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Original Research

The prognostic impact of primary tumour location in patients with stage II and stage III colon cancer receiving adjuvant therapy. A GISCAD analysis from three large randomised trials

S. Cascinu [a,*], D. Poli [b], A. Zaniboni [c], S. Lonardi [d], R. Labianca [e], A. Sobrero [f], G. Rosati [g], M. Di Bartolomeo [h], M. Scartozzi [i], V. Zagonel [d], N. Pella [j], M. Banzi [k], V. Torri [b]

[a] *Modena Cancer Center, Università di Modena e Reggio Emilia, Italy*
[b] *Laboratory of Methodology for Clinical Research, IRCCS-Istituto di Ricerche Farmacologiche Mario Negri, Milano, Italy*
[c] *Medical Oncology Unit, Fondazione Poliambulanza, Brescia, Italy*
[d] *Medical Oncology 1, Istituto Oncologico Veneto (IOV)-IRCCS, Padova, Italy*
[e] *Cancer Center, Ospedale Papa Giovanni XXIII, Bergamo, Italy*
[f] *Medical Oncology Unit, IRCCS San Martino-IST, Genova, Italy*
[g] *Medical Oncology Unit, Ospedale San Carlo, Potenza, Italy*
[h] *Medical Oncology Unit, Fondazione Istituto Nazionale Tumori-IRCCS, Milano, Italy*
[i] *Medical Oncology Unit, University Hospital and University of Cagliari, Cagliari, Italy*
[j] *Medical Oncology Unit, Azienda Ospedaliero Universitaria Santa Maria della Misericordia, Udine, Italy*
[k] *Medical Oncology Unit, Arcispedale Santa Maria Nuova-IRCCS, Reggio Emilia, Italy*

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Abstract ***Purpose:*** Because the role of the primary tumour location in the adjuvant setting has not been clearly established in colon cancer, we analysed the clinical outcome according to the primary tumour location from three Italian trials assessing adjuvant therapy in colon cancer.

Patients and methods: Overall survival (OS) and disease-free survival (DFS) were assessed globally and in each trial, according to right-sided, transverse and left-sided primary colon cancer. Analysis was planned to provide overall and stage-specific results.

Results: Individual data of 5239 patients were included in this analysis. The right-sided tumours were 1540 (29%), tumours originating in the transverse were 815 (16%) and left-sided tumours were 2884 (55%). At the multivariate analysis, DFS findings from the comparison

* *Corresponding author*: Modena Cancer Center, Università di Modena e Reggio Emilia, Via del Pozzo 71, 41121 Modena, Italy.
E-mail addresses: cascinu@yahoo.com, cascinu.stefano@unimore.it (S. Cascinu).

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of the right-sided versus left-sided tumours (hazard ratio [HR] = 1.00; 95% confidence interval [CI] = 0.89–1.14) were not statistically associated with clinical outcomes in the overall population. On the contrary, OS findings, from the comparison of the right-sided versus left-sided tumours, were significantly associated with outcomes (HR = 1.20; 95% CI = 1.04–1.39). In stage II patients, there was no difference in terms of DFS and OS among the three different tumour locations, whereas in stage III patients, the left-sided tumours showed an improved prognosis in terms of OS (HR: 1.36 95% CI = 1.14–1.62, $p < 0.001$).
Conclusion: This is the largest analysis demonstrating a prognostic effect of the tumour location on patients with colon cancer receiving adjuvant chemotherapy. Nevertheless, the effect is limited to OS in stage III colon cancer. In stage II tumours, the primary location has a lesser impact. The transverse tumours should be prognostically considered in between the right-sided and left-sided tumours.

1. Introduction

Colorectal cancer is the second leading cause of cancer death in the Western world [1]. Across the last 20 years, relevant gains in survival have been obtained both in the adjuvant and in the advanced setting [2,3]. Several prognostic factors have been identified to guide the decision process in this setting, with tumour sidedness recently acquiring a pre-eminent role as a prognostic and predictive factor, particularly in metastatic patients. Growing evidence showed, in fact, that the right-sided colon cancer is associated with a worse clinical outcome when compared with the left-sided tumours, whereas this latter group of patients seems to benefit the most from the use of anti–epidermal growth factor receptor (EGFR) monoclonal antibodies in presence of an all-RAS wild-type mutational status [4–13]. However, this prognostic effect has not been clearly confirmed in patients receiving adjuvant therapy, and conflicting results have been reported in early-stage colon cancer [14–17]. A major limitation of these studies was the inability to control for adjuvant chemotherapy use. Recently, two separate analyses investigated the prognostic role of tumour sidedness in patients with colon cancer receiving adjuvant therapy. In the N0147 trial, where FOLFOX was compared with a combination of FOLFOX + cetuximab, the left-sided tumours were associated with a better disease-free survival (DFS) compared with the right-sided tumours [18]. On the other hand, outcome data from two large adjuvant trials (VICTOR [19] and QUASAR2 [20]) showed that tumour sidedness was a prognostic factor in terms of overall survival (OS) but not in terms of DFS, suggesting that the primary tumour location might be, in fact, related to clinical outcomes once disease has recurred rather than influencing the risk of tumour recurrence after radical surgery and adjuvant chemotherapy. The authors concluded that, while in the metastatic setting, sidedness should be a stratification factor, this might not be the case in the patients receiving adjuvant treatment [21].

Nevertheless, only stage III colon cancers were included in the analysis from the N0147 trial [18], and in the British analysis, stages II and III were included altogether [21]; thus, introducing potential confounding factors makes findings less easily interpretable. To explore the prognostic role of tumour sidedness in the adjuvant setting, we analysed the outcome data from three Italian randomised trials (SITAC-1, SMAC and TOSCA), including 5239 colon cancer patients with stage II and III radically resected colorectal cancer [22–24]. Furthermore, because most previous trials were not statistically powered to assess the prognostic role of transverse colon cancer, we analysed this primary tumour site separately as it might have a different outcome compared with that of the right-sided and left-sided primary tumours.

2. Patients and methods

Three Italian randomised trials of adjuvant therapy (SITAC, 5fluorouracil [5FU]-folinic acid (FA)/versus control, 821 patients enrolled from 1992 to 1998; SMAC, intraportal 5FU versus systemic 5FU/FA, 990 patients enrolled from 1989 to 1992; TOSCA, FOLFOX/XELOX, 3428 patients enrolled from 2007 to 2013) were included in this analysis.

For statistical analysis, DFS was defined as the time from randomisation to the first local, regional or distant relapse, secondary colon cancer or death from any cause; survival after relapse (SAR) was defined as the time from evidence of any recurrence to death and OS was defined as the time from randomisation to death. DFS, SAR and OS were analysed globally and in each trial according to the primary tumour site. For study purposes, according to the surgical and pathological reports, tumours located within the caecum and the hepatic flexure were considered right-sided and tumours located within the splenic flexure and the rectum were considered left-sided. Tumours originating in the

transverse colon were considered as a separate group. Patients with multiple colon tumours were excluded. Statistical analysis considered all randomised patients according to the allocation arm, along with all available data on the primary tumour site and other putative prognostic factors. The Kaplan–Meier method estimates survival probability over time. Significant differences in the probability of survival between the strata were evaluated by log-rank test. The analysis focussing on effect of tumour sidedness on prognosis was also confirmed by mean of Cox regression analysis stratified by the study and adjusted by the stage (for overall analysis), age, sex and performance status. The hazard ratio (HR) for each pairwise comparison within the primary tumour site was calculated overall and by stage together with corresponding 95% confidence interval (CI).

3. Results

The present analysis included individual patient data from three Italian trials investigating adjuvant strategies for patients with stage II and III radically resected colon cancer: the SITAC trial, which included 821 patients, the SMAC trial, which included 990 patients and the TOSCA trial, which included 3759 patients [22–24].

Table 1 summarises all main patients' characteristics according to the corresponding trial in which they were randomised.

Globally, 5239 of 5324 patients enrolled in the three trials were included in this analysis; 2829 patients were men and 2410 were women. Median age was 64 years; 2211 patients had stage II colon cancer and 3028 had stage III colon cancer. The right-sided tumours were 1540 (29%), tumours originating in the transverse colon were 815 (16%) and left-sided primary tumours were 2884 (55%). Across all the primary tumour sites, more than 85% of patients were PS 0, 54% were men and 58% had stage III disease. The distribution of stage III tumour varied across different primary tumour sites. Stage III was observed in 59% of the right-sided tumours, in 51% of the tumours originating from the transverse colon and in 59% of the left-sided tumours, $p = 0.004$. Differences in the distribution of the stage and primary tumour site were found across studies. Stage II disease was observed in 52% of patients in the SITAC trial, 60% of patients in the SMAC trial and 34% of patients in the TOSCA trial, and left-sided tumours were present in 54% of patients in the SITAC trial, 58% of patients in the SMAC trial and 54% of patients in the TOSCA trial. Median age at surgery was 64 years (range 21–89 years).

Fig. 1A and B shows the Kaplan–Meier curves for DFS and OS, respectively, according to the primary tumour site. Five-year DFS was 74.3% for the right-sided tumours, 73% for tumours originating from the

Table 1
Patients characteristics according to the three trials.

Patients characteristics by the study and site	Study																					
	SMAC						SITAC						TOSCA						All			
	Right		Transverse		Left		Right		Transverse		Left		Right		Transverse		Left		Right		Transverse		Left	
	N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%
PS																								
0	166	73.5	136	72.3	425	73.8	187	77.6	105	76.1	342	77.4	1016	94.7	457	93.5	1784	95.6	1369	88.9	698	85.6	2551	88.5
1	57	25.2	51	27.1	146	25.3	51	21.2	26	18.8	90	20.4	57	5.3	32	6.5	81	4.3	165	10.7	109	13.4	317	11.0
>1	3	1.3	1	0.5	5	0.9	3	1.2	7	5.1	10	2.3	.	0.0	.	0.0	1	0.1	6	0.4	8	1.0	16	0.6
Sex																								
Male	122	54.0	79	42.0	296	51.4	128	53.1	67	48.6	232	52.5	565	52.7	273	55.8	1067	57.2	815	52.9	419	51.4	1595	55.3
Female	104	46.0	109	58.0	280	48.6	113	46.9	71	51.4	210	47.5	508	47.3	216	44.2	799	42.8	725	47.1	396	48.6	1289	44.7
Stage																								
II	124	54.9	116	61.7	354	61.5	124	51.5	79	57.2	224	50.7	376	35.0	201	41.1	613	32.9	624	40.5	396	48.6	1191	41.3
III	102	45.1	72	38.3	222	38.5	117	48.5	59	42.8	218	49.3	697	65.0	288	58.9	1253	67.1	916	59.5	419	51.4	1693	58.7

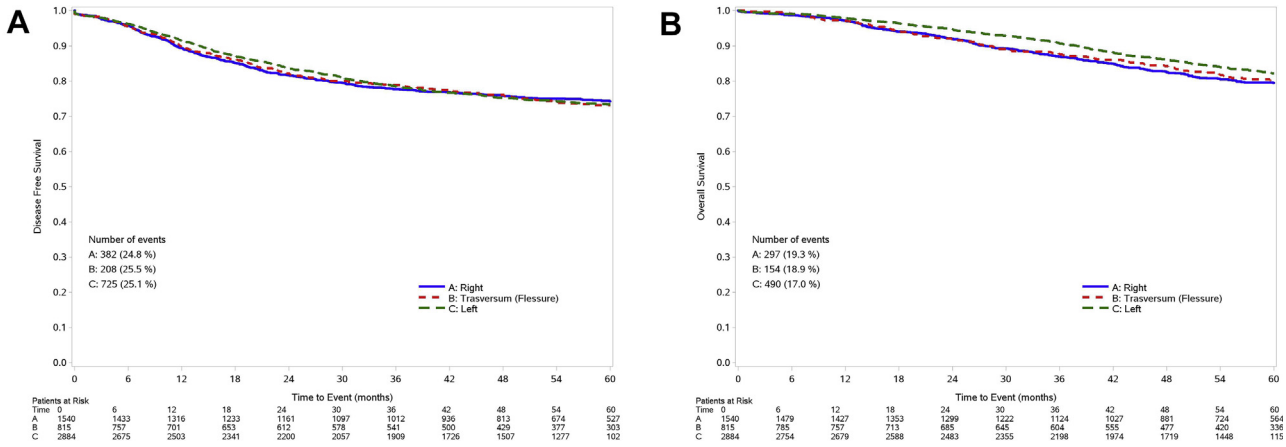

Fig. 1. Disease-free survival (A) and overall survival (B) according to the tumour location in the overall population.

transverse colon and 73% for the left-sided tumours. No difference was found in the hazard of progression/death among the primary tumour sites (log rank p = 0.959). Multivariate Cox analysis stratified by study and adjusted by age, PS, gender and stage, confirmed the results (overall Wald test p = 0.890).

Five-year OS was 79.5% for patients with right-sided tumours, 80% for patients with tumours originating from the transverse colon and 82% for patients with left-sided tumours. No differences were found in the hazard of death among different primary tumour sites (log rank p = 0.059). Multivariate Cox analysis stratified by study and adjusted by age, PS, gender and stage, showed a statistical significant association between primary tumour site and mortality (overall Wald test p = 0.044). The HR for death for right-sided tumours versus left-sided tumours was 1.20 (95% CI 1.04–1.39) p = 0.013, while it was 1.07 (95% CI 0.89–1.28) for tumour originating in the transverse colon versus left-sided tumours.

Fig. 2A and B shows the same analysis for stage II patients. Five-year DFS was 83.4% for patients with right-sided tumours, 81.1% for patients with tumours originating from the transverse colon and 79% for patients with left-sided tumours. No differences were found in the hazard of progression/death among different primary tumour sites (log rank p = 0.101). Multivariate Cox analysis stratified by the study and adjusted by age, PS and gender confirmed the results (overall Wald test, p = 0.214). Five-year OS was 87.0% for patients with the right-sided tumours, 84.7% for patients with tumours originating from the transverse colon and 85.0 for patients with the left-sided tumours (p = 0.452). These results were confirmed also at multivariate analysis (overall Wald test, p = 0.796).

Fig. 3A and B shows results for stage III patients. Five-year DFS was 68.1% for patients with the right-sided tumours, 65.9% for patients with tumours originating from the transverse colon and 69.6% for patients with the left-sided tumours. No differences were found in the hazard of progression/death among different primary sites (log rank p = 0.204). These findings were confirmed at multivariate Cox analysis (overall Wald test, p = 0.305). Five-year OS was 74.5% for patients with the right-sided tumours, 75.8% for patients with

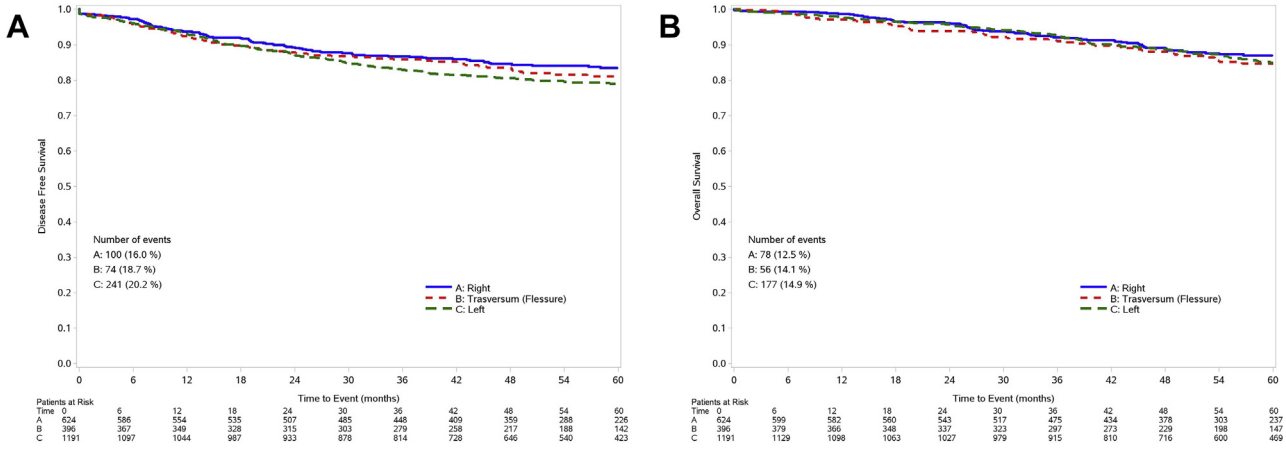

Fig. 2. Disease-free survival (A) and overall survival (B) according to the tumour location in stage II disease.

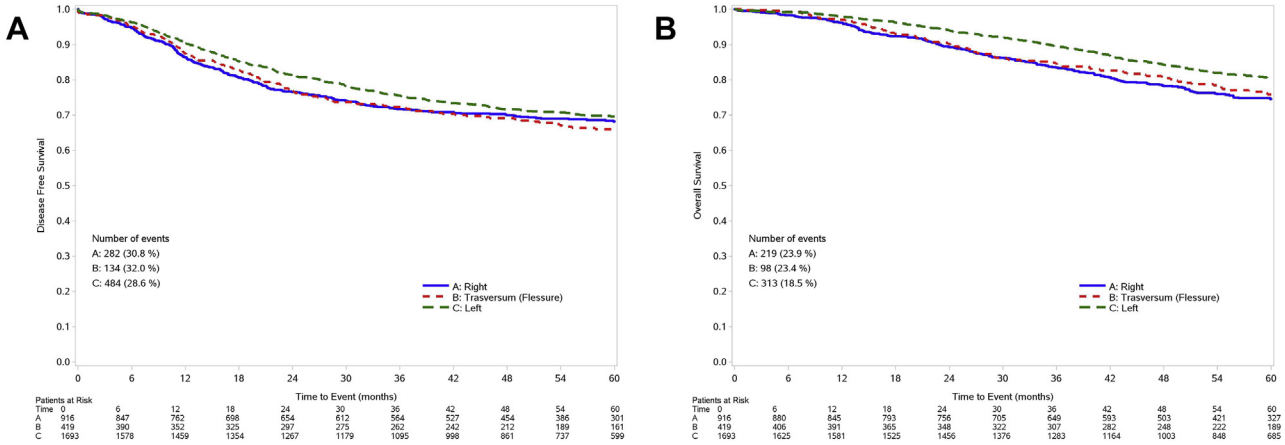

Fig. 3. Disease-free survival (A) and overall survival (B) according to the tumour location in stage III disease.

tumours originating from the transverse colon and 80.2% for patients with the left-sided tumours, ($p < 0.001$). Multivariate analysis showed a statistically significant association between the primary tumour site and mortality (overall Wald test, $p = 0.002$). The HR for death for patients with the right-sided versus left-sided tumours was 1.36 (95% CI 1.14–1.62) $p < 0.001$, while it was 1.12 (95% CI 0.89–1.42) for patients with tumours originating from the transverse colon versus left-sided tumours.

Table 2 reports the estimates of median durations of SAR together with their interquartile values. We observed a better SAR in the left-sided tumours in all the three studies and it was significantly longer in TOSCA trial compared with those observed in SITAC and SMAC trial.

Table 2
Survival after relapse according to the three trials.

Survival after relapse				
Study	Stage	Site	Median (months)	25%–75% quartiles
SMAC	II	Right	17.4	7.2–45.8
		Transverse	21.3	3.8–30.3
		Left	33.0	9.3–49.4
	III	Right	8.0	3.6–21.6
		Transverse	17.6	7.0–28.9
		Left	17.0	7.9–32.0
SITAC	II	Right	13.6	6.8–42.5
		Transverse	23.8	5.3–44.8
		Left	13.2	5.1–34.4
	III	Right	9.5	1.9–13.9
		Transverse	8.1	4.8–18.4
		Left	12.1	6.1–23.4
TOSCA	II	Right	27.5	10.4–61.1
		Transverse	20.8	5.8-
		Left	54.4	22.8–75.6
	III	Right	22.6	13.1–44.9
		Transverse	25.6	13.0–44.9
		Left	39.4	21.5-

P-value for interaction between the stage and site: $p = 0.06$.
P value for comparison of effect among sites: $p < 0.0001$.
P value for comparison of effect among studies: $p < 0.0001$.

4. Discussion

This is the largest analysis demonstrating a prognostic effect of the primary tumour location on patients with colon cancer receiving adjuvant chemotherapy. Until now, unlike the metastatic setting, there have been controversial results about the prognostic effect of the primary tumour location on early-stage colon cancer. Survival rates reported after radical surgery were in fact similar in stage II and III, between the right-sided and left-sided tumours in several analyses from cohort data or tumour registries. Benedix *et al.* [7] reported 5-year DFS rates of 73% and 74% for the right-sided and left-sided tumours in 17,641 patients, respectively. Similarly, Weiss *et al.*[14] showed that in a cohort of 53,801 patients, radically resected, tumour laterality was not associated with survival in stage I, II and III. Karim *et al.* [15] did not find any significant difference in long-term survival between the right-sided and left-sided tumours in more than 6000 patients with stage I to III colon cancer from the Ontario Cancer Registry. On the contrary, Meguid *et al.* reported a 4% increase in mortality for the right-sided tumours in 77,978 patients. However, a stratified analysis showed that in stage II disease, there was a better outcome for the right-sided tumours, whereas it was the contrary in stage III [16]. Warschkow *et al.* [25] reported an improved survival for the right-sided tumours in stage I/II but not III colon cancer. Kennecke *et al.* found that 5-year relapse-free survival was superior for the left-sided tumours in stage II but not in stage III disease. However, in patients who relapsed, those who initially had right-sided tumours had a worse 5-year SAR than patients with left-sided tumours [26]. Finally, a meta-analysis of 15 studies reported a worse prognosis for patients with right-sided tumours (HR = 1.14; 95% CI 1.06–1.22; $p < 0.01$) [9].

Of note, in all these analyses, a better outcome or a trend towards an improvement in clinical outcomes was observed in patients with right-sided tumours and stage II disease.

Nonetheless, these studies are quite contradictory in terms of findings, and a major limitation was their inability to control for the use of adjuvant therapy. Our data may give a contribution to clarify these controversial findings. In our analysis, the primary tumour location does not correlate with DFS when we consider stage II and III combined. This is likely the result of the opposing prognostic impact of the primary tumour location on stage II (better DFS in right-sided tumours) and in stage III (better DFS in left-sided tumours).

On the contrary, the left-sided location of the primary tumour correlates with survival in the overall population. This is likely to be the consequence of the prognostic impact of the tumour location in stage III (better OS in left-sided tumours) because no difference in stage II was observed.

Interestingly, we observed a better SAR in left-sided tumours, due to a specific effect of the tumour location on stage III patients, while this was not the case in stage II patients, where we observed a trend for a worse SAR in right-sided tumours. This may explain the lack of difference in OS for stage II patients, despite the improved DFS observed in right-sided tumours.

SAR was significantly longer in TOSCA trial compared with that observed in the SITAC trial. The latter trial was carried out in the 80s when the only available drug in the metastatic disease was 5FU, while in the TOSCA trial, at the time of recurrence, patients had the opportunity to receive oxaliplatin, irinotecan, cetuximab/panitumumab and bevacizumab when indicated. This effect seems to be more evident in left-sided tumours in comparison to the right-sided tumours. In right-sided tumours, SAR increased from 10 months in the SITAC trial to 24 months in the TOSCA trial, while in the left-sided tumours, SAR increased from 12 months in the SITAC trial to 36 months in the TOSCA trial. This increase in SAR in left-sided tumours may be explained by the higher incidence of RAS mutations, BRAF mutations and MSI in right-sided tumours, precluding the use or the efficacy of EGFR inhibitors and resulting in a loss of an effective treatment line in these patients [27–29].

An unanswered question is whether transverse primary colon cancers should be considered left-sided or right-sided tumours because they were included in right-sided colon cancer because of their embryogenesis or excluded in several analyses because of their small number. We included around 800 patients with transverse primary tumours in our analysis. Transverse-sided tumours showed a prognosis halfway between right-sided and left-sided tumours, even if they appear clinically more similar to right than left tumours, therefore justifying their inclusion in the right-sided tumours.

In conclusion, our analysis suggests that the tumour location may be associated with a different prognostic impact in stage II and III. The effect, in fact, is limited to OS in stage III, while in stage II colon cancer, the primary tumour location seems to have a lesser impact. Our data suggest that it is not essential to stratify for primary tumour location in stage III disease if the trial end-point is DFS, and in stage II tumours, it should be considered neither for DFS nor for OS.

The significant different SAR in left-sided-tumours registered in the trials carried out in the 80s in comparison to that of TOSCA trial, conducted in more recent years, is of note, and it is likely related to the availability of new effective drugs including biological agents for these patients. These findings, indirectly, confirm the undisputable advances made in the treatment of metastatic colorectal cancer during the years.

Author agreements

The authors of the manuscript have seen and approved its final version.

The authors warrant that the article is the authors' original work, has not received prior publication and is not under consideration for publication elsewhere.

Conflict of interest statements

All the authors do not have any conflict of interest, neither direct nor indirect related to this manuscript.

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