73%). Pathologic complete response (pCR) was achieved in 13 patients (17.6%). ACT was administered to 42 patients (56.8%). Five-year OS and DFS of patients who received ACT or not were 92 and 84.5% (p = ns), and 79.9 and 84.8% (p = ns), respectively. OS was related to TRG (cut-off value of 3) ($p = 0.001$). ACT administration was not correlated with improved outcomes in any TRG groups.

Conclusion TRG is a prognostic factor for both OS and DFS but does not appear to have a significant benefit for the selection of patients with LARC treated with NACRT who might benefit from the administration of ACT. Prospective randomized trials with larger populations are needed to identify factors that predict which patients may benefit from the administration of ACT.

Keywords Rectal cancer · Neoadjuvant chemoradiotherapy · Tumor regression grade · Dworak · Overall survival · Disease-free survival

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Introduction

Rectal cancer is newly diagnosed in approximately 39,910 per year in the USA [1]. At diagnosis, half of patients with rectal cancer have locally advanced stage (American Joint Committee on Cancer [AJCC] stage II or III) disease, defined as cancer in which tumors are infiltrating the perirectal fat (T3) or beyond (T4) and/or node-positive disease (stage III) [2]. Preoperative staging is of extreme importance due to differences in treatment modalities according to stage. The current standard treatment for locally advanced rectal cancer (LARC) is neoadjuvant radiotherapy combined with chemotherapy (NACRT) followed by oncologic resection with total mesorectal excision (TME) [3]. The role of adjuvant chemotherapy (ACT) as part of this strategy is still controversial. While the Dutch guidelines preclude the administration of ACT [3], the National Comprehensive Cancer Network (NCCN) guidelines from 2017 recommend the routine use of ACT in locally advanced rectal cancer treated with NACRT followed by oncologic resection and TME, independently of the pathologic stage (ypTNM stage) [4]. The European Society for Medical Oncology (ESMO) guidelines recommend ACT in all stage III patients and in stage II patients with high risk factors such as perineural invasion, and lymphatic and vascular embolism [5]. Currently, there is no definitive tool for selection of patients who might benefit from ACT.

Tumor regression grade (TRG) has been reported to be a potential test for measuring the effect of NACRT. TRG is determined by histopathologic examination of the resected operative specimen. It provides important prognostic information due to the fact that complete or subtotal tumor regression has been shown to be associated with better patient outcomes [6–9]. The value of TRG for the selection of patients who might benefit from ACT is not well established.

The aim of this retrospective study was to evaluate the role of TRG for the selection of patients treated for LARC with NACRT followed by surgical resection (TME) who might benefit from ACT.

Materials and methods

Design and population

A retrospective search was performed in our institutional prospective database (OriBase) for all patients diagnosed with primary non-metastatic LARC between January 2007 and December 2014, who were treated with NACRT followed by rectal resection and TME with or without ACT. Patients with proximal rectal cancer treated with anterior rectal resection and partial mesorectal excision (PME), and patients who received neoadjuvant chemotherapy before NACRT, were excluded. This retrospective study was approved by the ethics committee at Jules Bordet institute.

All patients underwent complete evaluation, including a physical examination with digital rectal examination (DRE). The diagnosis was confirmed by means of endoscopic biopsy. All patients underwent blood testing for the carcinoembryonic antigen (CEA) tumor marker. Total colonoscopy was performed to detect synchronous lesions. Clinical staging was determined by thoracic-abdominal computed tomography (CT) scan, endorectal ultrasound (EUS), and pelvic magnetic resonance imaging (MRI) in all patients. Positron emission tomography (PET)-CT scan was only performed if metastatic disease was suspected. Clinical and pathologic staging (cTNM, pTNM) were determined according to the AJCC TNM staging system, 7th edition [10].

Neoadjuvant treatment

All patients were assigned to NACRT. Preoperative radiotherapy consisted of 45–50 Gy, delivered in 25 fractions to the rectum and nodal areas. A simultaneous integrated boost (SIB) was also delivered based on the tumor gross volume (GTV) up to 50 Gy in 25 fractions. 5-Fluorouracil (5-FU) was administered as a continuous intravenous infusion at a dose of 250 mg/m^2 for 5 days per week during the 5 weeks of radiotherapy.

Surgery

Rectal surgical resection was performed by laparoscopy using oncologic rectal resection and TME according to current guidelines. The standard operation performed was lower anterior resection (LAR) and, in cases where negative longitudinal or circumferential margins could not be achieved, abdominoperineal resection (APR) was performed. Conversion to laparotomy was performed in cases involving technical difficulties.

Follow-up and adjuvant chemotherapy

Follow-up was conducted at 3-month intervals during the first 2 years after surgery, at 6-month intervals during the next 3 years, and annually thereafter. At each follow-up visit, a series of blood test were performed, including a serum CEA assay. Chest-abdomino-pelvic CT was performed every 3 months for the first 2 years, then every 6 months for 3 years, and annually thereafter. PET/CT scan was done only if recurrence was suspected. Chemotherapy was started as soon as possible after the patient recovered from surgery.

Tumor regression grade evaluation

The department of pathology assessed tumor response to NACRT using standardized 5-point tumor regression grading, as described by Dworak et al. [11]. The grading was as follows: grade 0, no regression; grade 1, minor regression (dominant tumor mass with obvious fibrosis in 25% or less of the tumor mass); grade 2, moderate regression (dominant tumor mass with obvious fibrosis in 26 to 50% of the tumor mass); grade 3, good regression (dominant fibrosis outgrowing the tumor mass; more than 50% tumor regression); and grade 4, total regression (no viable tumor cells, only fibrotic mass).

Statistical analysis

The data were analyzed with the statistical software SPSS v25. Clinical and histological parameters were compared in the group receiving chemotherapy with the Mann Whitney *U* test for continuous data and with the Chi-Square test for categorical variables. Overall survival (OS) was defined as the time from the date of surgery to the date of death from any cause. Disease-free survival (DFS) was considered to be the time from the date of surgery to the date of detection of recurrent disease or death, whichever occurred first. Patients with one recurrence who were disease free at the end of follow-up with a DFS of more than 5 years were also considered free of relapse. Survival curves were generated using the Kaplan-Meier method, and the effects of both TRG and ACT on survival were compared separately using Cox regression analysis. Based on TRG scores, two patient groups were created: patients with poor response vs patients with good response (0–2 vs 3–4, respectively), and the effect of ACT on survival was evaluated using Cox regression analysis. A p value of < 0.05 was considered statistically significant.

Results

Patient characteristics

A total of 74 patients with LARC treated with neoadjuvant CRT followed by TME were identified. Baseline patient characteristics are shown in Table 1. There were 38 males (51.4%) and 36 females (48.6%). The mean age was 62.7 years (median 63, range 33–84). According to EUS and MRI preoperative workup, 81.1% of patients were diagnosed with clinical stage III disease, and 18.9% were diagnosed with clinical stage II disease. A total of 69 patients (95.2%) underwent laparoscopic surgery. In 4 patients, surgery was converted to open surgery, 3 due to adhesions, and 1 due to very large tumor size. In 1 patient, surgery was started as open surgery because the patient had extensive surgical history. Most patients (65/74, 87.8%) underwent low anterior resection (LAR)

Table 1 Basic characteristics of patients with LARC who received neoadjuvant CRT followed by TME

Characteristics	LARC
Number	74 (100%)
Age (mean)	62.7 years (median 63; range 33–84)
Sex	
Male	38 (51.4%)
Female	36 (48.6%)
ASA score	
ASA I	10 (13.5%)
ASA II	56 (75.7%)
ASA III	8 (10.8%)
Clinical staging	
IIa	13 (17.57%)
IIb	1 (1.35%)
IIIa	5 (6.8%)
IIIb	54 (73%)
IIIc	1 (1.4%)
Surgery	
Laparoscopic	69 (93.2%)
lap converted to open	4 (5.4%)
LAR	65 (87.8%)
APR	9 (12.2%)
Pathologic stage	
0	12 (16.2%)
Ia	28 (37.8%)
IIa	14 (18.9%)
IIIa	6 (8.1%)
IIIb	12 (16.2%)
IIIc	2 (2.7%)
Retrieved LN (mean)	13.5 (median 12; range 3–37)
Invaded LN (mean)	0.9 (median 0; range 0–12)
Differentiation	
Poorly	5 (6.76%)
Moderately	40 (54.06%)
Well	21 (28.38%)
Missing	8 (10.8%)
Lympho-vascular embolism	10 (13.5%)
Perineural invasion	10 (13.5%)
Tumor regression grade	
0	5 (6.8%)
1	6 (8.1%)
2	16 (21.6%)
3	34 (45.9%)
4	13 (17.6%)
Adjuvant chemotherapy	
Yes	42 (56.8%)
No	32 (43.2%)
Median follow-up (months)	64
Relapse	15 (20.27%)
Loco-regional	5 (6.76%)

Table 1 (continued)

Characteristics	LARC
Pulmonary	4 (5.4%)
Liver	3 (4.05%)
Multiple	3 (4.05%)
Death	16 (21.6%)

ASA American Society of Anesthesiologists score, *LAR* low anterior resection, *APR* abdomino-perineal resection, *LN* lymph node, *CRT* chemoradiotherapy, *LARC* locally advanced rectal cancer, *TME* total mesorectal excision

with sphincter preservation. Of these, 62 (95.4%) had a diverting ileostomy, and the remainder had a definitive colostomy (4.6%) without digestive continuity restoration.

Pathology and TRG

A total of 40 patients (54%) had moderately differentiated adenocarcinoma, 10 patients (13.5%) had lymphatic and/or venous invasion, and 10 (13.5%) had perineural invasion. The median number of retrieved lymph nodes was 13 (range; 3–37).

Pathologic complete remission (pCR) (ypT0N0) was obtained in 13 patients (17.6%), 6 of whom received ACT and 7 who did not. A TRG of 3 was observed in 34 patients (45.9%), and 21 (62%) of these received ACT. Similarly, 16 patients (21.6%) had a TRG of 2 and 11 (68.8%) of them received ACT. A TRG of 0–1 was observed in 11 patients (14.9%), 8 of them (72.8%) did not receive ACT.

Adjuvant chemotherapy

ACT was administered in 42 patients (56.8%). The most frequently administered regimen was FOLFOX (leucovorin, 5-FU, oxaliplatin) (Table 2). The median number of administered cycles was 8, with a range of 3 to 12 cycles. The median follow-up period was 64 months (range; 0.82–126 months).

Outcomes

There were 15 cases (20.27%) of relapse, including 5 cases (6.7%) with loco-regional recurrence, and 10 cases (13.2%) with distant recurrence, including 4 cases with pulmonary metastases, 3 cases with liver metastases, and 3 with multiple metastatic locations. At the end of follow-up, we recorded 16 death events (21.6%).

The median follow-up was 64 months. Overall 5-year OS and DFS rates were 88.7 and 82%, respectively (Fig. 1 a, b).

Table 2 Type of adjuvant chemotherapy

Number	42
FOLFOX	24 (57.1%)
5-FU + leucovorin	8 (19%)
Capecitabine	4 (9.5%)
5-FU	3 (7.1%)
Other type	3 (7.1%)
No. of cycles	7.65 median 8 cycles (3–12)

FOLFOX leucovorin, 5-fluorouracil, oxaliplatin; *5-FU5* fluorouracil.

Outcomes according to administration of ACT

Using Cox regression curve analysis, ACT administration was not shown to improve outcomes for OS ($p = 0.49$ HR 1.42 [0.52–3.88]) or DFS ($p = 0.812$ HR 1.12 [0.438–2.86]). For patients who did not receive ACT (control group) and those who did receive ACT, Kaplan-Meier survival curves showed 5-year OS of 84.8 and 92% (log-rank 0.49) (Fig. 2a), and 5-year DFS of 84.8 and 79.9% (log-rank 0.812) (Fig. 2b), respectively.

The comparison between subgroups of patients depending on the administration of ACT or not (Table 3) showed significant statistical differences in terms of age, clinical staging, and type of surgery. ACT group patients were younger, 59.5 years compared to 67 ($p = 0.008$), had more advanced disease with more stage IIIb disease, 37 (88.1%) compared to 17 (53.1%) ($p = 0.003$), and had less abdomino-perineal resection, 1 (2.4%) compared to 8 (25%) ($p = 0.013$) in the group that did not receive ACT. However, both groups were similar regarding all other epidemiologic and laboratory characteristics, including p-Stage and TRG distribution.

Outcomes according to TRG

The TRG results from the pathology reports were correlated with survival. TRG was associated with better outcomes for both OS ($p = 0.003$; HR 5.627 CI [1.809–17.51]) and DFS ($p = 0.002$ HR 5.331 CI [1.9–15]) (cut-off value of 3). The Kaplan-Meier curves for comparison of the groups showed a significant difference in OS (log-rank 0.001) (Fig. 3a) and DFS (log-rank 0.001) (Fig. 3b) with 5-year OS and DFS of 97.9% compared to 73.7 and 93.6% compared to 62.1% in the TRG 3–4 and TRG 0–2, respectively.

TRG and ACT

The potential value of using Dworak's TRG for the selection of patients who might benefit from ACT was measured using Cox regression analysis. In TRG 0–2, ACT administration did not result in increased OS or DFS ($p = 0.936$ HR 1.05 (95%CI [0.32–3.46]) for OS and $p = 0.68$ HR 0.78 (95%CI [0.25–

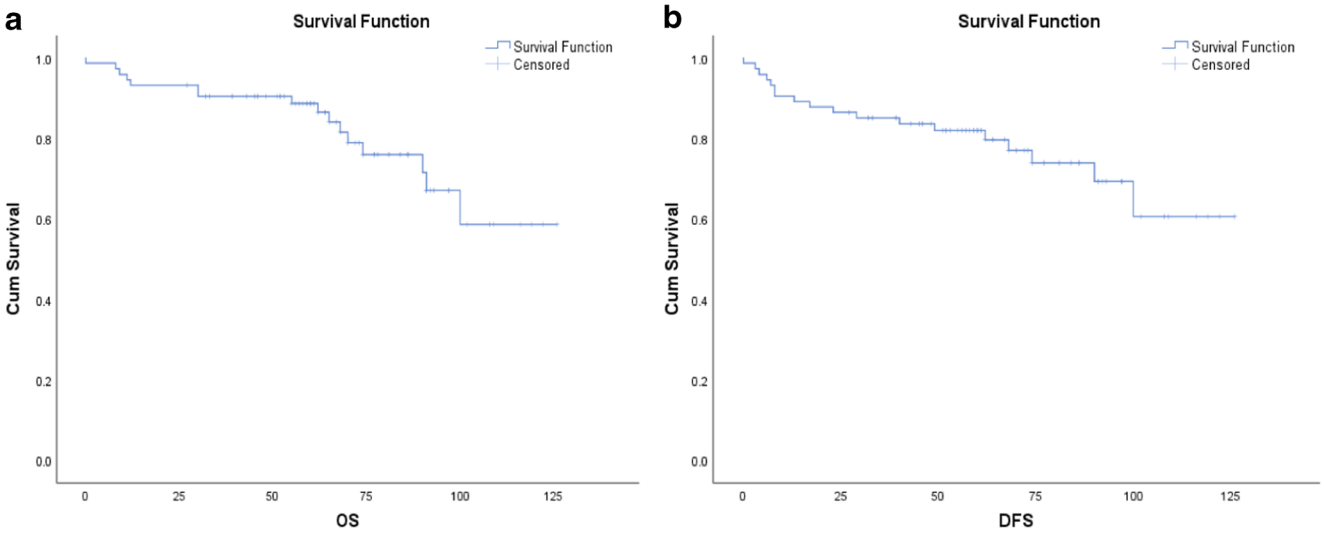

Fig. 1 Kaplan-Meier curves of **a** overall survival (OS) and **b** disease-free survival (DFS)

2.48]) for DFS). ACT administration also did not result in increased OS and DFS in TRG 3–4 ($p = 0.351$ HR 2.96 (95%CI [0.3–28.7]) for OS and $p = 0.594$ HR 1.64 (95%CI [0.27–10]) for DFS).

Discussion

There is no consensus regarding a clear benefit of ACT in LARC treated with NACRT followed by LAR and TME. The rationale behind administration of ACT in LARC was extrapolated from the clinical experience of using administration of ACT as an approach to treating stage III colon cancer. Although the colon and rectum share many histo-anatomical similarities, rectal and colon tumors have different biologies. A recent meta-analysis evaluating the role of ACT in rectal cancer reported improvements in OS of 17% and in DFS of 25% [12]. However, in the majority of these series, patients did not receive the NACRT that now represents the cornerstone of treatment of LARC along with surgery. Moreover, in the majority of these series, patients did not undergo guideline-recommended surgery including LAR with TME. The role of ACT is still controversial in rectal cancer, as all of the major clinical trials (EORTC 22921, Chronicle, and Proctor-Script trials) have reported no clear benefit of ACT [13–15].

Many studies have investigated predictive factors of chemotherapy response in order to identify a subset of patients who might benefit from the administration of ACT [16–21]. The EORTC 22921 trial showed that ACT had a potential benefit for patients who were down-staged by neoadjuvant treatment (CRT or radiotherapy alone) [16]. Unfortunately,

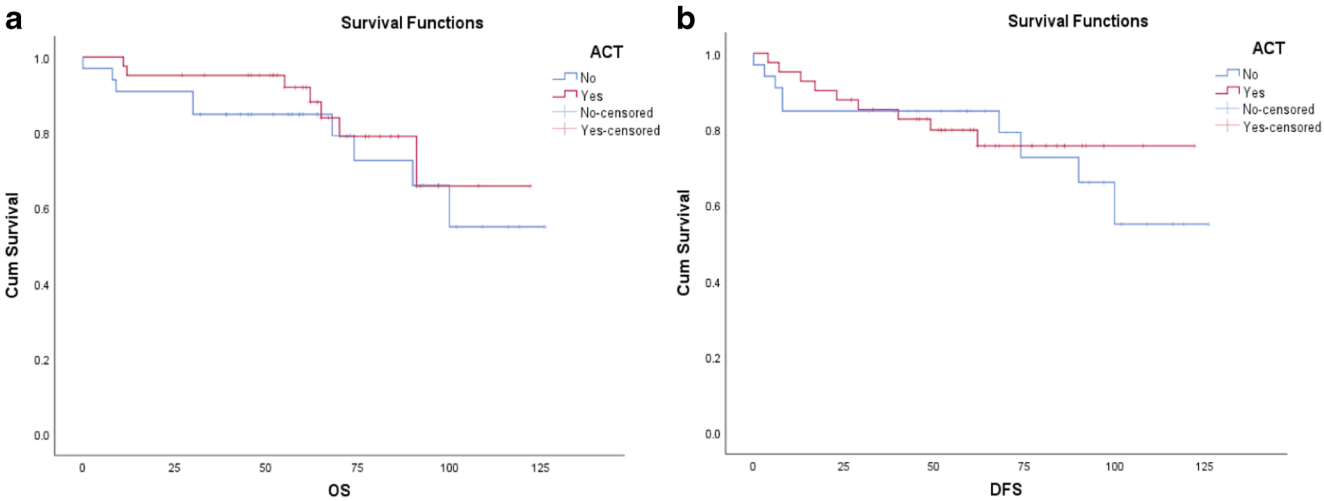

Fig. 2 Kaplan-Meier curves according to the administration of adjuvant chemotherapy (blue line represents the adjuvant chemotherapy (ACT) group and red line represents the non-ACT group) **a** overall survival (OS) and **b** disease-free survival (DFS)

Table 3 Comparison between subgroups of patients depending on the administration of ACT

Groups	ACT	No ACT	*p*
Number	42	32	
Age	59.5 year median 61.5(33–73)	67 years median 68 (37–84)	0.008
Sex			0.159
Male	25 (59.5%)	13 (40.6%)	
Female	17 (40.5%)	19 (59.4%)	
BMI (kg/m^2)	25.55 ± 4.8	26.27 ± 7.15	0.9
ASA score			0.635
ASA I	7 (16.7%)	3 (9.4%)	
ASA II	31 (73.8%)	25 (78.1%)	
ASA III	4 (9.5%)	4 (12.5%)	
Hemoglobin (g/dL)	13.6 ± 1.55	12.8 ± 1.76	0.057
Platelet (× 10^3)	254 ± 64	279 ± 81	0.241
Creatinine	0.82 ± 0.17	0.91 ± 0.35	0.706
Albumin (g/L)	34.7 ± 6.73	35.5 ± 7.4	0.569
CEA at diagnosis	8.7 (0.5–125)	6.03 (0.6–56.3)	0.119
CEA post NACRT	5.1 (0.6–92)	2.03 (0.5–5.8)	0.219
CEA first F/UP	2.2 (0.5–13.3)	3.87 (0.6–68.4)	0.361
Clinical staging			0.005
IIa	2 (4.8%)	11 (34.4%)	
IIb	0	1 (3.1%)	
IIIa	3 (7.1%)	2 (6.3%)	
IIIb	37 (88.1%)	17 (53.1%)	
IIIc	0	1 (3.1%)	
Surgery			0.013
LLAR	38 (90.5%)	22 (68.8%)	
LAPR	1 (2.4%)	8 (25%)	
OLAR	3 (7.1%)	2 (6.2%)	
Pathologic stage			0.258
0	6 (14.3%)	6 (18.8%)	
Ia	15 (35.7%)	13 (40.6%)	
IIa	6 (14.3%)	8 (25%)	
IIIa	6 (14.3%)	0	
IIIb	8 (19%)	4 (12.5%)	
IIIc	1 (2.4%)	1 (3.1%)	
Retrieved LN	12.86 median 12.5 (3–26)	14.32 median 12 (5–37)	0.572
Invaded LN	1 median 0 (0–9)	0.81 median 0 (0–12)	0.738
Differentiation			
Poorly	3 (7.3%)	2 (6.3%)	
Moderately	22 (53.7%)	18 (56.3%)	
Well	14 (34.1%)	7 (21.9%)	
Missing	2 (4.9%)	1 (3.1%)	
Lympho-vascular embolism	7 (16.7%)	3 (11.5%)	0.728
Perineural invasion	7 (16.7%)	3 (11.5%)	0.728
Tumor regression grade			0.247
0	1 (2.4%)	4 (12.5%)	
1	2 (4.8%)	4 (12.5%)	
2	11 (26.2%)	5 (15.6%)	
3	21 (50%)	13 (40.6%)	
4	7 (16.7%)	6 (18.8%)	

Table 3 (continued)

Groups	ACT	No ACT	*p*
Clavien-Dindo complications	3 (7.1%)	4 (12.5%)	0.585
I	1 (2.4%)	0	
II	1 (2.4%)	1 (3.1%)	
IIIb	1 (2.4%)	2 (6.3%)	
IVa	0	1 (3.1%)	
V	0	0	
Median follow-up	65 months ± 23.572	60 months	0.411
Relapse	10 (24%)	5 (15.5%)	0.477
Loco-regional	1 (2.4%)	1 (3.1%)	
Peritoneum	2 (4.8)	1 (3.1%)	
Pulmonary	3 (4.8%)	1 (3.1%)	
Liver	2 (4.8%)	1 (3.1%)	
Multiple	2 (4.8%)	1 (3.1%)	
Death	7 (16.7%)	9 (28.1%)	0.266

ACT adjuvant chemotherapy, *BMI* body mass index, *ASA* American Society of Anesthesiologists score, *CEA* carcinoembryonic antigen, *LLAR* laparoscopic low anterior resection, *LAPR* laparoscopic abdominoperineal resection, *OLAR* open low anterior resection, *LN* lymph node, *F/UP* follow-up, *NACRT* neoadjuvant chemoradiotherapy

this predictive effect was not supported by the updated long-term results at 10-year follow-up [17]. Other studies have failed to show a DFS benefit of ACT in patients down-staged by chemotherapy for LARC (ypT0-2N0 and ypT0-3N0) who were treated with NACRT followed by TME [18–20].

Interestingly, contrary to the approach of using ACT in down-staged tumors, a retrospective multicentric analysis conducted in 13 centers on 3133 patients showed that ACT could provide a DFS benefit in ypT1-2 and ypT3-4 patients compared to patients with ypT0N0, although this benefit was not statistically significant [21]. Accordingly, the ADORE trial showed that patients with ypN+ (stage III) could benefit more than patients with ypN0 disease in terms of DFS [22].

TRG is a well-known prognostic factor for OS and DFS in primary non-metastatic rectal cancer in the literature [6–9]. The hypothesis of our study was that TRG after NACRT could represent a tool for selection of patients who might benefit from ACT as we could hypothesize that patients who are "chemosensitive" to neoadjuvant therapy will be more sensitive to ACT and achieve better outcomes.

In the present study, ACT administered to patients with LARC who were treated with NACRT followed by LAR with TME did not appear to have any impact on OS or DFS. Both

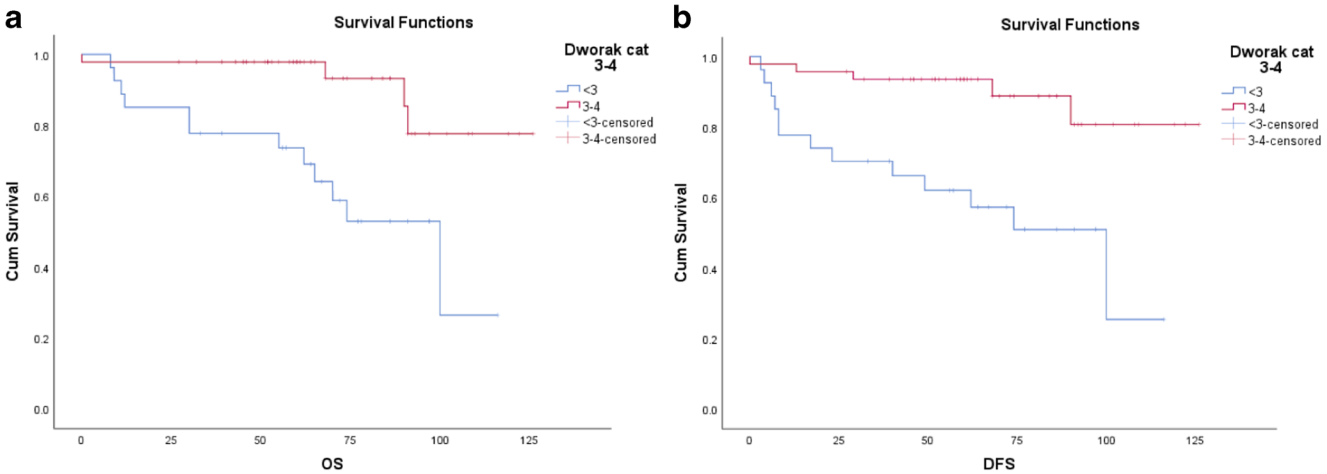

Fig. 3 Kaplan-Meier curves according to tumor regression grade (TRG) (blue line represents TRG 0–2 and red line represents TRG 3–4) **a** overall survival (OS) and **b** disease-free survival (DFS)

control (no ACT) and ACT groups had similar epidemiologic characteristics, pathologic staging, and TRG distribution (Table 3). However, these two groups were not similar regarding age, clinical stage, and type of surgery. If patients receiving ACT had more advanced initial disease, then it is possible that the administration of ACT could benefit a subset of patients, allowing them to achieve similar outcomes to patients with less aggressive tumor biology. However, ACT did not prevent the occurrence of distant metastases as 10 (24%) relapses occurred in the group who received ACT compared to 5 (15.5%) in the group who did not. Our data did confirm that TRG (cut-off 3) was related to OS and DFS.

This is the first reported study evaluating the potential role of TRG for the identification of a subset of patients who might benefit from the administration of ACT. In the present study, TRG failed to show a predictive value for the selection of patients who might benefit from the administration of ACT. This suggests that tumor response to NACRT does not predict which patients might benefit from ACT, and also emphasizes that TRG is a result of both preoperative radiotherapy and chemotherapy, not just chemotherapy alone. This confirms some data reporting that response to RCT treatment does not consistently imply a response and/or a clinical benefit to chemotherapy alone [20].

Limitations

Our study had several limitations, including its small population size and retrospective design. Moreover, despite the fact that the two groups were similar for the most important prognostic factor (pTNM), patients receiving ACT were younger and had more advanced clinical stage (cTNM) disease.

Conclusions

The administration of ACT in LARC treated with NACRT and TME is still controversial. However, it still might benefit a subset of patients. Dworak's TRG has a prognostic effect for both OS and DFS but failed to be a predictive tool for the selection of patients who might benefit from ACT. Larger prospective series are needed to evaluate other potential predictive factors that allow for the selection of patients who could benefit from ACT.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflicts of interest.

References

1. Siegel RL, Miller KD, Jemal A (2017) Cancer statistics, 2017. CA Cancer J Clin 67:7–30
2. Bufalari A, Boselli C, Giustozzi G, Moggi L (2000) Locally advanced rectal cancer: a multivariate analysis of outcome risk factors. J Surg Oncol 74:2–10
3. Dutch guideline colorectal cancer versie 3.0. http://www.oncoline.nl/colorectaalcarcinoom (updated 2014-04-16)
4. Rectal cancer, NCCN clinical practice guidelines in oncology, Version I; 2017. http://www.nccn.org/professionals/physician_gls/pdf/rectal. pdf. (accessed 12 March 2018)
5. Glynne-Jones R, Wyrwicz L, Tiret E, Brown G, Rödel C, Cervantes A, Arnold D, ESMO Guidelines Committee (2017) Rectal cancer: ESMO clinical practice guidelines for diagnosis, treatment and follow-up. Ann Oncol 28(suppl_4):iv22–iv40
6. Gash KJ, Baser O, Kiran RP (2017) Factors associated with degree of tumour response to neo-adjuvant radiotherapy in rectal cancer and subsequent corresponding outcomes. Eur J Surg Oncol 43: 2052–2059
7. Fokas E, Liersch T, Fietkau R, Hohenberger W, Beissbarth T, Hess C, Becker H, Ghadimi M, Mrak K, Merkel S, Raab HR, Sauer R, Wittekind C, Rödel C (2014) Tumor regression grading after preoperative chemoradiotherapy for locally advanced rectal carcinoma revisited: updated results of the CAO/ARO/AIO-94 trial. J Clin Oncol 32:1554–1562
8. Zhang LN, Xiao WW, Xi SY, OuYang PY, You KY, Zeng ZF et al (2016) Pathological assessment of the AJCC tumor regression grading system after preoperative chemoradiotherapy for Chinese locally advanced rectal cancer. Wall Medicine 95:e2272
9. Rodel C, Martus P, Papadoupolos T, Füzesi L, Klimpfinger M, Fietkau R et al (2005) Prognostic significance of tumor regression after preoperative chemoradiotherapy for rectal cancer. J Clin Oncol 23:8688–8696
10. Edge SB, Byrd DR, Compton CC, Fritz AG, Greene FL, Trotti A (eds) (2010) AJCC Cancer staging manual, 7th edn. Springer, New York
11. Dworak O, Keilholz L, Hoffmann A (1997) Pathological features of rectal cancer after preoperative radiochemotherapy. Int J Color Dis 12:19–23
12. Petersen SH, Harling H, Kirkeby LT, Wille-Jørgensen P, Mocellin S (2012) Postoperative adjuvant chemotherapy in rectal cancer operated for cure. Cochrane Database Syst Rev 3:CD004078
13. Bosset JF, Collette L, Calais G, Mineur L, Maingon P, Radosevic-Jelic L, Daban A, Bardet E, Beny A, Ollier JC, EORTC Radiotherapy Group Trial 22921 (2006) Chemotherapy with preoperative radiotherapy with rectal cancer. N Engl J Med 355:1114–1123
14. Glynne-Jones R, Counsell N, Quirke P, Mortensen N, Maraveyas A, Meadows HMJ et al (2014) Chronicle: results of a randomised phase III trial in locally advanced rectal cancer after neoadjuvant chemoradiation randomising postoperative adjuvant capecitabine plus oxaliplatin (XELOX) versus control. Ann Oncol 25:1356–1362
15. Breugom AJ, van Gijn W, Muller EW, Berglund A, van den Broek CBM, Fokstuen T, Gelderblom H, Kapiteijn E, Leer JWH, Marijnen CAM, Martijn H, Meershoek-Klein Kranenbarg E, Nagtegaal ID, Pahlman L, Punt CJA, Putter H, Roodvoets AGH,

Rutten HJT, Steup WH, Glimelius B, van de Velde CJH, Cooperative Investigators of the Dutch Colorectal Cancer Group and the Nordic Gastrointestinal Tumour Adjuvant Therapy Group (2015) Adjuvant chemotherapy for rectal cancer patients treated with preoperative (chemo)radiotherapy and total mesorectal excision: a Dutch Colorectal Cancer Group (DCCG) randomized phase III trial. Ann Oncol 26:696–701

16. Collette L, Bosset JF, den Dulk M, Nguyen F, Mineur L, Maingon P, Radosevic-Jelic L, Piérart M, Calais G, European Organisation for Research and Treatment of Cancer Radiation Oncology Group (2007) Patients with curative resection of cT3-4 rectal cancer after preoperative radiotherapy or radiochemotherapy: does anybody benefit from adjuvant fluorouracil-based chemotherapy? A trial of the EORTC Radiation Oncology Group. J Clin Oncol 25:4379–4386
17. Bosset JF, Calais G, Mineur L, Maingon P, Stojanovic-Rundic S, Bensadoun RJ, Bardet E, Beny A, Ollier JC, Bolla M, Marchal D, van Laethem J, Klein V, Giralt J, Clavère P, Glanzmann C, Cellier P, Collette L, EORTC Radiation Oncology Group (2014) Fluorouracil-based adjuvant chemotherapy after preoperative chemoradiotherapy in rectal cancer: long-term results of the EORTC 22921 randomised study. Lancet Oncol 15:184–190
18. Park IJ, Kim DY, Kim HC, Kim NK, Kim HR, Kang SB, Choi GS, Lee KY, Kim SH, Oh ST, Lim SB, Kim JC, Oh JH, Kim SY, Lee WY, Lee JB, Yu CS (2015) Role of adjuvant chemotherapy in ypT0-2N0 patients treated with preoperative chemoradiation therapy and radical resection for rectal cancer. Int J Radiat Oncol Biol Phys 92:540–547
19. Huh JW, Kim HR (2009) Postoperative chemotherapy after neoadjuvant chemoradiation and surgery for rectal cancer: is it essential for patients with ypT0-2N0? J Surg Oncol 100:387–391
20. Kim CG, Ahn JB, Shin SJ, Beom SH, Heo SJ, Park HS, Kim JH, Choe EA, Koom WS, Hur H, Min BS, Kim NK, Kim H, Kim C, Jung I, Jung M (2017) Role of adjuvant chemotherapy in locally advanced rectal cancer with ypT0-3N0 after preoperative chemoradiation therapy and surgery. BMC Cancer 17:615
21. Maas M, Nelemans PJ, Valentini V, Crane CH, Capirci C, Rodel C et al (2015) Adjuvant chemotherapy in rectal cancer: defining subgroups who may benefit after neoadjuvant chemoradiation and resection—a pooled analysis. Int J Cancer 137:212–220
22. Hong YS, Nam BH, Kim KP, Kim JE, Park SJ, Park YS, Park JO, Kim SY, Kim TY, Kim JH, Ahn JB, Lim SB, Yu CS, Kim JC, Yun SH, Kim JH, Park JH, Park HC, Jung KH, Kim TW (2014) Oxaliplatin, fluorouracil, and leucovorin versus fluorouracil and leucovorin as adjuvant chemotherapy for locally advanced rectal cancer after preoperative chemoradiotherapy (ADORE): an open-label, multicentre, phase 2, randomised controlled trial. Lancet Oncol 15:1245–1253