



Compliance to Adjuvant Chemotherapy of Patients Who Underwent Surgery for Rectal Cancer: Report from a Multi-institutional Research Network

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Abstract

Introduction Adjuvant chemotherapy for locally advanced rectal cancer is associated with improved overall survival. However, recent evidence from randomized trials showed a compliance rate of 43 to 73%, which may affect efficacy. The aim of this multicenter retrospective analysis was to investigate the compliance rate to adjuvant treatment for patients who underwent rectal surgery for cancer.

Methods Patients who underwent surgery with curative intent for rectal cancer in six Italian colorectal centers between January 2013 and December 2017 were retrospectively reviewed. Exclusion criteria were age less than 18 years, palliative or emergency surgery, and stage IV disease. Parameters of interest were patients' characteristics, preoperative tumor stage, neo-adjuvant chemoradiation therapy, intra-operative and postoperative outcomes. Although the participating centers referred to the same treatment guidelines for treatment, the chemotherapy regimen was not standardized across the institutions. Reasons for not starting adjuvant chemotherapy when indicated, interruption, and modification of drug regimen were collected to investigate compliance.

Results A total of 572 patients were included in the analysis. Two hundred and fifty-two (44.1%) patients received neo-adjuvant chemoradiation therapy. All patients underwent high anterior rectal resection, low anterior rectal resection, or Miles' procedure. Of 399 patients with an indication to adjuvant chemotherapy, 176 (44.1%) completed the treatment as planned. Compliance for patients who started chemotherapy was 56% (95% CI 50.4–61.6%). Sixty-six patients interrupted the treatment, 76 patients significantly reduced the drug dose, and 41 patients had to switch to other therapeutic regimens.

Conclusions The present multicenter investigation reports a low compliance rate to adjuvant chemotherapy after rectal resection for cancer. Multidisciplinary teams should focus on future effort to improve compliance for these patients.

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Background

Despite a low but constant decrease throughout time, the incidence of rectal cancer remains high [1]. A multidisciplinary approach to this particular disease is warranted, as multiple therapeutic strategies are available and treatment guidelines are constantly evolving [2].

Adjuvant chemotherapy (AC) appears to be independently associated with improved overall survival regardless of stage of disease, pathologic response, and patient factors [3, 4]. Recent papers have questioned the efficacy and compliance to AC [2, 5]. The European Society for Medical Oncology reports this uncertainty in its latest guidelines on postoperative therapy for rectal cancer [6].

Paradigm shift of the last 10 years has been the introduction of neo-adjuvant chemoradiation therapy (CRT), which provides a reduction in the risk of local recurrence. Recent trials are evaluating the efficacy of total neo-adjuvant treatment [7, 8], with the rationale to achieve a better control over distant recurrence by treating potential micrometastasis.

In fact, optimal control over recurrent disease requires a good compliance to both neo-adjuvant and adjuvant treatments. FOLFOX regimens have high toxicity rates [9], especially for patients who underwent surgery and suffered from complications. These factors may delay or even contraindicate chemotherapy, resulting in poor patient's compliance. The European Organization for Research and Treatment of Cancer (EORTC) trial [10] and the CHRONICLE trial [11] investigated the adherence to AC for patients who underwent rectal surgery, reporting a compliance rate of 43% and 48.1%, respectively. The Dutch PROCTOR/SCRIPT trial [12] reported a compliance rate of 73.6%. Referred reasons for not initiating or completing adjuvant therapy were postoperative complications, drug toxicity, disease progression, and patient refusal. Nevertheless, there is a lack of information about the actual compliance to adjuvant treatment for patients who underwent surgery for rectal cancer, especially among the Italian population and outside of prospective clinical trials.

For this reason, we designed the present multicenter retrospective analysis of prospectively collected data among different Italian colorectal centers, to investigate the compliance rate to adjuvant treatment for patients who underwent rectal surgery for cancer.

Methods

Data collection

After approval by the local ethic committees, patients who underwent surgery with curative intent for rectal cancer in six Italian colorectal centers between January 2013 and December 2017 were retrospectively reviewed. Exclusion criteria were: patients younger than 18 years, palliative and emergency surgery, and stage IV rectal cancers. All participating centers are required to maintain a prospective tumor registry of patients with colorectal cancer diagnosis. Patients' information was entered into a database designed specifically to investigate the compliance to AC. Periodical audit is performed to ensure consistency in the data collection process among centers and minimize variability.

Parameters of interest were patients' characteristics, preoperative tumor stage, neo-adjuvant chemoradiation therapy, surgical, intra-operative and postoperative parameters. Special focus was dedicated to the reasons for both not starting AC when it is indicated and why adjuvant therapy was interrupted and drug regimen was changed or reduced.

Preoperative assessment consisted in colonoscopy, chest and abdominal CT scan, and pelvic MRI. Endorectal ultrasound was also involved in preoperative tumor staging.

Indication for neo-adjuvant and adjuvant CT was given during a multidisciplinary assessment for each patient according to the NCCN Guidelines [13].

The primary aim was to investigate the rate of patients that received and completed the adjuvant treatment. Completion was considered when patients were fully compliant to the treatment as planned by the oncologist before starting AC. Failure was considered when AC was not started or it was interrupted, drug dose was significantly reduced, or adjuvant treatment had to be switched to another regimen.

The secondary aim was to investigate and report the reasons for interruption, delay, or contraindication to AC.

Statistical analysis

Continuous data are reported as median and interquartile ranges (IQRs). Categorical data are reported as counts and percentages.

Univariable log-binomial regression models were fitted to evaluate whether selected features were associated with the risk of not starting or interrupting AC. Factors significantly associated with the risk of not starting or interrupting AC at univariable analyses were considered in a final

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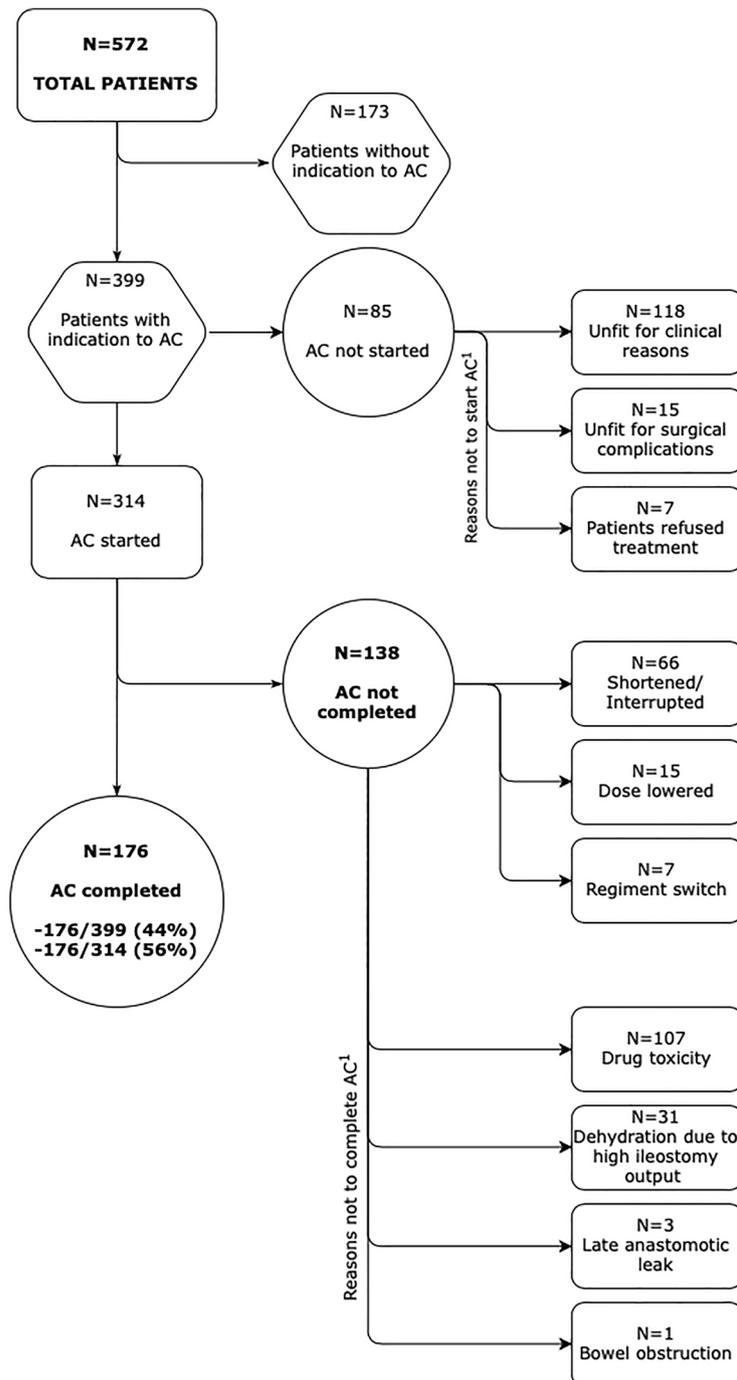
multivariable regression model. A p value < 0.05 was considered as statistically significant.

Based on the results of multivariate log-binomial regression model, a nomogram to evaluate graphically the effect of each included risk factor on the risk of not starting or interrupting adjuvant chemotherapy was developed.

A p value < 0.05 was considered as statistically significant.

All the analyses were performed using SAS software, version 9.4 (SAS Institute, Cary, NC).

Fig. 1 Study flowchart and selection of patients (PTs) evaluated for indication and compliance to adjuvant chemotherapy (CT)



AC: Adjuvant chemotherapy; ¹ more than one reason may apply.

Results

A total of 572 patients were included in the analysis (Fig. 1). Table 1 reports patients' characteristics. Two hundred and fifty-two patients received neo-adjuvant CRT. All patients underwent high anterior rectal resection, low anterior rectal resection, or Miles' procedure.

All patients received either TME or partial mesorectal excision (PME) in case of tumor of the upper third of the rectum.

Perioperative and oncological outcomes are described in Table 2. Median length of hospital stay was 9 [7–14] days. Sixty-one (10.7%) patients had a Clavien-Dindo complication score of 3 or higher. Thirty-day mortality was 1.7%.

Thirty-six patients had a pathological complete response (pCR), 173 had stage I disease, and 363 patients were stage II or III rectal cancer at pathological examination.

Table 1 Preoperative characteristics

	Total (N = 572)
Age (year), median (IQR)	71 (62–78)
Sex, N (%)	
Female	237 (41.4)
Male	335 (58.6)
BMI (kg/m ²), median (IQR)	25 (23–28)
Missing	61
Charlson score, median (IQR)	5 (4–6)
Tumor site, N (%)	
Low	239 (41.8)
Middle	217 (37.9)
High	116 (20.3)
Initial stage, N (%)	
I	133 (23.3)
II	113 (19.8)
III	300 (52.4)
Missing	26 (4.5)
Neo-adjuvant CT, N (%)	
No	312 (54.5)
Yes ^a	252 (44.1)
Missing	8 (1.4)
Post-neo-adjuvant CT stage, N (%)	
Complete response	11 (4.4)
I	36 (14.3)
II	64 (25.4)
III	84 (33.3)
Missing	57 (22.6)

IQR interquartile range, BMI body mass index, CT chemotherapy

^a252/413 = 61% of patients with II or III pre-surgery stage had neo-adjuvant CT

Table 2 Postoperative characteristics and outcomes

	Total (N = 572)
Tumor stage, N (%)	
0	4 (0.8)
Complete response	32 (5.7)
I	173 (30.2)
IIA	122 (21.3)
IIB	10 (1.7)
IIC	2 (0.3)
IIIA	52 (9.1)
IIIB	147 (25.7)
IIIC	30 (5.2)
Number of lymph nodes, median (IQR)	17 (13–24)
Missing	4
Number of positive lymph nodes (in N+), median (IQR)	2 (1–4)
Tumor type, N (%)	
Adenocarcinoma	547 (95.6)
Mucinous	25 (4.4)
Tumor grade, N (%)	
G1	54 (9.4)
G2	350 (61.2)
G3	88 (15.4)
Missing	80 (14.0)
Quirke, N (%)	
Complete (1)	356 (62.2)
Nearly complete (2)	53 (9.3)
Incomplete (3)	5 (0.9)
Missing	158 (27.6)
Mismatch repair, N (%)	
Absent	53 (9.3)
Present	237 (41.4)
Missing	282 (49.3)
Type of surgery, N (%)	
Open	84 (14.7)
VLS	454 (79.4)
Conversion	34 (5.9)
Complications: Clavien-Dindo, N (%)	
0	271 (47.4)
1	130 (22.7)
2	101 (17.7)
3a	19 (3.3)
3b	37 (6.5)
4a	2 (0.3)
4b	2 (0.3)
5	10 (1.7)
Relevant complications, N (%)	
None	271 (47.4)
Minor ^a	231 (40.4)
Major ^b	70 (12.2)

Table 2 continued

	Total (<i>N</i> = 572)
Free distal margin, <i>N</i> (%)	
No	12 (2.1)
Yes	560 (97.9)
Free circumference margin, <i>N</i> (%)	
No	42 (7.3)
Yes	530 (92.7)
Ileostomy, <i>N</i> (%)	
No	264 (46.2)
Yes	308 (53.8)
Colostomy, <i>N</i> (%)	
No	397 (69.4)
Yes	175 (30.6)
Days of hospitalization, median (IQR)	9 (7–14)
Missing	3
Hospital death, <i>N</i> (%)	
No	562 (98.3)
Yes	10 (1.7)

IQR: interquartile range

^aClavien-Dindo equals to 1 and 2

^bClavien-Dindo greater than 2

Patients with pCR received the indication for AC as well as patients with stage II and III. Of 399 patients with indication to AC, 314 (78.7%; 95% CI 74.3–82.6%) started chemotherapy. Reasons for not starting AC were age, poor clinical conditions, postoperative complications, and patients' choice (Fig. 1).

Of 399 patients with an indication to AC, 176 (44.1%, 95% CI 39.2–49.1%) completed the treatment as planned, whereas AC compliance considering only the patients who started AC was 56% (95% CI 50.4–61.6%). Sixty-six patients interrupted AC, 76 patients significantly reduced the drug dose, and 41 patients had to switch to other therapeutic regimens.

For 245 (78%) patients, chemotherapy was administered in the same hospital where surgery was performed.

Table 3 reports the association between patient and tumor characteristics and the risk of not starting or interrupting AC, evaluated by means of univariable and multivariable log-binomial regression models. The multivariable model showed that patient's age was positively associated with poorer compliance to AC with (RR = 1.11 for 10-year increase in age, 95% CI 1.02–1.20, $p = 0.011$), while neo-adjuvant CRT appeared to reduce the risk of not starting or interrupting AC (RR = 0.86, 95% CI 0.70–0.99, $p = 0.041$).

Development of the nomogram

By univariate analyses, three of ten clinical variables were significantly associated with compliance rate to AC ($p < 0.05$). These variables were used to build the multivariate log-binomial regression model. Age, Charlson score, and the previous neo-adjuvant chemotherapy were strong predictors of compliance to AC. The nomogram represents graphically the effect of each considered risk factor (Fig. 2).

Discussion

Surgery with mesorectal clearance is the mainstay of treatment for patients with locally advanced rectal cancer. However, multimodality therapy has significantly improved long-term survival. Preoperative CRT has shown its benefit in reducing local recurrence and in downstaging the primary tumor [14]. The use of postoperative chemotherapy in patients previously irradiated has been questioned. Our study reports a compliance rate of 44% of completing the adjuvant treatment among patients who received indication to AC. This result is in accordance with the findings from previously published trials, reinforcing the concept of low compliance to AC after rectal cancer surgery.

Recently, large national registries have shown that the use of AC is associated with improved overall survival, and this is true also for patients who previously underwent neo-adjuvant CRT. A low compliance rate translates into a lack of benefit and then poorer survival for patients who do not start or complete the treatment [3].

The adherence to AC for rectal cancer remains an issue even within the setting of clinical trials. The EORTC trial referred a 43% compliance rate, the CHRONICLE trial had a compliance rate of 48.1%, and in the Dutch PROCTOR/SCRIPT trial, the compliance rate was 73.6%. Main causes for not starting or completing adjuvant therapy were postoperative complications, drug toxicity, disease progression, and patient refusal. Eight NCCN centers collaborating on the colorectal cancer database estimated a compliance rate of approximately 80% [4].

Xu et al. queried the National Cancer Database for patients with clinical stage II/III rectal cancer who underwent neo-adjuvant CRT and surgical resection. They reported only 32% of eligible patients receiving AC, although stating several relevant biases in the performed analysis [3]. These results may highlight that patients are not receiving the treatment they deserve.

Our study retrospectively analyzed the data collected from high-volume colorectal centers in northern Italy outside a clinical trial. All centers have a multidisciplinary

Table 3 Association between patient and surgical factors and the risk of not starting or interrupting chemotherapy

Variable		N. not starting or interrupting/N Tot	%	Univariable models			Multivariable model*		
				RR	95% CI	<i>p</i> value	RR	95% CI	<i>p</i> value
All patients		223/399	56	–	–	–	–	–	–
Age	+10 years	–	–	1.21	1.12–1.30	<0.001	1.11	1.02–1.20	0.011
BMI	+1 kg/m ²	–	–	1.00	0.98–1.03	0.80			
Charlson score	+2 points	–	–	1.08	1.04–1.13	<0.001	1.08	1.00–1.17	0.39
Sex	Female	100/164	61	1.00					
	Male	123/235	52	0.86	0.72–1.02	0.08			
Tumor stage	0	6/18	33	1.00					
	I	23/54	43	1.28	0.62–2.63	0.51			
	II	63/106	59	1.78	0.91–3.49	0.09			
	III	131/221	59	1.78	0.92–3.45	0.09			
Neo-adjuvant CT	No	125/185	68	1.00			1.00		
	Yes	97/210	46	0.68	0.57–0.82	<0.001	0.86	0.70–0.99	0.041
	Missing	1/4	25	–					
Postsurgical complication	No	88/177	50	1.00					
	Minor ^a	105/175	60	1.21	1.00–1.46	0.05			
	Major ^b	30/47	64	1.28	0.99–1.67	0.06			
Type of surgery	VLS	168/304	55	1.00					
	Open	42/68	62	1.12	0.90–1.38	0.31			
	Conversion	13/27	48	0.87	0.58–1.31	0.50			
Ileostomy	No	105/186	56	1.00					
	Yes	118/213	55	0.98	0.82–1.17	0.83			
Colostomy	No	145/268	54	1.00					
	Yes	78/131	60	1.10	0.92–1.32	0.29			

Results from log-binomial univariable and multivariable regression analyses (N = 399)

RR risk ratio, CI confidence interval, CT chemotherapy

*Only statistically significant ($p < 0.05$) variables at univariable analysis entered the multivariable model

^aClavien-Dindo equals to 1 and 2

^bClavien-Dindo greater than 2

team dedicated to the treatment of rectal cancer. Data collected could be a good appraisal of the current state of art in a typical European setting.

Our described 44% compliance to AC is in line with the EORTC and the CHRONICLE trials [10, 11] while being lower than the reported rate from the Dutch trial [12].

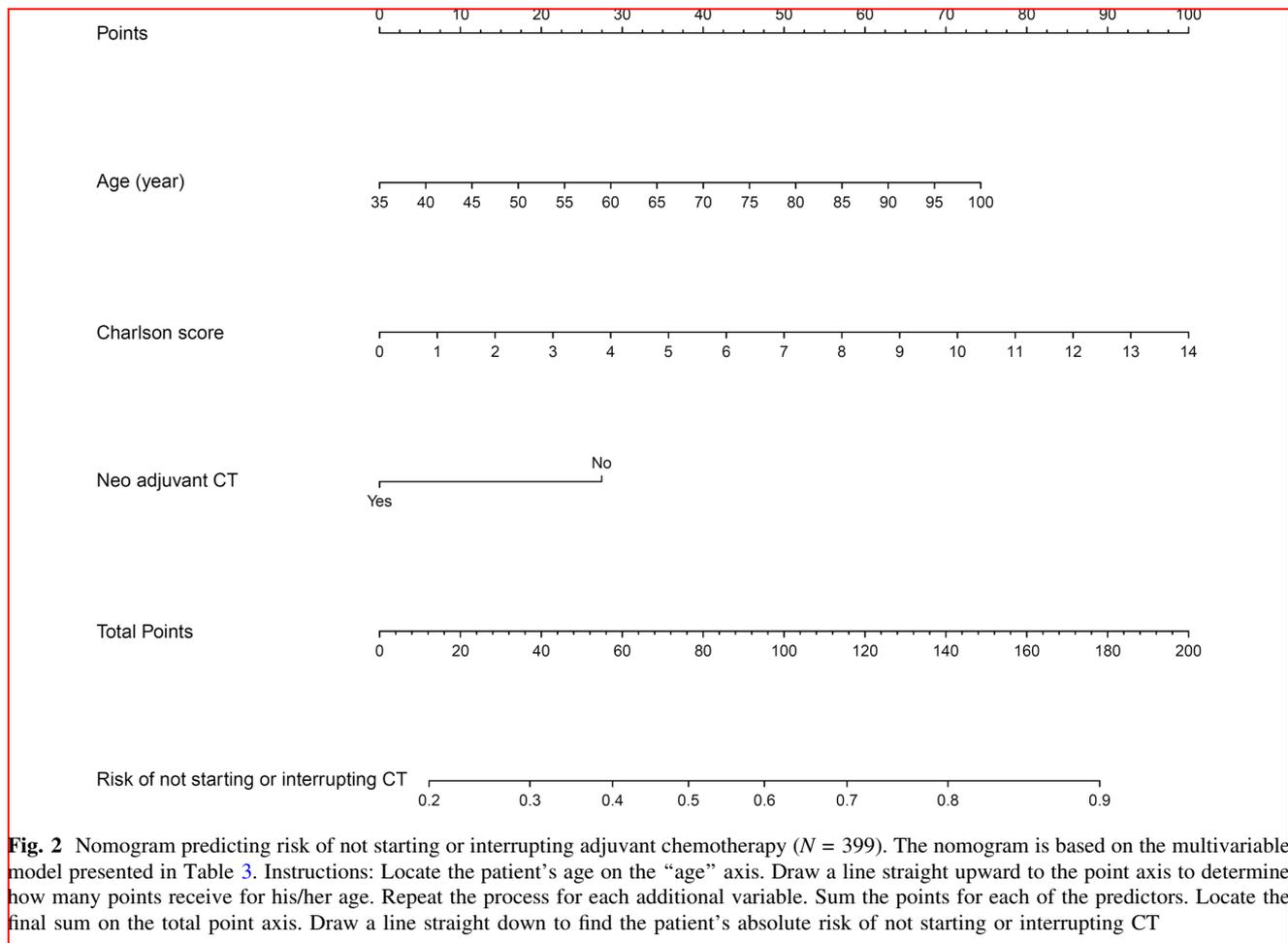
Our rigid primary endpoint of considering changes in dose and type of chemotherapy as a failure of the therapy may result in a lower compliance rate. Considering only the interruption of therapy as a failure, the recorded compliance rate would be similar to that reported by the Dutch trial. However, since there is no consistent evidence that reducing or changing AC for rectal cancer does not impact overall survival, patients who switch to another treatment or reduce chemotherapy dose should be acknowledged as failures.

Ileostomy-related events, although affecting a small number of patients, deeply impacted the adherence to AC.

Dehydration was the most common event that required hospital admission, leading to AC interruption. In only one hospital, ileostomy closure was routinely performed before AC started after anastomotic leak was endoscopically excluded. No patient had a delay in AC onset due to surgery for ileostomy closure. Such a behavior could be extended to selected fragile patients for whom stoma-related dehydration represents a threatening complication.

We did not consider the patient's age as a contraindication for AC. As reported by Bergquist et al., the use of adjuvant therapy in patients 80 and older is associated with a significant improvement in overall survival compared to surgery alone [15].

Multivariable analysis showed an augmented risk of poor compliance to AC with increasing age, while preoperative CRT appeared to be a protective factor for completing AC, both in univariate and in multivariate analyses. The main reason for this important finding could be that



AC for patients who received preoperative CRT is significantly shorter compared to naive patients. Thus, shortening AC, as previously reported, is related to better overall compliance [16].

In our series, all patients with a pCR received AC. As recently, reported AC is associated with improved overall survival in locally advanced rectal cancer also for patients with pCR after neo-adjuvant CRT and radical surgery [17].

This result of poor compliance to AC in an Italian population of patients who underwent surgery for rectal cancer suggests that a change in treatment is needed. The concept of a totally neo-adjuvant setting could be taken into consideration as new therapeutic approach to improve compliance.

Our study has several limitations, beyond its retrospective nature. Although there are several accepted regimens for AC in rectal cancer, our network could only standardize the surgical technique without unifying the AC regimen. Therefore, there were different AC protocols that may have influenced the final results. Finally, the nomogram needs to be externally validated by a second cohort.

In conclusion, the present study of a large cohort of patients from multiple centers reports a low compliance rate to AC after rectal resection. Multidisciplinary teams should focus on future effort to improve compliance for these patients. Total neo-adjuvant chemotherapy may be an option, but future research is needed to validate this therapeutic approach.

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Compliance with ethical standards

Conflict of interest The authors declare no conflicts of interest in relation to the present manuscript.

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