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Original Research

Evaluation of two nutritional scores' association with systemic treatment toxicity and survival in metastatic colorectal cancer: an AGEO prospective multicentre study

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Abstract ***Introduction:*** The Patient-Generated Subjective Global Assessment (PG-SGA) is currently the standard nutritional assessment tool for patients with cancer. In a retrospective assessment of a prospective cohort, we showed that the Nutritional Risk Index (NRI) seemed to be associated with treatment toxicity and survival in patients with metastatic colorectal cancer (mCRC).

Objective: The objective of this study was to compare these two nutritional tools (PG-SGA and NRI) on their correlation with chemotherapy-related toxicity and survival in non–pre-treated patients with mCRC.

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Prognosis

Methods: This prospective multicentre observational study enrolled non–pre-treated patients with mCRC. PG-SGA and NRI were performed at the onset of first-line chemotherapy. Treatment-related toxicities were registered according to National Cancer Institute Common Toxicity Criteria Adverse Event version 4.0. Progression-free survival (PFS) and overall survival (OS) were calculated from the start of treatment.

Results: A total of 168 patients were included from eight French centres. Patients were considered malnourished in 41% of cases according to PG-SGA and 56% of cases according to the NRI. In multivariate analysis, malnutrition according to PG-SGA was significantly associated with chemotherapy-related grade $\geq$2 clinical toxicities (odds ratio: 3.7; 95% confidence interval [CI]: 1.7–8.4; p = 0.001) and OS (hazard ratio [HR]: 2.6; 95% CI: 1.3–5.3; p = 0.006), but not with PFS (HR: 1.5; 95% CI: 0.8–2.6; p = 0.2). Conversely, malnutrition according to the NRI was not significantly associated with these tolerance and efficacy parameters.

Conclusion: Although more complex to perform in daily oncology practice, the PG-SGA score appears to be the best nutritional assessment tool because of its strong association with clinically relevant oncological outcomes such as OS and treatment-related toxicities in patients with mCRC.

1. Introduction

Depending on the disease stage, about 40–65% of patients with colorectal cancer (CRC) are diagnosed with malnutrition [1,2]. Malnutrition management in patients with metastatic CRC (mCRC) actually belongs to the overall management of the disease to improve the tolerance and efficacy of increasingly aggressive treatments and also improve patients' quality of life [3,4]. Malnutrition assessment by a suitable measurement tool, correlated with clinically relevant parameters such as treatment toxicities and patient survival, could allow early nutritional intervention and prevent the adverse effects linked to malnutrition [5].

Several studies have shown the negative impact of malnutrition on postoperative results in patients with non-mCRC [6,7], whereas the association between nutritional assessment and outcomes is less clear in metastatic patients. To guide a possible nutritional intervention, it is necessary to validate, in a prospective study, a standardised tool for nutritional assessment in this setting.

Nutritional assessment is neither systematic nor standardised in digestive oncology. A weight loss of more than 10% in the last 6 months, the body mass index (BMI) and albuminemia are useful measures, but many clinical conditions in patients with cancer may interfere with these measures [3,8].

Among the variety of nutritional scores, the scored "Patient-Generated Subjective Global Assessment" (PG-SGA) has become a standard in oncology for nutritional assessment in Australia and the United States of America [8,9] and is mentioned in the European guidelines [4]. PG-SGA is not a malnutrition screening score, such as Malnutrition Universal Screening Tool (MUST) [10] or Nutrition Risk Screening 2002 (NRS-2002) [11,12], which are validated in oncology but without reaching a consensus. In fact, PG-SGA is a comprehensive approach to assess several dimensions of malnutrition after the screening stage. Thus, PG-SGA has a subjective part and is time-consuming, making it difficult to integrate in our daily practice. In addition, the association of PG-SGA with chemotherapy-related toxicities has not been reported to date. PG-SGA has been evaluated in two studies on CRC showing a possible association with patient survival but not with treatment-related toxicities [13,14].

In a previous work [1], we used the Nutritional Risk Index (NRI) as a screening tool [15], which is easy to perform during an oncology consultation as it depends only on the albumin level and 6-month weight loss, and found that severe malnutrition, according to the NRI, was associated with chemotherapy toxicities and poor overall survival (OS). However, this study included patients with mCRC at different stages of their therapeutic management, and toxicities were assessed retrospectively.

The aim of the present work was to compare prospectively the NRI with PG-SGA on their correlation with treatment-related toxicities and patient survival in a homogeneous population of non–pre-treated patients with mCRC.

2. Patients and methods

2.1. Patients

This prospective, multicentre observational study involved eight French medical centres. The inclusion criteria included age >18 years, histologically proven mCRC, prior adjuvant chemotherapy allowed if ended at least 6 months before patients' enrolment and no

previous chemotherapy for metastatic disease. Patients with a non-adenocarcinomatous colic tumour, a surgery within two months, a history of previously treated mCRC and another cancer considered not cured were not included.

2.2. Data collection

Data collection was done on a computer platform at the beginning of first-line chemotherapy (day 0 [D0]).

2.3. Nutritional assessment

The nutritional data collected were the following: patients' weight at D0 and before 6 months, BMI, a potential nutritional intervention (type and calories), albuminemia and the PG-SGA and NRI scores.

The PG-SGA score is fully described in the Appendix. It included an overall assessment by the physician classifying the patient as category A (no malnutrition), B (moderate malnutrition) or C (severe malnutrition) and a numerical score, the values of each section (the questionnaire completed by the patient and physical examination) being summed up. Malnutrition was defined by a grade B–C of PG-SGA and/or a PG-SGA score $\geq$9, and severe malnutrition was defined by a grade C of PG-SGA, as previously described [16].

The NRI was calculated using the following formula ($1.519 \times$ albumin level $+ 0.417 \times$ current weight/basal weight x 100). An NRI between 83.5 and 97.5 defined moderate malnutrition and <83.5 defined severe malnutrition [15] (Supplementary Table 1).

2.4. Oncological data

Data collected were the following: the date of diagnosis of CRC and metastatic disease, the number of metastatic sites, performance status, chemotherapy protocol and the plasma levels of lymphocytes, haemoglobin, platelets, carcinoembryonic antigen, alkaline phosphatase and lactate dehydrogenase.

Chemotherapy dosage reduction and tolerability were collected every two weeks from D0 to day 60 (D60) and were evaluated using National Cancer Institute Common Toxicity Criteria version 4.0 [17].

Progression-free survival (PFS) and OS were evaluated from the start of treatment.

The study was approved by our institutional ethics committee.

2.5. Statistical analyses

The qualitative variables were compared using the chi-square test or Fisher test.

Agreement between the PG-SGA and NRI was analysed using the κ statistic. The value of κ varies from 0 to 1; a value of 0.4 or less indicates that chance alone can account for the observed agreement, and a value of 1 indicates perfect concordance. Univariate and multivariate logistic regressions were performed to investigate factors independently associated with the clinically significant toxicities of chemotherapy (grade $\geq$ 2). The factors associated with PFS and OS were investigated using univariate and multivariate Cox models. The adjustment factors used in the multivariate analyses for toxicities and survival were the variables with a p value < 0.05 and/or relevant variables in the univariate analyses. Correlation between variables was assessed before constructing multivariate models; thus, albuminemia and the percentage of weight loss were not included in the multivariate models including PG-SGA and NRI scores. The two scores were not included in the same multivariate model for two reasons: the aim of the study was to assess their individual prognostic values, and the patient's percentage of weight loss was needed for the evaluation of both scores, leading to redundant information in the same model. The discrimination ability of the models with PG-SGA and NRI scores was assessed using Harrell's concordance index (C-index). Random samples (bootstrap procedure with 1000 iterations) of the population were used to derive 95% confidence interval (CI) for the C-index. PFS and OS were described using the Kaplan–Meier method and compared using log-rank tests; log-rank p-values were not corrected for multitests.

Table 1
Oncological characteristics of the population.

Patients' oncological characteristics		D0 N = 168 (%)	Missing data, n
Age, years	Median (range)	70 (33–93)	0
	<65	63 (37%)	
	≥65	106 (63%)	
Gender	Male	95 (56%)	0
	Female	74 (44%)	
Number of metastatic sites	≤2	30 (18%)	0
	>2	138 (82%)	
Chemotherapy protocol	5-FU–based	162 (96%)	0
	Capecitabine-based	7 (4%)	
	Oxaliplatin-based	109 (65%)	
	Irinotecan-based	65 (38%)	
	Bevacizumab	76 (45%)	
	Anti-EGFR therapy	15 (9%)	
	Single-agent	14 (8%)	
	Doublet	134 (80%)	
	Triplet	20 (12%)	
PS	0–1	141 (84%)	0
	2–3	28 (17%)	
CEA (ng/mL)	median (range)	29 (0–10000)	4
Lymphocytes (/mm^3)		1540 (518–6800)	3
Haemoglobin (/mm^3)		12.1 (8.9–16.2)	0
ALP (UI/L)		111 (22–1898)	5
LDH (UI/L)		239 (190–446)	42

D0: day 0; 5-FU: 5-fluorouracil; EGFR: epidermal growth factor receptor; CEA: carcinoembryonic antigen; ALP: alkaline phosphatase; PS: performance status; LDH: lactate dehydrogenase.

Table 2
Nutritional characteristics of the population.

Patients' nutritional characteristics			D0 N = 168 (%)	Missing data, n
Weight loss in the last 6 months		≤10%	122 (73%)	1
>10%	46 (27%)			
BMI (kg/m^2)		Median (range)	23.8 (14.9–37.7)	0
<18.5	16 (9%)			
18.5–24.9	138 (82%)			
≥25	15 (9%)			
Nutritional intervention		None	130 (85%)	16
Oral nutritional supplements	22 (14%)			
Enteral nutrition	0			
Parenteral nutrition	1 (0.6%)			
Caloric value (kcal): median (range)	600 (300–1200)			
Albuminemia (g/L)		median (range)	38 (16.7–49)	0
PG-SGA	**Category letter**	A	96 (57%)	1
		B	54 (32%)	
		C	18 (11%)	
	Numerical score	Median (range)	7 (1–34)	2
		<9	98 (59%)	
		≥9	69 (41%)	
NRI		Median (range)	95.7 (66.1–119.2)	0
>97.5	75 (45%)			
83.5–97.5	74 (44%)			
<83.5	20 (12%)			

D0: day 0; BMI: body mass index; PG-SGA: Patient-Generated Subjective Global Assessment; NRI: Nutritional Risk Index.

3. Results

3.1. Patient characteristics

A total of 168 patients with newly diagnosed mCRC between July 2013 and November 2016 with a median age of 70 years (range, 33–93) were enrolled, with 56% of them being men and 82% of patients having more than two metastatic sites (Table 1).

At D0, 43%, 41% and 56% of the patients were classified as malnourished according to the PG-SGA (B–C) category, the PG-SGA score (≥9) and the NRI score (<97.5), respectively. Severe malnutrition was observed in 11% of patients according to PG-SGA (C category) and 12% of patients according to the NRI (<83.5) (Table 2). The κ coefficient between PG-SGA and NRI was 0.21 (Table 3).

Table 3
Concordance between PG-SGA and NRI for the diagnosis of malnutrition.

Nutritional status according to PG-SGA/NRI	Malnutrition according to PG-SGA (category B–C)	No malnutrition according to PG-SGA (category A)	Total
Malnutrition according to NRI (<97,5)	49	44	93
No malnutrition according to NRI (>97,5)	23	52	75
Total	72	96	168

κ coefficient: 0.21.
PG-SGA: Patient-Generated Subjective Global Assessment; NRI: Nutritional Risk Index.

In the overall population at D0, only 9% of patients had a BMI <18.5 kg/m^2, 27% had weight loss >10% in the last six months and 31% had albuminemia <35 g/L, generally accepted as malnutrition indicators.

Twenty-two patients (14%) had benefited from nutritional intervention with oral nutritional supplements on D0, and one patient, with parenteral nutrition. All of them were malnourished according to the PG-SGA.

Chemotherapy protocol was 5-fluorouracil 5-FU, leucovorin, and oxaliplatin/capecitabine and oxaliplatin (FOLFOX/CAPOX) in 53% of cases, 5-FU, leucovorin, and irinotecan (FOLFIRI) in 27% of cases, 5-FU, leucovorin, irinotecan, and oxaliplatin (FOLFIRINOX) in 12% of cases and capecitabine/5-FU in 8% of cases. Combined targeted therapies were bevacizumab in 45% of cases and anti–epidermal growth factor receptor in 9% of cases.

At D60, the patients had received an average of 4.2 cycles of chemotherapy. During the two first months of treatment, dose reduction, in at least one drug of the therapeutic regimen, was necessary in 38% of patients (10–25% reduction in 23% of patients; 30–50% in 8%; 70–100% in 7%).

3.2. Nutritional status and early-onset treatment tolerability

The proportion of patients with grade ≥2 clinical toxicities in the first two months of treatment was 26%: 15% for nausea/vomiting, 8% for diarrhoea, 4% for mucositis, 0.6% for hand-foot skin reactions and 4% for alopecia.

According to the PG-SGA category, PG-SGA score and NRI, well-nourished patients developed grade ≥2

clinical toxicities in 20%, 18% and 32% of cases, respectively, whereas patients diagnosed as malnourished developed these toxicities in 34%, 38% and 21% of cases, respectively. Patients diagnosed as severely malnourished according to the PG-SGA category and NRI developed grade ≥2 clinical toxicities in 45% and 25% of cases, respectively (Supplementary Table 2).

In univariate analysis, severe malnutrition and malnutrition defined by the category letter of PG-SGA and the numerical score of PG-SGA ≥ 9 were significantly associated with the development of grade ≥2 clinical toxicities as age <65 years, female gender and irinotecan-based chemotherapy (Table 4).

By contrast, severe malnutrition and malnutrition defined by the NRI were not significantly associated with the development of grade ≥2 clinical toxicities as well as BMI <18.5 kg/m^2, weight loss >10% in the last 6 months, albuminemia <35 g/L and all biological parameters evaluated (Table 4).

In multivariate analysis, age <65 years and a PG-SGA score ≥9 remained the only two factors significantly associated with the occurrence of grade ≥2 clinical toxicities (odds ratio [OR]: 5.0; 95% CI: 2.0–10; $p < 10^{-4}$ and OR: 3.7; 95% CI: 1.6–8.1; p = 0.001, respectively) (Table 4).

No association between nutritional scores and grade ≥2 haematological toxicities was found (Table 4).

3.3. Nutritional status and survival

In the overall population, after a median follow-up of 23 months (95% CI: 21–26), the median PFS was 8 months (95% CI: 7–9), and the median OS was 25 months (95% CI: 20–31).

At the end of follow-up, 140 patients (83%) progressed and 86 patients (51%) died.

Patients with a PG-SGA score ≥9 and those with a PG-SGA score <9 had a median PFS of 6 and 10 months, respectively (p = 0.002), and a median OS of 16 and 29 months, respectively (p = 0.001). Patients with or without malnutrition according to the NRI had a median PFS of 7 and 10 months, respectively (p = 0.04), and a median OS of 21 and 30 months, respectively (p = 0.004) (Fig. 1).

In univariate analysis, the PG-SGA score ≥9, the PG-SGA category B–C, the NRI score <97.5 and hypoalbuminemia <35 g/L were significantly associated with shorter PFS and OS. BMI <18.5 kg/m^2 was not significantly associated with PFS or OS, and weight loss in the last 6 months >10% was significantly associated only with OS (hazard ratio [HR]: 1.8; 95% CI: 1.1–2.9; p = 0.01) (Table 4).

In multivariate analysis, the PG-SGA score ≥ 9 was significantly associated with OS (HR: 2.0; 95% CI: 1.1–3.8; p = 0.03) and with a non-significant trend with PFS (HR: 1.5; 95% CI: 0.9–2.5; p = 0.1), whereas the NRI score < 97.5 was not associated with OS or PFS (HR: 1.1; 95% CI: 0.6–2.2; p = 0.8 and HR: 1.0; 95% CI: 0.6–1.7; p = 1.0, respectively) (Table 4). The multivariate models exhibited acceptable discrimination ability (Table 5).

In the subgroup of malnourished patients according to the PG-SGA score (≥9), nutritional intervention at D0 was not associated with an improved OS (p = 1.0).

3.4. Nutritional status and chemotherapy regimen

Between malnourished and non-malnourished patients, according to the PG-SGA score, the proportions of single-agent chemotherapy (11% versus 6%, respectively) and the triplet regimen (14% versus 10%, respectively) were similar (p = 0.32). At D60, the mean number of cycles of chemotherapy was not significantly different between patients with a PG-SGA score ≥9 and those with a PG-SGA score < 9 (4.2 versus 4.2, p = 0.97, respectively), and a dose decrease of at least 10% of one of the regimen drugs was observed in 37% and 33% of patients, respectively (p = 0.62).

4. Discussion

To our knowledge, this study is the first study prospectively assessing the association of nutritional scores with treatment toxicities in patients with mCRC. It shows that in a homogenous population of patients with mCRC at the beginning of treatment, 43% and 56% were diagnosed as malnourished according to PG-SGA and NRI scores, respectively, corroborating the data published in the literature [14,18]. This high malnutrition rate would not have been accurately diagnosed by criteria performed in routine clinical practice such as the percentage of weight loss during the past six months, BMI or albuminemia.

The κ concordance coefficient between PG-SGA and NRI for malnutrition diagnosis is low (0.21). This is consistent with data reported in the literature for gastric cancer [19] and CRC [18].

On multivariate analysis, we found that malnutrition defined by a baseline PG-SGA, category B–C or a score ≥9, was significantly associated with clinically significant toxicities (grade ≥ 2) in the first two months of chemotherapy. Grade ≥2 toxicities are relevant because they may result in a change in the treatment dose and alter patients' quality of life. A substantial proportion of patients did not receive targeted therapy (37%). This may be explained, on the one hand, by the fact that some patients with a resectable metastatic disease were enrolled and, on the other hand, that some patients in poor condition were not eligible for targeted agents in this real-life study.

Table 4
Factors associated with grade ≥2 toxicities of chemotherapy, progression-free survival (PFS) and overall survival (OS) in univariate and multivariate analyses.

Variables		Chemotherapy toxicities grade ≥ 2									PFS	
		Univariate analyses						Multivariate analysis			Univariate analyses	
		Clinical toxicities (excluding neurotoxicity)			Haematological toxicities			Clinical toxicities (excluding neurotoxicity)				
		OR	CI95%	p	OR	CI95%	p	OR	CI95%	p	HR	CI95%
Age < 65 years		3.3	2.0-10.0	**$< 10^{-4}$***	0.6	0.3-1.2	0.1	5	2.0-10.0	**$< 10^{-4}$***	0.9	0.6-1.3
Female gender		2.1	1.0-4.1	**0.04***	1.5	0.7-3.1	0.3	2.1	1-4.6	0.06	1.2	0.8-1.6
Number of metastatic sites >2		0.8	0.3-2.2	0.7	1.1	0.4-2.9	0.9				1.7	1.1-2.6
PS 2-3		1.2	0.5-3.0	0.7	0.6	0.2-1.7	0.3				1.8	1.1-2.7
Oxaliplatin		0.6	0.3-1.3	0.2	1.6	0.7-3.7	0.2				1.2	0.8-1.6
Irinotecan		2.1	1.0-4.2	**0.04***	0.8	0.4-1.7	0.6	2	0.9-4.3	0.09	0.7	0.5-1.1
Single agent		0.4	0.1-2.1	0.3	1	0.3-3.9	1				2.7	1.5-4.9
Triplet		1.2	0.4-3.2	0.8	1.6	0.6-4.6	0.4				1.3	0.8-2.1
Bevacizumab		1.0	0.5-2.0	1	0.3	0.1-0.7	**0.005***				1.0	0.7-1.4
Anti-EGFR therapy		0.8	0.2-3.1	0.8	1.1	0.3-4.1	0.9				0.6	0.3-1.2
BMI < 18.5 kg/m^2		2.1	0.7-6.4	0.2	0.2	0.02-1.5	0.1				0.9	0.5-1.6
Weight loss >10%		0.8	0.4-1.8	0.6	0.8	0.3-1.8	0.6				1.2	0.8-1.7
Nutritional intervention		1.7	0.6-4.4	0.3	0.5	0.1-1.9	0.3				1.6	1.0-2.5
CEA > 200 ng/mL		0.4	0.2-1.1	0.08	1.3	0.5-3.0	0.6				1.5	1.0-2.1
LDH > 250 UI/L		1.0	0.4-2.2	0.9	1.9	0.8-4.5	0.1				2.0	1.3-2.9
Platelets > 400000/mm^3		1.9	0.9-4.1	0.07	0.9	0.4-2.1	0.9				2.2	1.5-3.2
ALP > 300 UI/L		1.2	0.5-2.9	0.6	0.9	0.3-2.4	0.8				2.4	1.6-3.7
Hg < median (12.1g/dL)		1.6	0.8-3.1	0.2	2.8	1.3-6.2	**0.009***				1.2	0.9-1.7
Lymphocytes < 1000/mm3		1	0.3-3.4	1	2.6	0.9-8.0	0.085				1.9	1.1-3.3
Albuminemia < 35g/L		0.9	0.4-1.9	0.8	1.8	0.8-3.7	0.1				2.0	1.4-2.9
Malnutrition	**PG-SGA ≥ 9**	2.8	1.4-5.7	**0.004***	1.1	0.5-2.4	0.7	3.7	1.6-8.1	**0.001***	1.7	1.2-2.4
	PG-SGA B-C	2.2	1.1-4.4	**0.03***	0.9	0.4-1.9	0.8				1.6	1.2-2.3
	NRI < 97.5	0.6	0.3-1.2	0.1	1.4	0.7-3.1	0.3				1.4	1.0-2.0
Severe malnutrition	**PG-SGA C**	2.5	0.9-6.8	0.07	0.2	0.02-1.4	0.6				1.4	0.8-2.4
	NRI < 83.5	0.7	0.2-2.2	0.5	1.4	0.4-4.7	0.5				1.8	1.1-3.1

OR: odds ratio; CI: confidence interval; HR: hazard ratio; EGFR: epidermal growth factor receptor; BMI: body mass index; PG-SGA: Patient-Generated Subjective Global Assessment; NRI: Nutritional Risk Index; PFS: progression-free survival; OS: overall survival; PS: performance status; CEA: carcinoembryonic antigen; ALP: alkaline phosphatase; LDH: lactate dehydrogenase; p-value in bold*: $p < 0.05$.

Surprisingly, we did not confirm an association between malnutrition assessed by the NRI and treatment toxicity, as observed in a previous work from our group [1]. This might be explained by the inclusion of a less number of patients with various treatment lines in our previous work.

Thus, although the NRI seems useful to identify patients at risk of postoperative complications [15], it seems to have limited sensitivity for the diagnosis of malnutrition and the prediction of chemotherapy-related toxicities in patients with CRC in a metastatic setting.

In the present study, an age less than 65 years appears to be significantly associated with grade ≥2 clinical toxicities. This age-protective effect on treatment-related toxicities could be explained by a greater proportion of patients being treated with a triplet regimen among younger patients (24% versus 5% in patients older than 65 years) and no patients being treated with single-agent chemotherapy among younger patients (0% versus 13% in patients older than 65 years). We decided to include irinotecan-based chemotherapy in the multivariate analysis and not the type of chemotherapy protocol (triplet, doublet or single-agent chemotherapy) because of its significant association with grade ≥ 2 clinical toxicities in univariate analysis, unlike the type of protocol.

On multivariate analysis, this study has shown that malnutrition defined by PG-SGA, but not by NRI, was also associated with a significantly shorter OS. In patients with mCRC, the study by Read *et al.* [13] also demonstrated the prognostic value of the PG-SGA, however not confirmed in multivariate analysis, probably due to a small number of patients (n = 51).

The prognostic value of malnutrition according to the PG-SGA is independent of the first-line chemotherapy protocol (single-agent, doublet or triplet chemotherapy) in multivariate analysis; and malnourished and non-malnourished patients according to PG-SGA had an

PFS							OS							
Univariate analyses	Multivariate models						Univariate analyses			Multivariate models				
	Including PG-SGA			Including NRI						Including PG-SGA			Including NRI	
p	HR	CI95%	p	HR	CI95%	p	HR	CI95%	p	HR	CI95%	p	HR	CI95%	p
0.5							0.9	0.6-1.4	0.7						
0.3							1.1	0.7-1.6	0.8						
0.02*	1.4	0.7-2.8	0.3	1.4	0.7-2.7	0.3	1.6	1.0-2.7	**0.08**	0.9	0.4-2.2	0.9	1.0	0.4-2.3	1.0
0.01*	1.1	0.5-2.4	0.9	1.2	0.5-2.7	0.7	2.5	1.5-4.1	**$<10^{-4}$***	1.2	0.5-2.8	0.7	1.2	0.5-3.0	0.6
0.4							1.1	0.7-1.7	0.6						
0.1							0.6	0.3-0.9	**0.03***						
0.01*	3.1	1.4-6.7	**0.01***	3.2	1.5-6.9	**0.01***	2.9	1.6-5.5	**0.003***	2.6	1.1-6.4	0.06	2.9	1.2-7.2	0.06
	0.9	0.4-2.0		0.9	0.4-2.0		1.1	0.5-2.1		2.2	0.8-6.2		1.7	0.6-4.9	
1.0							1.1	0.7-1.7	0.6						
0.1							0.5	0.2-1.4	0.2						
0.6							1.0	0.5-2.1	0.3						
0.3							1.8	1.1-2.9	**0.01***						
0.07	0.8	0.3-1.9	0.6	0.9	0.4-2.2	0.9	2.2	1.3-3.8	**0.004***	0.6	0.2-1.7	0.3	0.8	0.3-2.3	0.7
0.051	1.3	0.7-2.3	0.4	1.2	0.7-2.2	0.5	1.4	0.8-2.2	0.2	1.1	0.5-2.5	0.7	0.9	0.4-2.0	0.8
0.001*	1.6	0.9-2.8	0.08	1.7	1.0-2.8	0.06	2.3	1.4-3.8	**0.001***	1.1	0.5-2.2	0.8	1.4	0.7-2.7	0.3
$<10^{-4}$*	1.9	1.1-3.3	**0.02***	2.1	1.1-3.7	**0.01***	2.5	1.6-3.8	**$<10^{-4}$***	3.3	1.6-6.6	**0.001***	3.6	1.7-7.5	**0.001***
$<10^{-4}$*	0.9	0.4-1.7	0.7	1.0	0.5-2.0	0.9	2.2	1.3-3.6	**0.002***	0.6	0.3-1.5	0.3	0.9	0.4-2.2	0.9
0.2							1.4	0.9-2.2	0.1						
0.02*	1.9	0.9-4.1	0.1	1.8	0.8-4.1	0.1	1.4	0.7-3.0	0.4						
$<10^{-4}$*							2.5	1.6-3.8	**$<10^{-4}$***						
	1.5	0.8-2.6	0.2				2.0	1.3-3.1	**0.001***	2.6	1.3-5.3	**0.006***			
0.002*															
							2.2	1.5-3.5	**$<10^{-4}$***						
0.004*															
0.04*	0.9	0.5-1.6	0.7				1.9	1.2-3.0	**0.005***				0.9	0.4-1.8	0.7
0.2							2.3	1.3-4.2	**0.004***						
0.02*							2.5	1.3-4.8	**0.008***						

equivalent proportion of single-agent and triplet chemotherapy at the onset of treatment, suggesting comparable first-treatment intensity in both groups.

Severe malnutrition according to PG-SGA (category C) was not significantly associated with chemotherapy-related toxicities and PFS, probably due to a small number of patients (n = 18) and therefore a lack of statistical power.

The strengths of this work are its multicentric, prospective nature and a homogeneous population of chemotherapy-naive patients with mCRC.

However, this work also has some limitations, in particular, the diversity of first-line treatment regimens used although reflecting real-life practices, the limited number of patients precluding from performing multiple subgroup analyses and the limited number of events that occurred regarding the evaluation of OS (51% of patients). In addition, we cannot conclude with this work on the late side-effects of chemotherapy, especially on the neurotoxicity induced by oxaliplatin, owing to the two-month follow-up to assess toxicities. Finally, other interesting nutritional assessment tools, such as the MUST or NRS-2002 screening tests, may deserve further evaluation and to be compared with the PG-SGA.

In conclusion, in contrast to the NRI, the PG-SGA score is associated with treatment-related toxicities and survival and thus appears to be a better reliable nutritional assessment tool for patients with mCRC. Although PG-SGA is time-consuming, it seems necessary to raise awareness among oncologists, nutritionists and dieticians to this score to improve the future management of patients with mCRC. An interventional study assessing the efficacy of an early nutritional intervention in patients with mCRC using this score would be of interest.

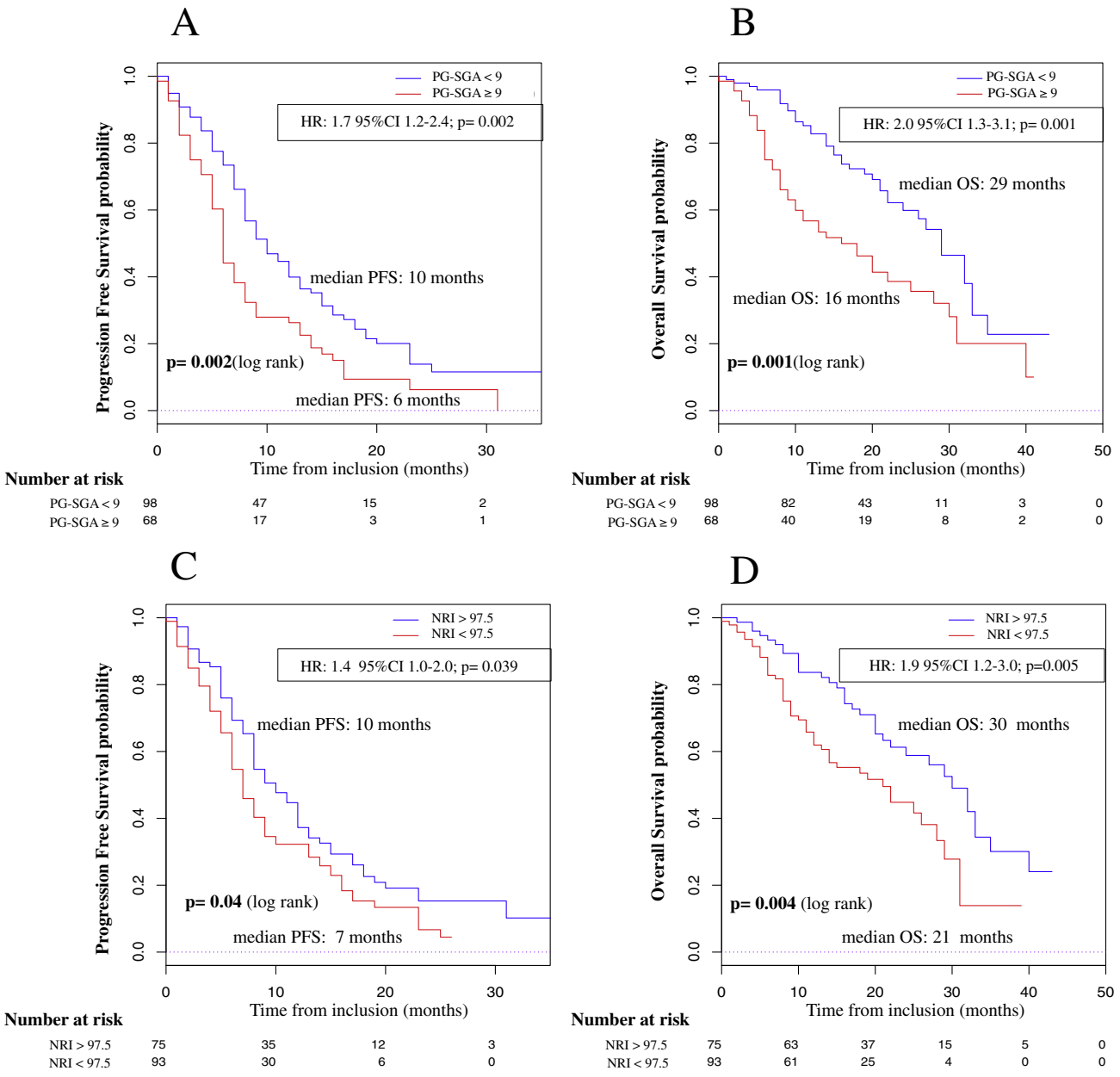

Fig. 1. **Kaplan–Meier curves of progression-free survival (PFS) and overall survival (OS) according to nutritional status defined by the PG-SGA score and NRI.** (A) PFS according to nutritional status defined by the PG-SGA score, (B) OS according to nutritional status defined by the PG-SGA score, (C) PFS according to nutritional status defined by the NRI, and (D) OS according to nutritional status defined by the NRI. HR: hazard ratio; 95% CI: 95% confidence interval; PG-SGA: Patient-Generated Subjective Global Assessment; NRI: Nutritional Risk Index; PFS: progression-free survival; OS: overall survival.

Table 5
Harrell's concordance index (C-index) for PFS and OS multivariate models including PG-SGA and NRI.

Multivariate models	PFS	OS
	C-index (95% bootstrap percentile CI)	C-index (95% bootstrap percentile CI)
Multivariate models including PG-SGA	0.69 (0.65–0.76)	0.73 (0.69–0.84)
Multivariate models including NRI	0.69 (0.65–0.76)	0.71 (0.66–0.82)

C-index: Harrell's concordance index; CI: confidence interval; PFS: progression-free survival; OS: overall survival; PG-SGA: Patient-Generated Subjective Global Assessment; NRI: Nutritional Risk Index.

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Nutricia provided financial support for study management.

Conflict of interest statement

A.L. has participated in consulting or/and advisory boards for Merck, Amgen, Shire, Bayer and Ipsen, has received honoraria for lecture from Merck, Amgen, Roche, Servier, BMS, Novartis and Ipsen and received support for travel to meetings from Novartis and Ipsen. C.L. has received personal fees from Merck and support for travel to meetings from Novartis and Roche. S.P. has participated in consulting or/and advisory boards for Amgen, has received support for travel to meetings from Amgen, Bayer and Servier and has received research grant from Roche. M.B. has received consulting fee for Nutricia Medical (2011–2012). J.T. has participated in consulting or/and advisory boards for Lilly, Celgene, Shire, Servier, Merck KGaA, Sanofi, Roche Genentech, Pfizer and Amgen. The other authors declare no conflict of interest.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ejca.2019.07.011.

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