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ORIGINAL RESEARCH

Prognostic role of a new inflammatory index with neutrophil-to-lymphocyte ratio and lactate dehydrogenase (CII: Colon Inflammatory Index) in patients with metastatic colorectal cancer: results from the randomized Italian Trial in Advanced Colorectal Cancer (ITACa) study

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Aim: The aim of this study was to investigate the role of a new inflammatory index (Colon Inflammatory Index [CII]) as a predictor of prognosis and treatment efficacy in patients with metastatic colorectal cancer (mCRC) enrolled in the prospective multicenter randomized ITACa (Italian Trial in Advanced Colorectal Cancer) trial to receive first-line chemotherapy (CT)+ bevacizumab or CT alone.

Patients and methods: Between November 14, 2007 and March 6, 2012, 276 patients diagnosed with CRC were available for baseline neutrophil-to-lymphocyte ratio (NLR) and lactate dehydrogenase (LDH). We divided the population into three groups on basis of the CII index.

Results: At baseline in all populations, median PFS and OS was predictive of clinical outcome ($p<0.0001$). Following adjustment for clinical covariates, multivariate analysis confirmed CII index as an independent prognostic factor. The CII index was also predictive when we evaluated the two distinct arms with ($p=0.0009$) or without bevacizumab ($p=0.0001$). When we divided right side versus left side for treatment regimen (CT plus bevacizumab versus only bevacizumab), we found a benefit of bevacizumab versus only CT in the right side in patients treated with bevacizumab and not in patients treated with only chemotherapy. Conversely, we found no difference the left side, but we found a difference in the poor group of 4 months in favor to only chemotherapy.

Conclusion: Our results indicate that the CII index is a good prognostic marker for mCRC patients in first line treatment with CT with or without bevacizumab.

Trial registration: NCT01878422 ClinicalTrials.gov; date of registration: June 7, 2013.

Keywords: metastatic colorectal cancer, bevacizumab, first-line, prognosis, lactate dehydrogenase, neutrophil-to-lymphocyte ratio

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Introduction

Colorectal cancer (CRC) is one of the major causes of comorbidity and death from cancer worldwide.[1]

Bevacizumab (B) is a monoclonal antibody that binds to the vascular endothelial growth factor with antiangiogenic activity. The use of B combined with fluoropyrimidine-based chemotherapy (CT) plus oxaliplatin and/or irinotecan is considered standard of care in first- and second-line treatment for patients with metastatic CRC (mCRC).[2,3]

There are no current validated factors that can predict sensitivity or resistance to B. Several studies have investigated this issue in recent years, but with poor results.

The literature has demonstrated the relationship between systemic chronic inflammation and various types of cancer, including CRC.[4] The activation of the inflammation by the tumor determines the inhibition of apoptosis and can promote angiogenesis.[5,6]

Several papers in the literature have shown that neutrophil-to-lymphocyte ratio[7-12] (NLR) and lactate dehydrogenase (LDH)[13–17] have a predictive and prognostic role in various diseases, including CRC. We have previously demonstrated in separate studies the correlation between LDH serum levels[18] and NLR[19] and clinical outcome in first-line mCRC. NLR is a good peripheral inflammatory index and LDH serum levels are an indirect marker of tumor hypoxia, neo-angiogenesis, metastasis development and poor prognosis in many cancers.[20]

Based on these results, we have created a new inflammatory index (CII: colon inflammatory index), composed of NLR and LDH. We considered CII as a predictor of prognosis and treatment efficacy in patients with mCRC enrolled in the prospective multicenter randomized ITACa (Italian Trial in Advanced Colorectal Cancer)[21] trial to receive first-line CT+B or CT alone.

Patients and methods

The ITACa trial

The study population consisted of patients with advanced CRC confirmed by pathological analysis. No patient had received previous systemic therapy.

All eligible patients were randomly assigned in a 1:1 ratio to receive CT+B or CT alone as first-line therapy. CT consisted of either FOLFOX4 or FOLFIRI at the clinician's discretion.[18] The full protocol of the ITACa trial is available in the first publication of the trial.[21]

Treatment continued until either progressive disease (PD) or unacceptable toxicity or withdrawal of consent. Tumor assessment was performed before the start of treatment and repeated every 8 weeks until PD. Responses were defined according to the Response Evaluation Criteria in Solid Tumors (RECIST 1.1) guidelines (per investigator assessment). The National Cancer Institute Common Toxicity Criteria (NCI-CTC 3.0) were used for evaluating adverse events.

All patients provided written informed consent before enrollment in the study. The study was approved by the local ethics committee (Comitato Etico Area Vasta Romagna) on September 19, 2007, and registered in our National Clinical Trials Observatory (Osservatorio delle Sperimentazioni Cliniche) and in the European Clinical Trials Database (EudraCT no. 2007–004539-44) before patient recruitment began. Registration on ClinicalTrials.gov (NCT01878422) was not mandate and was completed at a later date after the end of the study (June 7, 2013).

The study was carried out in accordance with the Declaration of Helsinki under good clinical practice conditions and after full approval from the ethics committees of all participating centers.

Statistical analysis

The objectives of this secondary analysis were to examine the association between baseline CII and progression-free survival (PFS) and overall survival (OS) in the ITACa study. CII was developed combining NLR and LDH. Patients were divided into three risk groups depending on their CII: good (0 factor: NLR <3 and LDH ≤upper limit of normal-ULN), intermediate (1 factor: NLR ≥3 or LDH >ULN) and poor (2 factors: NLR ≥3 and LDH >ULN). The cutoff of NLR ≥3 was previously determined (Passardi A et al, Oncotarget 2016) and the ULN for LDH was defined according to the limit of each center (Passardi A et al, PloSOne 2015).

PFS was defined as the time from random assignment to the first documentation of PD (as per investigator assessment), or death from any cause. Patients undergoing curative metastasectomy were censored at the time of surgery. OS was defined as the time between random assignment and death or last follow-up visit.

Association between risk groups of CII and baseline characteristics was tested using Chi-squared or Fisher exact test. PFS, OS and their two-sided 95% CI were estimated by the Kaplan–Meier method and curves were compared by the log-rank test (at a significance level of 5%). Estimated HRs and their two-sided 95% CI were calculated using the Cox-proportional hazard model. HRs adjusted by center and baseline characteristics (gender, age, performance status, KRAS status, tumor site [rectum/colon], CT regimen [FOLFOX4/FOLFIRI] and ITACa treatment [CT+B vs CT alone]) were calculated using the Cox-proportional hazard model. Covariate selection was based on a list of suspected prognostic factors derived from the ITACa study.

The ORR was classified into partial response (PR), stable disease (SD) and PD. Either Chi-squared or Fisher's exact test was used to evaluate the association between CII and ORR. All *p*-values were based on two-sided testing, and statistical analyses were performed using SAS statistical software version 9.4 (SAS Inc., Cary, NC, USA).

Results

Patient characteristics

Between November 14, 2007, and March 6, 2012, 276 patients diagnosed with CRC were available for baseline NLR and LDH (Figure 1): 164 (59.4%) were males and 112 (40.6%) females with a median age at diagnosis of 66 years (range 33–83). Median follow-up was 36 months (range 1–65). Overall, median PFS was 9.1 (95% CI 8.5–9.9) and median OS was 21.4 months (95% CI 19.3–24.5).

We divided the population into three groups on the basis of CII. The three groups of patients were comparable for age, gender, tumor site, KRAS status and ITACa treatment. A considerable proportion of patients with poor CII had a performance status 1–2 (Table 1). Table S1 shows the characteristics of patients treated with and without B.

CII and clinical outcome in all patients

Median PFS was 10.3 months (95% CI 9.3–13.1), 8.7 months (95% CI 6.9–10.3) and 7.3 months (95% CI

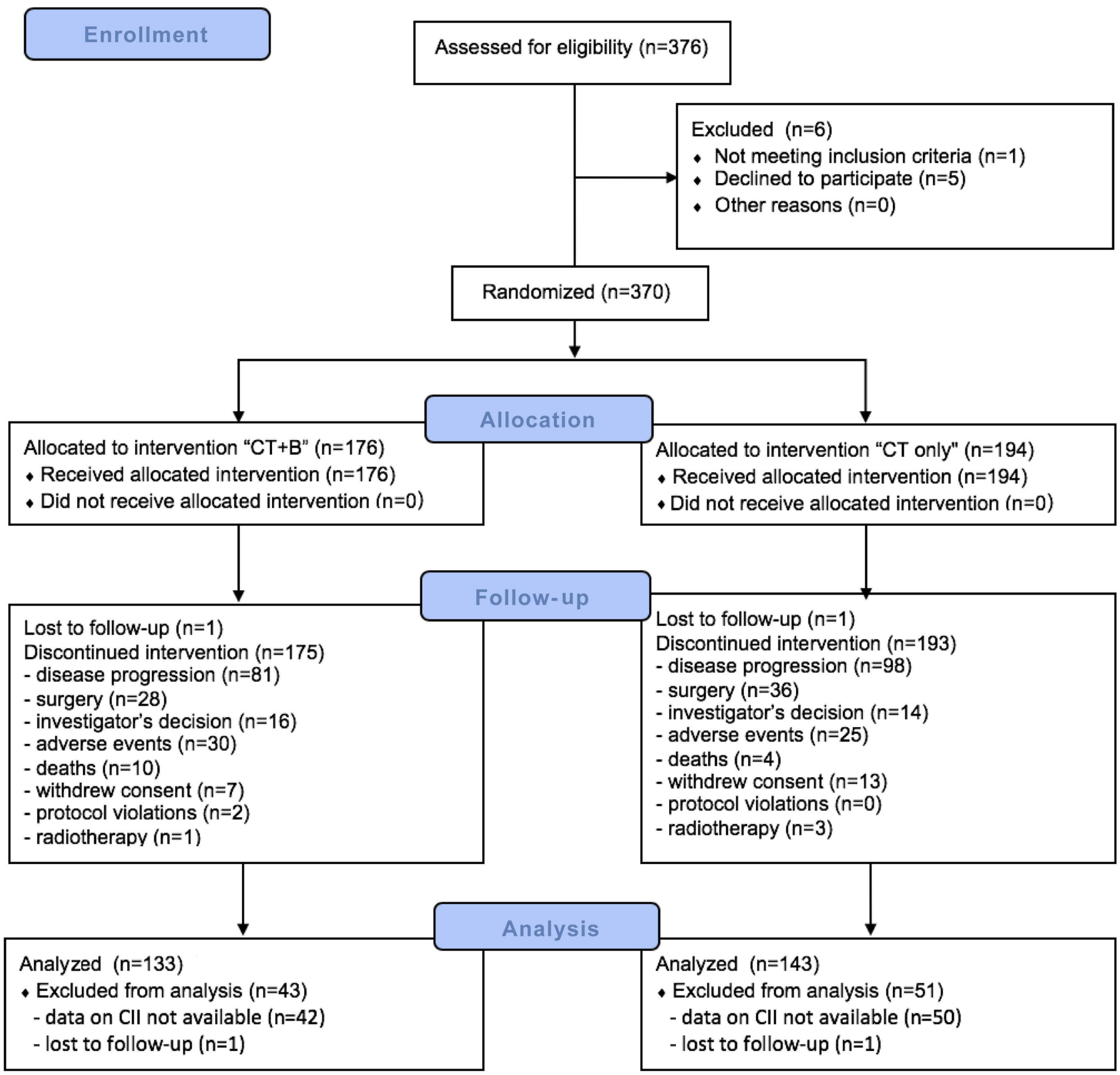

Figure 1 Flowchart of the study.
Abbreviation: CII, Colon Inflammatory Index.

Table 1 Baseline characteristics according to CII. Good (0 factor: NLR<3 e LDH≤UNL); intermediate (1 factor: NLR≥3 o LDH>UNL); poor (2 factors: NLR≥3 e LDH>UNL)

	Good (0 factor)	Intermediate (1 factor)	Poor (2 factors)	Overall	*p*
	N=114, 41.3%	N=98, 35.5%	N=64, 23.2%	N=276, 100%	
	n (%)	n (%)	n (%)	n (%)	
Median age (range)	66 (33–83)	65 (34–82)	65 (37–81)	66 (33–83)	0.877
Gender					
Male	73 (64.0)	55 (56.1)	36 (56.2)	164 (59.4)	
Female	41 (36.0)	43 (43.9)	28 (43.8)	112 (40.6)	0.254
ECOG PS					
0	98 (86.0)	85 (86.7)	37 (57.8)	220 (79.7)	
1–2	16 (14.0)	13 (13.3)	27 (42.2)	56 (20.3)	<0.0001
Tumor localization					
Rectum	30 (26.3)	27 (27.5)	15 (23.4)	72 (26.1)	
Colon	84 (73.7)	71 (72.5)	49 (76.6)	204 (73.9)	0.732
Right-sided	65 (58.0)	68 (70.1)	44 (68.7)	177 (64.8)	
Left-sided	47 (42.0)	29 (29.9)	20 (31.3)	96 (35.2)	0.102
Stage at diagnosis					
I–III	36 (34.0)	24 (25.3)	6 (9.7)	66 (25.1)	
IV	70 (66.0)	71 (74.7)	56 (90.3)	197 (74.9)	0.0006
Grade					
1	5 (5.1)	3 (4.1)	4 (8.5)	12 (5.5)	
2	68 (69.4)	45 (61.6)	25 (53.2)	138 (63.3)	
3	25 (25.5)	25 (34.3)	18 (38.3)	68 (31.2)	0.263
CT regimen					
FOLFOX4	71 (62.3)	59 (60.2)	41 (64.1)	171 (62.0)	
FOLFIRI	43 (37.7)	39 (39.8)	23 (35.9)	105 (38.0)	0.877
KRAS status[a]					
Wild type	70 (61.4)	63 (64.3)	41 (64.1)	174 (63.0)	
Mutated	44 (38.6)	35 (35.7)	23 (35.9)	102 (37.0)	0.688
ITACa treatment					
CT+B	62 (54.4)	42 (42.9)	29 (45.3)	133 (48.2)	
CT	52 (45.6)	56 (57.1)	35 (54.7)	143 (51.8)	0.171

Notes: [a]Mandatory as consequence of amendment n. 1 of May 3, 2009.
Abbreviations: ECOG, Eastern Cooperative Oncology Group; ITACa, Italian Trial in Advanced Colorectal Cancer; CT, chemotherapy; B, bevacizumab; CII, Colon Inflammatory Index; NLR, neutrophil-lymphocyte ratio; PS, performance status.

5.5–8.9) for patients with good, intermediate and poor CII, respectively (*p*<0.0001) (Figure 2A). Median OS was 29.9 months (95%CI 24.3–37.3), 20.9 months (95%CI 16.8–25.4) and 14.4 months (95% CI 11.4–17.1) for patients with good, intermediate and poor CII, respectively (*p*<0.0001) (Figure 2B). The three categories were associated with different toxicities (Table 2).

In multivariate analysis, CII showed an independent prognostic factor predictive of PFS and OS after adjustment for clinical covariates (ITACa treatment, center, CT regimen, KRAS status and baseline characteristics) (Table 3).

CII classification was not associated with response (Table 4).

CII and clinical outcome in patients treated with CT+B

Among patients treated with CT+B, median PFS was 12.1 months (95% CI 9.8–14.7), 10.0 months (95% CI 6.9–12.9) and 8.6 months (95% CI 3.7–9.4) for patients with good, intermediate and poor CII, respectively (*p*=0.0004) (Figure 3A). Median OS was 31.6 months

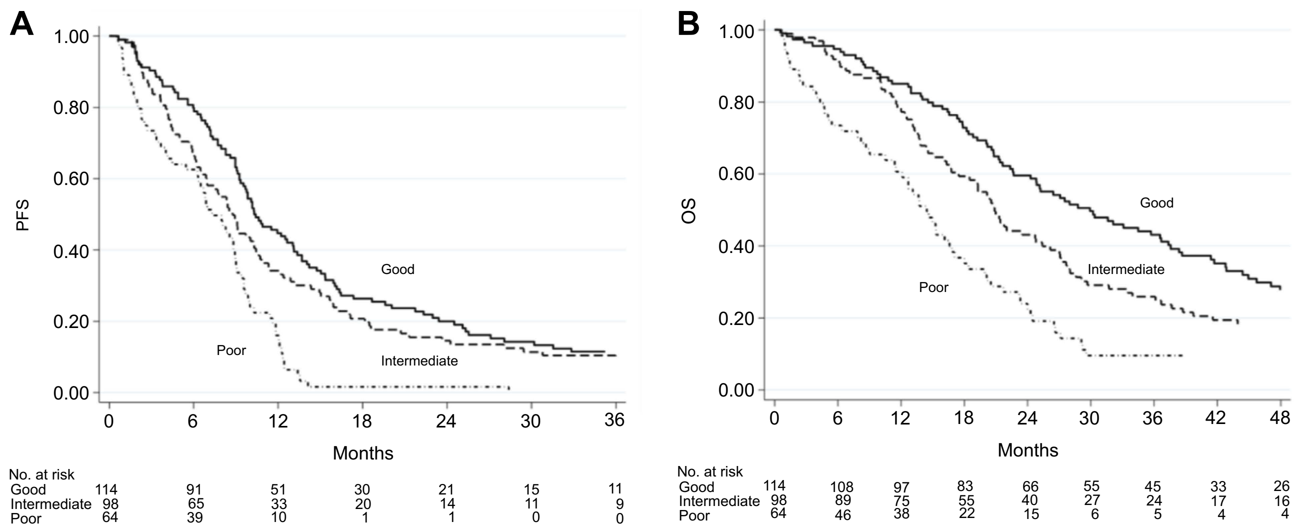

Figure 2 Kaplan–Meier curves of progression free survival (PFS) (**A**) and overall survival (OS) (**B**) of patients for the Colon Inflammatory Index.

(95% CI 22.3–41.7), 20.6 months (95% CI 13.6–27.0) and 12.7 months (95% CI 5.4–14.6) for patients with good, intermediate and poor CII, respectively (p=0.0009) (Figure 3B).

Following adjustment for the same clinical covariates, multivariate analysis confirmed CII as an independent prognostic factor for predicting PFS and OS (Table 3).

CII and clinical outcome in patients treated with CT alone

Median PFS was 9.6 months (95% CI 8.6–13.0), 8.4 months (95% CI 6.2–9.1) and 7.3 months (95% CI 4.5–9.0) for patients with good, intermediate and poor CII, respectively (p=0.002) (Figure 4A). Median OS was 27.1 months (95%CI 20.8–38.7), 21.3 months (95%CI 16.8–28.0) and 17.1 months (95% CI 11.5–23.2) for patients with good, intermediate and poor CII, respectively (p=0.0001) (Figure 4B).

Following adjustment for the same clinical covariates, multivariate analysis confirmed CII as an independent prognostic factor for predicting PFS and OS (Table 3).

CII and tumor site

For tumors located in the right side, median PFS was 10.4 months (95% CI 8.3–13.7), 7.7 months (95% CI 5.1–10.2) and 8.9 months (95% CI 1.0–10.3) for patients with good, intermediate and poor CII, respectively (p=0.002) (Table 5). Median OS was 26.4 months (95% CI 19.2–35.7), 15.0 months (95%CI 11.5–20.9) and 15.0 months (95% CI 2.4–24.5) for patients with good, intermediate and poor CII, respectively (p=0.004). Following adjustment for clinical covariates (ITACa treatment, center, CT regimen, KRAS status and baseline characteristics), multivariate analysis confirmed CII as an independent prognostic factor for predicting PFS and OS (Table 5).

For tumors located in the left side, median PFS was 10.3 months (95% CI 9.1–13.7), 9.1 months (95% CI 6.5–11.3) and 6.5 months (95% CI 3.7–8.8) for patients with good, intermediate and poor CII, respectively (p<0.0001). Median OS was 36.6 months (95% CI 24.8–44.4), 24.8 months (95% CI 19.3–28.0) and 13.7 months (95% CI 8.2–16.8) for patients with good, intermediate and poor CII, respectively (p<0.0001). Following adjustment for clinical covariates (ITACa treatment, center, CT regimen, KRAS status and baseline characteristics), multivariate analysis confirmed CII as an independent prognostic factor for predicting PFS and OS (Table 5).

When we considered left-sided and right-sided tumors separately by treatment regimen (CT+B vs CT alone), we observed a greater benefit of CT+B than CT alone in patients with a right-sided tumor. In particular, administration of CT+B yielded a 3-month longer OS for the good-CII group of patients, whereas a decrease in OS for the poor-CII group of patients. Conversely, no difference was found in patients with left-sided tumors, although the poor-CII group experienced a 4-month longer OS with CT+B than with CT alone (Table 6).

Table 2 Association between Colon Inflammatory Index and toxicity

	Grade	Good	Intermediate	Poor	*p*
		n	n	n	
Nausea	0	58	52	39	
	1–2	50	46	24	
	3–4	6	0	1	0.100
Vomiting	0	86	76	51	
	1–2	24	20	13	
	3–4	4	2	0	0.299
Diarrhea	0	57	43	43	
	1–2	47	50	19	
	3–4	10	5	2	0.034
Stomatitis	0	93	70	52	
	1–2	20	25	9	
	3–4	1	3	3	0.401
Fatigue	0	61	55	38	
	1–2	47	36	20	
	3–4	6	7	6	0.857
Anemia	0	96	78	47	
	1–2	18	17	15	
	3–4	0	3	2	0.045
Neutropenia	0	34	37	28	
	1–2	26	22	8	
	3–4	53	39	28	0.187
Thrombocytopenia	0	89	72	54	
	1–2	22	24	9	
	3–4	3	2	1	0.433
Febrile neutropenia	0	111	95	64	
	1–2	1	1	0	
	3–4	2	2	0	0.333
Hemorrhage	0	101	84	56	
	1–2	13	14	8	
	3–4	0	0	0	0.757
Hypertension	0	79	84	54	
	1–2	32	11	9	
	3–4	3	3	1	0.017
Thrombosis	0	92	85	48	
	1–2	6	5	8	
	3–4	16	5	8	0.905
Proteinuria	0	92	76	45	
	1–2	22	21	19	
	3–4	0	1	0	0.125
Neurologic system	0	69	65	45	
	1–2	35	28	16	
	3–4	10	5	3	0.126

Discussion

CII, based on NLR and LDH, allowed us to divide the patient population treated in the ITACa study into three categories: good, intermediate and poor. Good-CII patients (114 out of 276) achieved a median PFS of 30 months vs 14 months for the poor-CII patients. Interestingly, administration of CT+B resulted in a 4-month longer OS than CT alone in good-CII patients. The intermediate category of patients, however, showed no difference between the two regimens, while B+CT administration proved detrimental for the poor-CII group. When left-sided and right-sided tumors

Table 3 Prognostic/predictive value of the Colon Inflammatory Index in the total population (overall) and in CT plus B and CT-only treatment arms

	n patients	n events	Median PFS (months) (95% CI)	*p*	HR (95%CI)[a]	*p*	n events	Median OS (months) (95% CI)	*p*	HR (95% CI)[a]	*p*
Overall											
Good	114	104	10.3 (9.3–13.1)		1.00		88	29.9 (24.3–37.3)		1.00	
Intermediate	98	93	8.7 (6.9–10.3)		1.21 (0.90–1.63)		82	20.9 (16.8–25.4)		1.51 (1.09–2.08)	
Poor	64	63	7.3 (5.5–8.9)	<0.0001	2.27 (1.59–3.23)	<0.0001	60	14.4 (11.4–17.1)	<0.0001	2.38 (1.64–3.44)	<0.0001
CT+B											
Good	62	56	12.1 (9.8–14.7)		1.00		49	31.6 (22.3–41.7)		1.00	
Intermediate	42	40	10.0 (6.9–12.9)		1.31 (0.86–2.00)		36	20.6 (13.6–27.0)		1.63 (1.02–2.60)	
Poor	29	29	8.6 (3.7–9.4)	0.0004	1.97 (1.20–3.24)	0.027	28	12.7 (5.4–14.6)	0.0009	2.34 (1.37–3.99)	0.006
CT											
Good	52	48	9.6 (8.6–13.0)		1.00		39	27.1 (20.8–38.7)		1.00	
Intermediate	56	53	8.4 (6.2–9.1)		1.29 (0.83–1.99)		46	21.3 (16.8–28.0)		1.58 (0.98–2.52)	
Poor	35	34	7.3 (4.5–9.0)	0.002	2.40 (1.43–4.01)	0.004	32	17.1 (11.5–23.2)	0.0001	2.25 (1.31–3.87)	0.010

Notes: [a]Adjusted by ITACa treatment, center, CT regimen, KRAS status and baseline characteristics.
Abbreviations: PFS, progression-free survival; OS, overall survival; CT, chemotherapy; B, bevacizumab; ITACa, Italian Trial in Advanced Colorectal Cancer.

Table 4 Association between the Colon Inflammatory Index and response

	Good	Intermediate	Poor	p^a
	n (%)	n (%)	n (%)	
Overall				
CR+PR	69 (46.9)	46 (31.3)	32 (21.8)	
SD+PD	45 (35.2)	51 (39.8)	32 (25.0)	0.136
CT+B				
CR+PR	37 (51.4)	21 (29.2)	14 (19.4)	
SD+PD	25 (41.7)	20 (33.3)	15 (25.0)	0.530
CT				
CR+PR	32 (42.7)	25 (33.3)	18 (24.0)	
SD+PD	20 (29.4)	31 (45.6)	17 (25.0)	0.214

Notes: [a]Adjusted by ITACa treatment, center, CT regimen, KRAS status and baseline characteristics.

Abbreviations: LIPI, lung immune prognostic index; CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease; ITACa, Italian Trial in Advanced Colorectal Cancer; CT, chemotherapy; B, bevacizumab.

were considered separately, the good- and intermediate-CII groups with left-sided tumors had a benefit of almost 10 months compared to the right-sided tumors. No difference was seen in the poor-CII category. By assigning CT+B to right-sided tumors and CT alone to left-sided tumors we observed that B has a greater benefit in right-sided cancers, especially in CII-poor patients. This could be explained by the different tumor biology of the tumors classified according to the CII. There are no important differences with the data collected in the study. Unfortunately, we did not have the data on the BRAF that might explain this difference. The increased aggressiveness of tumors classified as poor can be seen in Table 1, where 90% of poor-CII tumors and only 66% of good-CII tumors were metastatic at diagnosis. The lower response to B in intermediate-CII and poor-CII patients can also

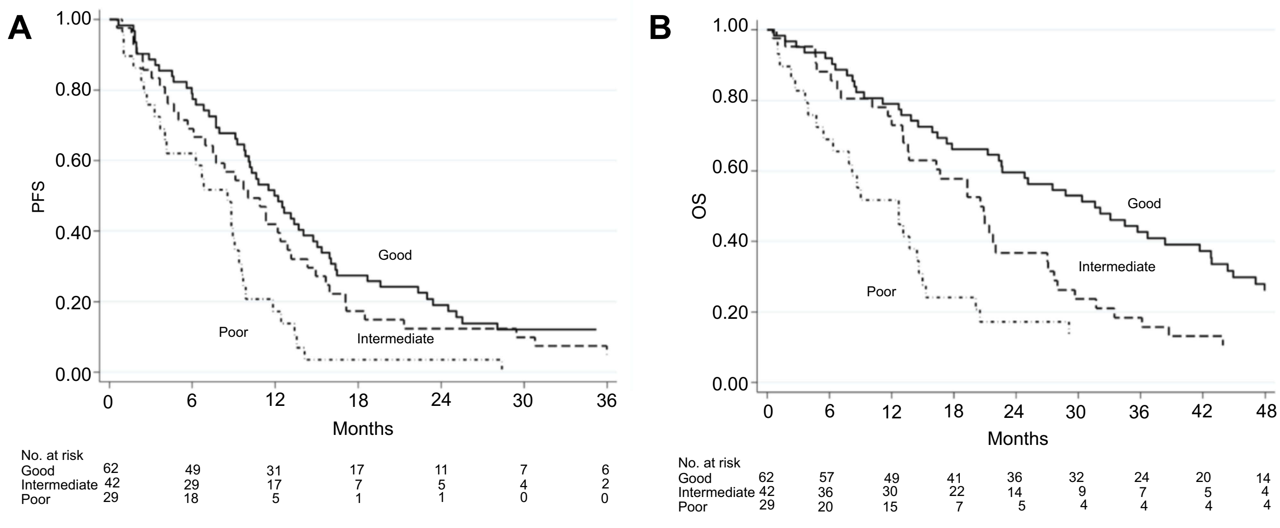

Figure 3 Kaplan–Meier curves of PFS (**A**) and OS (**B**) for the Colon Inflammatory Index patients treated with CT +B.
Abbreviations: CT, chemotherapy; B, bevacizumab.

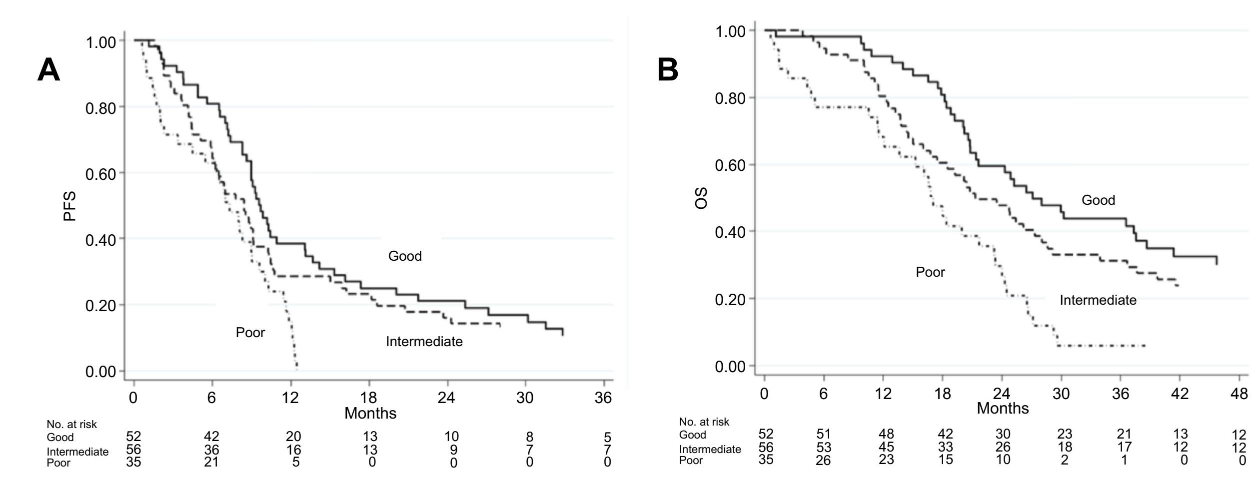

Figure 4 Kaplan–Meier curves of progression free survival (PFS) (**A**) and overall survival (OS) (**B**) for Colon Inflammatory Index in patients treated with chemotherapy alone.

Table 5 Colon Inflammatory Index in relation to tumor localization in the overall/total population

	n patients	PFS			HR (95%CI)[a]	p	OS			HR (95% CI)[a]	p
		n events	Median PFS (months) (95% CI)	p			n events	Median OS (months) (95% CI)	p		
Right-sided											
Good	47	44	10.4 (8.3–13.7)		1.00		38	26.4 (19.2–35.7)		1.00	
Intermediate	29	28	7.7 (5.1–10.2)		2.10 (1.20–3.65)		24	15.0 (11.5–20.9)		2.17 (1.20–3.93)	
Poor	20	20	8.9 (1.0–10.3)	0.002	2.44 (1.32–4.50)	0.005	19	15.0 (2.4–24.5)	0.004	2.69 (1.43–5.08)	0.003
Left-sided											
Good	65	58	10.3 (9.1–13.7)		1.00		48	36.6 (24.8–44.4)		1.00	
Intermediate	68	65	9.1 (6.5–11.3)		1.07 (0.73–1.56)		58	24.8 (19.3–28.0)		1.34 (0.89–2.03)	
Poor	44	43	6.5 (3.7–8.8)	<0.0001	2.33 (1.47–3.70)	0.0005	41	13.7 (8.2–16.8)	<0.0001	2.29 (1.41–3.72)	0.003

Notes: [a]Adjusted by ITACa treatment, center, CT regimen, KRAS status and baseline characteristics.
Abbreviations: PFS, progression-free survival; OS, overall survival; CT, chemotherapy; B, bevacizumab; ITACa, Italian Trial in Advanced Colorectal Cancer.

be explained with a high LDH value, which underlies a hypoxic microenvironment. In hypoxia, Von Hippel Lindau (VHL) suppressor dissociates from its hypoxia-inducible factor-1 (HIF-1) subunit. HIF-1 once dissociated allows the transcription of several gene targets implicated in neoangiogenesis, including LDH.

The lower efficacy of B in poor-CII patients may be attributable to a lower efficacy of the drug in inflammatory and hypoxic conditions, as for high NLR and LDH levels. Inflammation is a common feature of cancer and is due to several proinflammatory cytokines such as TNF-alpha, IL-1, IL-6, reactive oxygen and nitrogen species, prostaglandins and microRNAs, which accumulate contributing to creating a pro-tumorigenic microenvironment. A strong link between inflammation and hypoxia has already been demonstrated, with a series of common activators such as HIFs and nuclear factor-κB (NF-κB).[22,23] NF-kB is activated in CRC in response to inflammation, promoting tumorigenesis and cancer progression.[24] A number of NF-kB target genes, such as IL-8 and VEGF, are known to be involved in the angiogenic process, and to be also target of HIF-1 alpha, highlighting the existence of an intricate crosstalk between inflammation and hypoxia in cancer cells.[25] Hypoxia could be responsible for a lower efficacy of B in these tumors, as this condition has been known to induce resistance to antiangiogenic treatments.[22] We observed a detrimental effect of B in poor-CII patients with a right-sided tumor. Right-sided tumors have a series of features associated with higher hypoxic and inflammation conditions. Higher expression levels of COX-2 and eNOS, both markers associated with hypoxia,[27,28] have been observed in patients with these tumors,[26] Moreover, high frequency of microsatellite instability (MSI), as well as elevated microsatellite alterations at selected tetranucleotide repeats (EMAST) has been observed in right-sided CRC compared to left-sided ones.[29,30] Both these markers are associated with higher tumor inflammation and hypoxia.[31,32]

Although it is only a hypothesis, which must be evaluated in future translational studies, CII based on NLR and LDH could be an indirect index of tumor hypoxia.

In conclusion, CII appears to be a good index for identifying the prognosis of patients on first-line CT. Furthermore, the data suggest a possible role of CII in

Table 6 Colon Inflammatory Index in relation to tumor localization in the overall/total population

		PFS			HR (95%CI)[a]	p^a	OS			HR (95% CI)[a]	p^a
	n patients	**n events**	**Median PFS (months) (95% CI)**	***p***			**n events**	**Median OS (months) (95% CI)**	***p***		
Right-sided											
CT+B											
Good	26	25	12.6 (8.0–22.3)		1.00		23	28.2 (15.9–36.7)		1.00	
Intermediate	14	13	7.5 (4.7–12.9)		1.28 (0.50–3.25)		11	16.3 (6.8–21.8)		1.44 (0.57–3.65)	
Poor	7	7	8.6 (1.0–8.9)	0.027	2.87 (0.99–8.34)	0.140	7	9.0 (1.0–14.6)	0.003	4.46 (1.43–13.95)	0.031
CT											
Good	21	19	9.5 (5.6–13.1)		1.00		15	21.6 (17.9–68.6)		1.00	
Intermediate	15	15	8.4 (2.3–9.1)		2.01 (0.96–4.22)		13	15.0 (10.1–20.8)		3.07 (1.23–7.66)	
Poor	13	13	9.0 (1.0–11.4)	0.113	1.56 (0.70–3.48)	0.178	12	23.3 (2.4–26.6)	0.157	2.28 (0.97–5.40)	0.043
Left-sided											
CT+B											
Good	36	31	11.3 (7.7–14.0)		1.00		26	34.5 (21.3–48.0)		1.00	
Intermediate	28	27	11.1 (6.9–14.3)		1.08 (0.62–1.86)		25	21.2 (13.7–27.7)		1.85 (1.02–3.35)	
Poor	22	22	7.7 (3.3–9.7)	0.009	2.01 (1.08–3.71)	0.070	21	12.9 (4.7–15.3)	0.013	2.40 (1.25–4.64)	0.019
CT											
Good	29	27	9.7 (8.6–17.3)		1.00		22	36.6 (20.8–45.7)		1.00	
Intermediate	40	38	8.1 (5.9–10.7)		1.07 (0.61–1.86)		33	26.2 (18.5–36.7)		1.16 (0.65–2.07)	
Poor	22	21	6.3 (2.0–8.0)	0.001	1.84 (0.93–3.62)	0.185	20	16.6 (10.5–19.9)	<0.0001	2.55 (1.24–5.27)	0.031

Notes: [a]Adjusted by center, CT regimen, KRAS status and baseline characteristics.
Abbreviations: PFS, Progression-dree survival; OS, overall survival; CT, chemotherapy; B, bevacizumab.

the identification of patients who may have an advantage from the use of B in first-line treatment.

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Author contributions

All authors contributed toward data analysis, drafting and critically revising the paper, gave final approval of the version to be published, and agree to be accountable for all aspects of the work.

Disclosure

The authors report no conflicts of interest in this work.

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Supplementary material

Table S1 Patient characteristics (N=276)

	CT+B arm (N=133)	CT arm (N=143)	
	n (%)	n (%)	*p*
Median age, years (IQR)	66 (58–72)	66 (57–74)	1.000
Gender			
Female	52 (39.1)	60 (42.0)	
Male	81 (60.9)	83 (58.0)	0.629
Performance status (ECOG)			
0	109 (82.0)	111 (77.6)	
1–2	24 (18.0)	32 (22.4)	0.372
Tumor localization			
Rectum	31 (23.3)	41 (28.7)	
Colon	102 (76.7)	102 (71.3)	0.311
Stage at diagnosis			
I–III	31 (24.0)	35 (26.1)	
IV	98 (76.0)	99 (73.9)	0.697
Grade			
1	3 (3.0)	9 (7.6)	
2	65 (65.0)	73 (61.9)	
3	32 (32.0)	36 (30.5)	0.413
CT regimen			
FOLFOX4	82 (61.6)	89 (62.2)	
FOLFIRI	51 (38.4)	54 (37.8)	0.921
KRAS status			
Wild-type	70 (58.8)	74 (58.3)	
Mutated	49 (41.2)	53 (41.7)	0.930
Prior cancer therapy			
Surgery	100 (75.2)	104 (72.7)	0.642
Radiotherapy	13 (9.8)	13 (9.1)	0.846
Adjuvant chemotherapy	27 (20.3)	25 (17.5)	0.550

Abbreviations: CT, chemotherapy; B, bevacizumab; ECOG, Eastern Cooperative Oncology Group.