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Neoadjuvant Conformal Chemoradiation with Induction Chemotherapy for Rectal Adenocarcinoma. A Prospective Observational Study

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ABSTRACT

Background & Aims: The purpose of this prospective observational study was to evaluate the rate and the prognostic factors for down-staging and complete response for rectal adenocarcinoma after induction chemotherapy and neoadjuvant chemoradiation followed by surgery, and to analyze the rate of sphincter-saving surgery.

Methods: We included from March 2011 to October 2013 a number of 88 patients hospitalized with locally advanced rectal adenocarcinoma in the Prof. Dr. Ion Chiricuta Institute of Oncology, Cluj. The treatment schedule included 2-4 cycles of Oxaliplatin plus a fluoropyrimidine followed by concomitant chemoradiation with a dose of 50 Gy in 25 fractions combined with a fluoropyrimidine monotherapy.

Results:The rate of T down-staging was 49.4% (40/81 evaluable patients). Independent prognostic factors for T down-staging were: age >57 years ($p<0.01$), cN0 ($p<0.01$), distance from anal verge >5 cm ($p<0.01$), initial CEA <6.2 ng/ml ($p<0.01$), higher number of chemotherapy cycles with Oxaliplatin (pROC=0.05) and protraction of radiotherapy of >35 days ($p<0.01$). Nine patients from 81 (11.1%) presented complete response (7 pathological and 2 clinical); the independent prognostic factors were stage cT2 versus cT3-4 ($p<0.01$), initial tumor size ≤3.5 cm and distance from anal verge >5 cm ($p=0.03$). Sixty-eight patients (79.1%) underwent radical surgery and among them 35 patients (51.5 %) had a sphincter saving procedure.

Conclusions: Induction chemotherapy with neoadjuvant chemoradiation produced important down-staging in rectal adenocarcinoma. Independent prognostic factors for T down-staging were: age, cN0, distance from anal verge, initial CEA, the number of Oxaliplatin cycles and duration of radiotherapy; for complete response: cT2, initial tumor size and distance from the anal verge.

Key words: rectal adenocarcinoma – conformal chemoradiation – induction chemotherapy – down-staging – complete remission – sphincter sparing surgery.

Abbreviations: 5FU: 5-fluorouracil; AJCC: American Joint Committee on Cancer; AV: anal verge; CAPOX: Capecitabine plus Oxaliplatin; CCR: clinical complete response; CRT: chemoradiation; CTC4.0: Common Terminology Criteria for Adverse Events, version 4.0; ECOG: Eastern Collaborative Oncology Group; EUS: endorectal ultrasound; FOLFOX: 5-fluorouracil plus Oxaliplatin; LARC: locally advanced rectal cancer; PCR: pathological complete response; PS: performance status; PTV: planning target volume; R0: Resection, 0 (microscopically clear resection margin); ROC curve: receiver operating characteristic curve; TME: total mesorectal excision; TRG: tumor regression grade.

INTRODUCTION

The standard treatment for rectal adenocarcinoma has changed over time. In 1982, Heald et al introduced the concept of total mesorectal excision (TME), but this was adopted as standard treatment only during the nineties. In 1990 the Consensus Panel of the National Institutes of Health from the USA recommended adjuvant chemoradiation (CRT) as the standard of care for stage II and III rectal cancer [1]. In 2004 this standard was changed to neoadjuvant CRT for

locally advanced rectal cancer (LARC: cT3/cT4&N0/N+, cT2N+) following the results of the CAO/ARO/AIO Rectal Cancer Trial [2]. The most important advantage of neoadjuvant CRT is a decreased local relapse rate when compared to surgery alone or surgery plus adjuvant CRT. This effect is due to the higher rate of (true-) R0 resections (microscopically clear resection margins) and partial or complete response of nodal or extranodal pelvic metastases. Neoadjuvant CRT also yields an increased rate of sphincter preserving surgery. Furthermore, compared with surgery and adjuvant CRT there is less combined toxicity of neoadjuvant CRT plus surgery.

In clinically complete responders after neoadjuvant CRT an experimental approach is the follow-up with salvage surgery if necessary. Radiotherapy doses of 45 to 50 Gy with concomitant chemotherapy yield a clinical complete response (CCR) rate between 10.4% [3] and 27% [4]. The pathological complete response (PCR) can be higher, up to 35.1% [4-7]. Brachytherapy or orthovoltage boost approaches can yield a CCR of about 81% in selected patients [8, 9].

The current prospective observational study was performed with the aim to find prognostic factors related to down-staging and complete response (clinical or pathological) when an intensified neoadjuvant schedule is used, consisting of induction chemotherapy and concomitant CRT with a dose of 50 Gy in 25 fractions to all macroscopic lesions (tumor and suspicious lymph nodes).

METHODS

We have prospectively included in our observational study in a set timeframe between March 2011 and October 2013, 88 patients with LARC (including patients with metastases confined to a single organ or site) who received neoadjuvant treatment at the Institute of Oncology Prof. Dr. Ion Chiricuta, Cluj.

Inclusion criteria were: biopsy proven adenocarcinoma of the rectum with a distal tumor border within 15 cm from the anal verge (AV) as measured with digital rectal examination, rigid proctoscopy and/or MRI; extension to the sigmoid was allowed; age between 18-80 years; clinical stage II (T3-4, N0), stage III (any T, N1-2), stage IV A (any T, any N, M1a, i.e. metastases confined to a single organ or site); Eastern Collaborative Oncology Group performance status (ECOG PS) of 0 or 1; Hb > 9 g/dl, neutrophil count >1500/μl, platelets > 100,000/μl; proper liver function and indication of neoadjuvant treatment.

Exclusion criteria were: recurrent rectal adenocarcinoma; multiple colon adenocarcinomas; prior pelvic irradiation.

Staging, evaluation and treatment protocol

Local and lymph node staging was performed by MRI and/or endorectal ultrasound (EUS). In addition, patients underwent a full colonoscopy (if there was no stenosis at the level of the rectal tumor), CT examination with iodinated contrast of the abdomen and pelvis, a chest x-ray or chest CT examination. Carcinoembryonic antigen (CEA) and CA 19-9 antigen were recommended to be measured in serum before any treatment.

The neoadjuvant treatment protocol for LARC at our Institute of Oncology includes optional induction chemotherapy (2 to 4 cycles) before CRT. Induction chemotherapy is offered to all rectal adenocarcinoma patients without contraindications to chemotherapy. If surgery is delayed more than 8 weeks after the completion of CRT, additional chemotherapy cycles are recommended until surgery. The induction chemotherapy includes optionally a fluoropyrimidine and Oxaliplatin or fluoropyrimidine monotherapy. The CAPOX regimen is administered every 21 days with Oxaliplatin 130 mg/m^2, day 1 and Capecitabine 2000 mg/m2, days 1-14, PO bid. The FOLFOX4 regimen is administered every 14 days with Oxaliplatin 85 mg/m^2 on day 1 and 5FU (bolus 400 mg/m^2 and continuous infusion 600 mg/m^2) on day 1 and 2.

Chemotherapy with fluoropyrimidines is contraindicated when there is significant cardiac disease or the left ventricular ejection fraction is lower than 50%. In these cases Irinotecan can be used with monitoring of the heart rate and blood pressure. Dose reduction of fluoropyrimidines and Oxaliplatin is applied when creatinine clearance is <30 ml/min.

Radiotherapy is administered according to an institutionally approved protocol. It is delivered with a conformal technique, using 15 MV beams; combination with a 6MV beam could be used to compensate low close-to-surface dose. The prescription dose is 46 Gy in 23 fractions (31 days) to the primary PTV (PTV1, planning treatment volume 1) and 50 Gy in 25 fractions (33 days) to the secondary PTV (PTV2). PTV1 includes the whole rectum (except the sphincter in middle or upper tumors), the whole mesorectum, the internal iliac lymph nodes and the obturatory lymph nodes in tumors within 10 cm from the AV. PTV2 includes the tumor with a 2 cm cranial and caudal margin, the whole mesorectum and all suspicious lymph nodes. The concomitant chemotherapy is Capecitabine 1650 mg/m^2/day, every day with radiotherapy (5 days/week).

After neoadjuvant treatment patients are referred for surgical intervention, which is recommended to be performed at 6-8 weeks after the last radiotherapy fraction. In a subset of patients who refuse to undergo surgery, tumor response is assessed by MRI or EUS combined with rectoscopy at 6-8 weeks from the end of CRT. The definition of a CCR is: (1) no residual tumor or only residual fibrosis on MRI or EUS; (2) no suspicious lymph nodes on MRI or EUS; (3) no residual tumor on rectoscopy and digital rectal examination.

Data analysis

The down-staging data was analyzed by comparison of the initial clinical stage with the one obtained on the surgical specimen or on clinical restaging, if patients did not undergo surgery. Each staging component (T, N) was analyzed separately.

For prognostic factors, T down-staging was analyzed instead of combined T and N down-staging, since MRI and US evaluation of T stage is more reliable. Furthermore we analyzed the tumor response grade (TRG) for radically operated patients.

For prognostic factor analysis of complete response we combined the numbers of pathological and clinical complete responders (since there were patients who refused surgery

upon achieving CCR). The analysis of CCR in all patients was not one of the goals of this study.

Staging and TRG measurement were performed according to the American Joint Committee on Cancer (AJCC) Cancer Staging, 7th edition [10]. Acute side-effects were graded according to the Common Terminology Criteria for Adverse Events version 4 (CTC4.0).

ROC curves and chi square test with Yates correction were used for analysis of the prognostic factors for T down-staging and complete response. The cut-off values for numerical variables were chosen based on the minimal distance of the ROC curve from point (0,1). Confidence intervals were estimated at a threshold of 95%. Statistical significance was set at $p \leq 0.05$. FileMaker was used for data entry and Excel for data analysis.

The Kaplan-Meier method with log-rank test was used for survival analysis.

Informed consent was acquired for all patients regarding the use of radiation therapy, chemotherapy, surgery, clinical tests, analysis and publication of anonymized medical information. The treatment protocol was approved by the Digestive Tumor Board of the Institute of Oncology and the study protocol by the Iuliu Hatieganu University of Medicine and Pharmacy Ethics Committee. Patient data was handled according to Directive 95/46/EC of the European Parliament.

RESULTS

A total of 88 patients met initially all eligibility criteria and were enrolled in this observational study. From the 88 patients, 2 did not finish CRT: one developed G3 diarrhea and decided to interrupt the treatment and one patient died in the course of CRT due to venous thromboembolism. These two patients were not included in the analyses (Table I).

Seventy-one (82.6%) patients received the standardized 50 Gy in 25 fractions to the PTV2. Protocol deviation was encountered in 15 patients (17.4%): 6 patients received a dose between 44-48 Gy, 3 patients 50.4 Gy in 28 fractions (1.8 Gy/fraction) and 6 patients 52-54 Gy in 26-27 fractions.

From the 86 patients, 79 patients received induction chemotherapy (91.9%) and 54 patients (62.8%) received

Table I. Patients' characteristics (N=86)

Characteristics	Patients Number (%)
Age, years, median (range, standard deviation)	59.4 (33-80, 11)
Gender	
males	56 (65.1)
females	30 (34.9)
Distance from anal verge (cm)	
≤5	43 (50)
5-10	42 (48.8)
>10	1 (1.2)
Tumor size (largest diameter/length in cm)	2.5-13
Range (median; mean)	(6; 6.4)
Clinical stage (cTNM)	
cT2	7 (8.1)
cT3	59 (68.6)
cT4a	2 (2.3)
cT4b	18 (20.9)
cN0	12 (13.9)
cN1a	6 (7)
cN1b	16 (18.6)
cN2a	30 (34.9)
cN2b	22 (25.6)
cM0	77 (89.5)
cM1a	9 (10.5) (8 liver and one pelvic bone)
Tumor grade (N=86); when initial grading was Gx, final grading was used, if available	
G1	16 (18.6)
G2	42 (48.8)
G3	6 (7)
Gx	22 (25.6)
CEA at diagnosis (N=60), ng/ml, range (median; mean)	0.5-846.7 (17.3; 66.35)
- detection threshold 0.2 ng/ml; normal values: <3.4 ng/ml (non-smokers), <4.3 ng/ml (smokers)	
CA 19-9 at diagnosis (N=33), U/ml, range (median; mean)	0.7-364.6 (3.75; 17.24)
- detection threshold 0.6 U/ml, normal values <27 U/ml	
Type of surgery (N=71)	
Anterior resection	34 (47.9)
Abdomino-perineal resection	33 (46.5) (1 pelvic exenteration)
Endoscopic resection	1 (1.4)
Laparotomy (non-radical surgery)	3 (4.2)

the recommended 2-4 cycles. Seven patients did not receive induction chemotherapy (started CRT directly), 6 patients received only one cycle and 19 patients received 5 or more cycles (range 5-14). From the 79 patients who received induction chemotherapy, 62 patients (78.5%) received the CAPOX regimen, 3 patients (3.8%) FOLFOX4, 9 patients (11.4%) 5FU and folinic acid and 5 patients (6.3%) Capecitabine monotherapy (2500 mg/m^2/day, days 1-14, every 21 days).

Seventy-nine patients (91.9%) received concomitant chemotherapy and from these: 65 patients (82.3%) Capecitabine, 12 patients (15.2%) weekly 5FU (600 mg/m^2/week with folinic acid 30 mg/m^2/week) and 2 patients (2.5%) Irinotecan (180 mg/m2 days 1 and 15, every 28 days).

Sixty-eight patients (79.1%) underwent radical surgery and 3 patients palliative surgery. Five patients (5.8%) were considered inoperable on post-CRT imaging. Ten patients (11.6%) refused radical surgery. From these, 2 patients had CCR and 8 had residual disease. From the patients with residual disease 3 had no down-staging on MRI and 5 refused any re-staging.

From the 68 patients who underwent radical surgery, 34 (50 %) had anterior resection, 32 (48.5%) abdomino-perineal resection, one pelvic exenteration and one endoscopic resection.

Seven cases presented ypT0 stage on the final pathology from 68 patients who underwent radical surgery (10.3%) and from these 6 were ypN0. Only one case of the 7 ypT0 cases had ypN1a, presenting a metastasis in a single lymph node, but with extensive necrosis. This case was considered for further analyses as having PCR. If we combine the 7 ypT0N0 (PCR) cases with the 2 CCR cases, 9 patients out of 81 evaluable patients presented complete response (11.1%).

Overall, severe acute toxicity was low: G3 digestive toxicity in 11.7% of cases, G3 and G4 hematologic toxicity in 2.4%, G3 radiation dermatitis in 5.8% and G3 peripheral sensory neuropathy in 10.8%. (Table II)

Down-staging analysis

When analyzing the down-staging of the primary tumor we compared the initial clinical T stage and the pathological T stage. Furthermore, in 5 of the 10 patients who refused surgery, we were able to obtain clinical restaging: 2 of them had CCR and 3 had stable T stage. We also included in the analysis the 5 inoperable patients after CRT.

Thus we analyzed the T down-staging for 68 radically and 3 palliatively operated patients, including the 2 patients with CCR, the 5 patients with inoperable disease and the 3 patients who refused surgery but had stable disease.

In these 81 patients T down-staging was present in 40 (49.4%). A stable T stage was found in 37 (45.7%) and a higher T stage in 4 (4.9%). (Individual T down-staging is shown in Table III).

We analyzed the TRG for the 68 radically operated patients. Seven patients (10.3%) had TRG=0 (PCR), 12 patients (17.6%) moderate response (TRG=1), 29 patients (42.6%) minimal response (TRG=2) and 20 patients (29.4%) poor response (TRG=3). Tumor down-staging and TRG were correlated (p=0.05).

For analysis of N down-staging we compared the initial cN and the final pN stage for the 68 radically operated patients, including the 2 cases with CCR and the 3 patients who refused surgery but underwent clinical restaging. Thus 49/73 (67.1%) patients had a smaller yN stage; 10 patients (13.7%) had N0 both on the initial and post-CRT staging; 11 patients a stable N stage (15.1%) and 3 patients (4.4%) a higher N stage.

Using ROC curve analysis and chi square test for potential prognostic factors for T down-staging we found statistical significance for: age older than 57 years, cN0 stage versus cN1-2, distance of the lower pole of the tumor from the AV > 5 cm, initial CEA < 6.2 ng/ml, higher number of Oxaliplatin containing chemotherapy cycles and a protraction of radiotherapy of more than 35 days (Table IV). All these were independent factors. Other factors analyzed which did not reach statistical significance for T down-staging were: gender, cT stage and cM stage, tumor grade, initial tumor length, involvement of the sigmoid, macroscopic subtype, invasion of the perirectal fascia on MRI and number of non-Oxaliplatin chemotherapy cycles.

The statistically significant independent prognostic factors for complete response were cT2 stage versus cT3-T4, tumor size ≤3.5 cm and tumor distance of >5 cm from the AV (Table V).

Table II. Acute toxicity according to Common Terminology Criteria for Adverse Events version 4 (CTC4.0) (N=86)

Variable	CTC 0	CTC 1-2	CTC 3	CTC4
Digestive				
diarrhea	67 (77.9%)	13 (15.1%)	6 (7%)	-
vomiting	81 (94.2%)	1 (1.2%)	1 (1.2%)	-
Proctitis	29 (33.7%)	54 (62.8%)	3 (3.5%)	-
Noninfective cystitis	81 (94.2%)	5 (5.8%)	-	-
Hematologic				
anemia	45 (52.3%)	41 (47.7%)	-	-
febrile neutropenia	85 (98.8%)	NA	1 (1.2%)	-
platelet count decreased	63 (73.2%)	22 (25.6%)	-	1 (1.2%)
Radiation dermatitis	36 (41.9%)	45 (52.3%)	5 (5.8%)	-
Nervous system (N=65, patients receiving Oxaliplatin containing regimen)				
peripheral sensory neuropathy	3 (4.6%)	55 (84.6%)	7 (10.8%)	
peripheral motor neuropathy	53 (81.5%)	12 (18.5%)	-	-

Table III. Tumor down-staging by initial clinical stage (cT) in surgical patients, 2 clinical complete responders, 5 inoperable patients and 3 patients who refused surgery, but were evaluable (N=81). Percentages are from the initial cT stages.

	Final T stage ypT(+ycT)					
Initial cT stage	ypT0(ycT0) N=9	ypT1(ycT1) N=3	ypT2(ycT2) N=22	ypT3(ycT3) N=36	ypT4a(ycT4a) N=2	ypT4b(ycT4b) N=9
cT2 N=7	1 (+2 ycT0) (42.8%)	0	2 (28.6%)	2 (28.6%)	0	0
cT3 N=55	4 (7.3%)	2 (3.6%)	19 (34.5%)	23 (+5 ycT3) (51%)	0	1 (+1ycT4b) (3.6%)
cT4a N=2	0	0	0	2 (100%)	0	0
cT4b N=17	2 (11.8%)	1 (5.9%)	1 (5.9%)	4 (23.5%)	2 (11.8%)	2 (+5ycT4b) (41.1%)

Tumor markers

We obtained initial CEA values for 60 patients, and CA 19-9 values in 33 from these patients. CEA was increased in 60% (36/60) and CA 19-9 in 39.4% (13/33). CA 19-9 was increased without an accompanying CEA increase in 15.4% of patients (2/13). CEA value depended on the clinical stage (III vs. IV), but CA 19-9 did not show such a dependence in our patient series (Figs. 1 and 2). A value of CEA > 6 ng/ml was inversely correlated with survival (p=0.03).

Higher values of CA 19-9 were found in G3 tumors. When a cutoff of 80 U/ml was chosen, 75% of G3 tumors had a CA 19-9 > 80 U/ml, versus only 10.5% of G1/2 tumors (p=0.03).

Table IV. Studied prognostic factors for T down-staging

Prognostic factor	Down-staged number	Not down-staged number	p
Gender			
female	13 (52%)	12 (48%)	0.26
male	29 (65.9%)	15 (34.09%)	
Age			
≤57 years	9 (30%)	21 (70%)	<0.01
>57 years	31 (60.8%)	20 (39.2%)	
cT stage			
T2	3 (42.9%)	4 (57.1%)	0.56
T3	25 (45.5%)	30 (54.5%)	
T4a-b	12 (63.2%)	7 (36.8%)	
cN stage			
N0	9 (75%)	3 (25%)	0.05
N1/2	31 (44.9%)	38 (55.1%)	
M stage			
M0	38 (52.8%)	34 (47.2%)	0.17
M1a	2 (22.2%)	7 (77.8%)	
Tumor grade (N=63)			
G1	8 (50%)	8 (50%)	0.71
G2-3	26 (55.3%)	21 (44.7%)	
Initial distance from anal verge (cm)			
≤5	15 (37.5%)	25 (62.5%)	0.03
>5	25 (61%)	16 (39%)	
Involvement of the sigmoid			
Yes	8 (53.3%)	7 (46.7%)	0.73
No	32 (48.5%)	34 (51.5%)	
Invasion of the perirectal fascia			
Yes	11 (44%)	14 (56%)	0.87
No	18 (46.2%)	21 (53.8%)	
CEA value			< 0.01
<6.2 ng/ml	21 (60%)	14 (40%)	
>6.2 ng/ml	4 (30.8%)	19 (69.2%)	
Number of chemotherapy cycles with Oxaliplatin			
≤3	12 (37.5%)	20 (62.5%)	p=0.08
>3	18 (60%)	12 (40%)	P_{ROC} =0.05
Duration of radiotherapy (days)			
≤35	12 (33.3%)	24 (66.7%)	<0.01
>35	28 (62.2%)	17 (37.8%)	

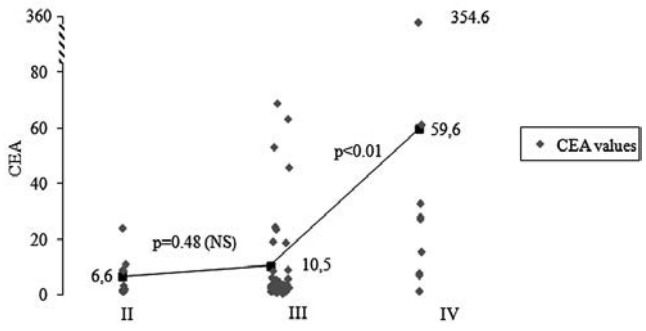

Fig.1. CEA, including mean values (ng/ml) and clinical stage (N=60)

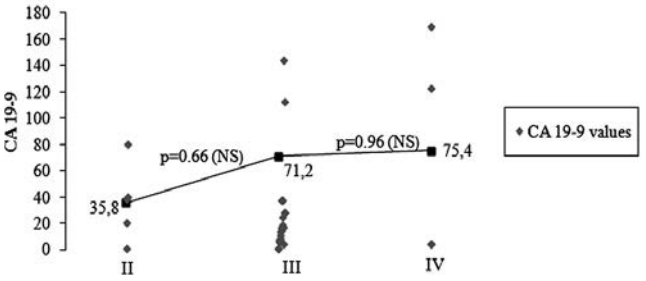

Fig.2. CA 19-9, including mean values (U/ml) and clinical stage (N=33)

Table V. Independent prognostic factors for complete tumor response (ycT0 plus ypT0)

Significant prognostic factors	T0 number	Non-T0 number	p
Clinical T stage (N=86)			
cT2	3 (42.9%)	4 (57.1%)	<0.01
cT3-T4	6 (8.3%)	66 (91.7%)	
Initial tumor size (cm) (N=69)			
≤3.5	3 (50%)	3 (50%)	<0.01
>3.5	4 (6.3%)	59 (93.7%)	
Initial distance from anal verge (cm) (N=86)			
≤5	1 (2.3%)	42 (97.7%)	0.03
>5	8 (18.6%)	35 (81.4%)	

G3 frequency was independent from tumor stage (in stage II there were 10% G3 tumors, in stage III 9.09% and in stage IV 12.5%, p=ns).

Relapse and survival

The median follow-up from diagnosis was 16.7 months (3.8-33.4). From the 68 patients who underwent radical surgery only 1 presented local plus nodal relapse and 3 presented metastases. Fourteen deaths were recorded in the follow-up (14/86, 16.3%), 11 caused by the rectal cancer and 3 by cardiovascular disease.

The overall survival at 18 months was 86% for M0 cases and 57% for M1a (p<0.01).

DISCUSSION

The rate of T down-staging (49.4%) was similar to what other teams described when studying CRT including Oxaliplatin, i.e., around 43-58% [11, 12]. The rate of complete responses (11.1%) was similar with the reported 10.4-25.6% in studies including several stages [13], although on the lower end of the range, probably due to a large number of advanced cases (cT3N2 35/81 or 43.2%; cT4b 19/81 or 23.5%).

Adjuvant chemotherapy containing Oxaliplatin is a recognized option as an adjuvant treatment for T3N0, any-T and N+, and T4 and any-N rectal adenocarcinoma [14]. Oxaliplatin chemotherapy during radiotherapy was tested in several clinical trials. Four phase III clinical trials added weekly Oxaliplatin (50 or 60 mg/m2) in one arm of radiotherapy plus concurrent 5FU or Capecitabine (STAR-01 [5], ACCORD12/0405 Prodige 2 [15], NSABP R-04 [16], CAO/ARO/AIO-04 [17]).

The STAR-01 and NSABP R-04 clinical trials could not demonstrate an increase in the PCR rate, but in the STAR-01 there was a decrease in the rate of intra-abdominal metastases (ypM1 2.9% for 5FU vs. 0.5% for Oxaliplatin; p=0.014).

The ACCORD clinical trial intensified both the chemotherapy schedule by adding Oxaliplatin and the RT dose, by increasing the total dose from 45 Gy/25 fr to 50 Gy/25 fr (and increasing the dose per fraction from 1.8 to 2 Gy). There was an increase in the PCR (when a cutoff of 2 mm was used to define it): 9.9% with Capecitabine plus 45 Gy and 19.3% with CAPOX plus 50 Gy (p=0.02).

The CAO/ARO/AIO-04 demonstrated that PCR could be increased by concomitant Oxaliplatin, although the difference was small (17% vs. 13%, p=0.038).

GCR-3 was a phase II randomized clinical trial where Oxaliplatin 50 mg/once every week was administered with radiotherapy in both arms; additionally 4 cycles of CAPOX were included, in arm A as adjuvant, in arm B as neoadjuvant treatment [11]. Down-staging and PCR were similar, and when analyzing the 3-year results the authors stated: "although not powered to draw any comparative conclusions, induction chemotherapy … yields similar three-year outcomes as standard strategy." As a benefit for the neoadjuvant approach there was less acute toxicity and better compliance than with the adjuvant chemotherapy [11].

We studied Oxaliplatin used as the induction chemotherapy followed by CRT without concomitant Oxaliplatin. Induction chemotherapy for LARC is an optional treatment in the protocol for rectal adenocarcinoma of the Institute of Oncology Prof. Dr. Ion Chiricuta. Although it is not a standard option internationally, it was adopted for potential benefits such as better compliance, early treatment of subclinical metastases and possibly better down-staging.

In our observational study, down-staging was more frequent with a higher number of Oxaliplatin containing chemotherapy cycles, although a cut-off number of cycles could not be established.

Similar results have been described by Calvo et al [18]. They compared the down-staging and PCR rate between two consecutive groups of patients. One group comprised 114 patients and received only concomitant CRT with oral

Tegafur and the other group, consisting of 52 patients, received additionally 2 cycles of FOLFOX4 as an induction chemotherapy. Downstaging two or more T categories was significantly better in the FOLFOX4 group (44% vs. 24% in the CRT-only group, p=0.029); the PCR rate was also significantly higher (29% vs. 8% in the CRT-only group, p=0.006).

A randomized clinical trial with induction chemotherapy before CRT might further clarify the role of Oxaliplatin in the neoadjuvant treatment of rectal adenocarcinoma, especially regarding reduction of the rate of metastases.

The most intriguing finding was that a length of radiotherapy of more than 35 days influenced down-staging beneficially. This aspect might be somewhat similar to when a longer wait period (>6-8 weeks) is used from the end of CRT until the moment of surgery [19]. Hypotheses for the phenomenon observed by us are: better revascularization, tumor reorganization and/or higher chance to have mitotic cancer cells when treatment is delivered (synchronization). Nonetheless, the protraction of treatment or increase of wait before surgery might negatively influence the rate of local relapses and metastases due to relatively radioresistant clones and accelerated repopulation.

CEA was described recently by Yeo et al as one of the important factors predicting down-staging. The ypT0-2 rate was 57.1% when CEA was ≤5 ng/ml vs. 27.4% when CEA was >5 ng/ml [20]

CA 19-9 is becoming an important marker in colorectal cancer, although it is not included yet in standard protocols. It has been shown since the nineties that it is an independent prognostic factor [21] and is useful in metastatic disease [22]; recently its value has been demonstrated for follow-up [23]. Increased CA 19-9 has been correlated with high CEA, lymph node metastasis, right colon tumors, large tumor size and peritoneal seeding [24]. We have shown that CA 19-9 is more frequently increased in G3 tumors, independently of the (clinically established) stage.

The limits of our study are the relatively small number of patients, a certain degree of heterogeneity of the patient groups and the fact that it was only an observational study and not a randomized clinical trial.

CONCLUSIONS

Neoadjuvant chemoradiation with induction chemotherapy containing Oxaliplatin produces important down-staging in rectal adenocarcinoma and results in a high rate of sphincter preserving surgery. There are several prognostic factors for T down-staging and complete response. Based on our results, we consider that a randomized clinical trial in LARC with Oxaliplatin induction chemotherapy in one arm to compare the down-staging, complete response, local relapse and metastasis rate should be performed.

Conflicts of interest. None to declare.

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