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

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Abstract

Introduction

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

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-pretreated mCRC patients.

Methods

This prospective multicenter observational study enrolled non-pretreated mCRC patients. PG-SGA and NRI were performed at the onset of first-line chemotherapy. Treatment related toxicities were registered according to the National Cancer Institute Common Toxicity Criteria Adverse Event v4.0. Progression-free survival (PFS) and overall survival (OS) were calculated from treatment start.

Results

168 patients were included in eight French centers. Patients were considered malnourished in 41% of cases according to PG-SGA and 56% of cases according to NRI. In multivariate

analysis, malnutrition according to PG-SGA was significantly associated with chemotherapy-related grade ≥ 2 clinical toxicities (OR 3.7 95%CI 1.7-8.4, $p = 0.001$) and OS (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 NRI was not significantly associated with these tolerance and efficacy parameters.

Conclusion

Though 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.

Keywords

Metastatic colorectal cancer; malnutrition; PG-SGA; NRI; chemotherapy toxicity; prognosis

Introduction

Depending on disease stage, about 40% to 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 in order 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 non-metastatic CRC patients [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 standardized in digestive oncology. Weight loss of more than 10% in the last 6 months, body mass index (BMI), albuminemia are useful but many clinical conditions in cancer patients 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 USA [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] that are validated in oncology but without reaching 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 in CRC showing a possible association with patients survival but not with treatment related toxicities [13,14].

In a previous work [1], we used as a screening tool, the Nutritional Risk Index (NRI) [15], easy to perform during an oncology consultation as depending only on albumin level and 6-months weight loss, and found that severe malnutrition, according to NRI, was associated with chemotherapy toxicities and poor overall survival. 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 NRI to PG-SGA on their correlation with treatment related toxicities and patient survival in a homogeneous population of non pre-treated mCRC patients.

Patients and methods

Patients

This prospective, multicenter observational study involved eight French medical centers. Inclusion criteria included age > 18 years, histologically proven mCRC, prior adjuvant chemotherapy allowed if ended at least 6 months before patients' enrolment, no previous chemotherapy for metastatic disease. Patients with a non-adenocarcinomatous colic tumor, a surgery within two months, a history of previously treated mCRC, and another cancer considered as not cured, were not included.

Data collection

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

Nutritional assessment

The nutritional data collected were: patients' weight at D0 and 6 months before, BMI, a potential nutritional intervention (type and calories), albuminemia, 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 (questionnaire completed by the patient and physical examination) being summed. Malnutrition was defined by a grade B-C of PG-SGA and / or a PG-SGA score ≥ 9 and severe malnutrition was defined by a grade C of PG-SGA, as previously described [16] .

The NRI was calculated using the formula: $(1.519 \times \text{albumin level} + 0.417 \times \text{current weight} / \text{basal weight} \times 100)$. A NRI between 83.5 and 97.5 defined a moderate malnutrition and < 83.5 a severe malnutrition [15] (supplementary Table 1).

Oncological data

Data collected were: date of diagnosis of CRC and metastatic disease, number of metastatic sites, performance status (PS), chemotherapy protocol, and the plasma levels of lymphocytes, hemoglobin, platelets, carcinoembryonic antigen (CEA), alkaline phosphatase (ALP), and lactate dehydrogenase (LDH).

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

PFS and OS were evaluated from treatment start.

The study was approved by our institutional Ethics Committee.

Statistical analyses

The qualitative variables were compared using Chi2 test or Fisher test.

Agreement between the PG-SGA and NRI was analysed with 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 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 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 with the Harrell's concordance index (C-index). Random samples (bootstrap procedure with 1000 iterations) of the population were used to derive 95% confidence interval 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.

Results

Patient characteristics

A total of 168 patients with newly diagnosed mCRC were enrolled between July 2013 and November 2016 with a median age of 70 years (range 33-93), 56% of men, 82% of patients with 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) and 12% according to NRI (< 83.5) (Table 2). The κ coefficient between PG-SGA and NRI was 0.21 (Table 3).

In the overall population at D0, only 9% of patients had a BMI < 18.5 kg/m², 27% had weight loss in the last six months $> 10\%$, 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 assessment.

Chemotherapy protocol was FOLFOX/CAPOX in 53% of cases, FOLFIRI in 27% of cases, FOLFIRINOX in 12% of cases and Capecitabine/LV5FU2 in 8% of cases. Combined targeted therapies were bevacizumab in 45% of cases and anti-epidermal growth factor receptor (EGFR) in 9% of cases.

At D60, 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 to 25% reduction in 23% of patients; 30 to 50% in 8% ; 70 to 100% in 7%).

Nutritional status and early-onset treatment tolerability

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

According to 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 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 numerical score $PG-SGA \geq 9$ 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 NRI were not significantly associated with the development of grade ≥ 2 clinical toxicities as well as $BMI < 18.5 \text{ kg/m}^2$, weight loss $> 10 \%$ in the last 6 months, albuminemia $< 35 \text{ g/L}$ and all biological parameters evaluated (Table 4).

In multivariate analysis, an age < 65 years and a PG-SGA score ≥ 9 remained the two only factors significantly associated with the occurrence of grade ≥ 2 clinical toxicities (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).

Nutritional status and survival

In the overall population, after a median follow-up of 23 months (95%CI 21-26), median PFS was 8 months (95%CI 7-9) and 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 an 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 ($p = 0.004$) (Figure 1).

In univariate analysis, the PG-SGA score ≥ 9 , the PG-SGA category B-C, NRI < 97.5 and hypoalbuminemia < 35 g/L were significantly associated with shorter PFS and OS. BMI < 18.5 kg/m² was not significantly associated with PFS or OS and weight loss in the last 6 months $> 10\%$ was significantly associated only with OS (HR: 1.8 95%CI 1.1-2.9, $p = 0.01$) (Table 4).

In multivariate analysis, PG-SGA ≥ 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 NRI < 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, $p = 1.0$) (Table 4). The multivariate models exhibited acceptable discrimination ability (Table 5).

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

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 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 PG-SGA < 9 (4.2 versus 4.2, $p=0.97$) and a dose decreased of at least 10% of one of the regimen drugs was observed in 37% and 33% of patients, respectively ($p = 0.62$).

Discussion

To our knowledge, this study is the first study assessing the association of nutritional scores with treatment toxicities in patients with mCRC prospectively. It shows that in a homogenous population of mCRC patients 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].

We found that malnutrition defined by a baseline PG-SGA, B-C or a score ≥ 9 , was significantly associated with clinically significant toxicities (grade ≥ 2) in the first two months of chemotherapy, in multivariate analysis. Grade ≥ 2 toxicities are relevant because they may result in a change in 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 that on the

other hand some patients in poor condition were not eligible for targeted agents in this real-life study.

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 smaller number of patients with various treatment lines in our previous work.

Thus, even though NRI seems useful to identify patients at risk for post-operative 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 metastatic setting.

An age lower than 65 years appears in the present study 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 treated with triplet regimen among younger patients (24% versus 5% in patients over 65 years old) and no patient treated with single agent chemotherapy (versus 13% in patients over 65 years old). We decided to include in the multivariate analysis irinotecan-based chemotherapy 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.

This study has shown that malnutrition defined by PG-SGA, but not by NRI, was also associated with a significantly shorter OS in multivariate analysis. In mCRC patients, 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 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 the 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 mCRC patients.

However, this work has also some limitations, in particular the diversity of first line treatment regimens used though 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 can not conclude with this work on the late side effects of chemotherapy, especially on the neurotoxicity induced by oxaliplatin, due to the two months 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 NRI, the PG-SGA score is associated with treatment-related toxicities and survival, and thus appears to be a better reliable nutritional assessment tool in 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 mCRC patients. An interventional study assessing the efficacy of an early nutritional intervention in mCRC patients using this score would be of interest.

Role of the funding source

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Conflict of interest statement

AL has participated in consulting or/and advisory boards for Merck, Amgen, Shire, Bayer, Ipsen, has received honoraria for lecture from Merck, Amgen, Roche, Servier, BMS, Novartis, Ipsen and received support for travel to meetings from Novartis, Ipsen. CL has received personal fees from Merck and support for travel to meetings from Novartis and Roche. SP has participated or/and advisory boards for Amgen, has received support for travel to meetings from Amgen, Bayer, Servier and has received research grant from Roche. MB has received consulting fee for Nutricia medical (2011 - 2012). JT 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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Table 1. Oncological characteristics of the population

| | | 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 (/mm³) | | 1540 (518-6800) | 3 |
| Hemoglobin (/mm³) | | 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; LDH: lactate dehydrogenase.

Table 2. Nutritional characteristics of the population

| | | D0 N=168 (%) | Missing data, n | |
|---|-------------------------------|-------------------------|----------------------------|---|
| Weight loss in the last 6 months | ≤10% | 122 (73%) | 1 | |
| | >10% | 46 (27%) | | |
| BMI (kg/m²) | 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 | 600 | | |
| | (range) | (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

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

| | Malnutrition according to PG-SGA (B-C) | No malnutrition according to PG-SGA (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

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

| | Chemotherapy toxicities grade ≥ 2 | | | | | | PFS | | | | | | OS | | | | | | | | | | | | | | | |
|-------------------------------|--|----------|------------------------------|--|----------|---------------------|---------------------|---------------------|---------------------|---------------------|------------------|---------------------|---------------------|---------|---------------|-----|---------|---------------|-----|---------|---------------------|-----|---------|------|-----|---------|------|--|
| | Univariate analyses | | | Multivariate analysis | | | Univariate analyses | Multivariate models | | | | Univariate analyses | Multivariate models | | | | | | | | | | | | | | | |
| | Clinical toxicities (excluding neurotoxicity) | | Haematological toxicities | Clinical toxicities (excluding neurotoxicity) | | Including PG-SGA | | Including NRI | | Including PG-SGA | Including NRI | | | | | | | | | | | | | | | | | |
| | OR | CI95% | p | OR | CI95% | | | p | OR | | CI95% | | p | OR | CI95% | p | OR | CI95% | p | | | | | | | | | |
| 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 | 0.5 | | | | 0.9 | 0.6-1.4 | 0.7 | | | | | | | | | | |
| 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 | 0.3 | | | | 1.1 | 0.7-1.6 | 0.8 | | | | | | | | | | |
| 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 | 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 | |
| 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 | 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 | |
| Oxaliplatin | 0.6 | 0.3-1.3 | 0.2 | 1.6 | 0.7-3.7 | 0.2 | | | | 1.2 | 0.8-1.6 | 0.4 | | | | | | | 1.1 | 0.7-1.7 | 0.6 | | | | | | | |
| 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 | 0.1 | | | | | | | 0.6 | 0.3-0.9 | 0.03 * | | | | | | | |
| Single agent | 0.4 | 0.1-2.1 | 0.3 | 1 | 0.3-3.9 | 1 | | | | 2.7 | 1.5-4.9 | 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 | |
| Triplet | 1.2 | 0.4-3.2 | 0.8 | 1.6 | 0.6-4.6 | 0.4 | | | | 1.3 | 0.8-2.1 | | 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 | | |
| Bevacizumab | 1.0 | 0.5-2.0 | 1 | 0.3 | 0.1-0.7 | 0.005 * | | | | 1.0 | 0.7-1.4 | 1.0 | | | | | | | 1.1 | 0.7-1.7 | 0.6 | | | | | | | |
| 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 | 0.1 | | | | | | | 0.5 | 0.2-1.4 | 0.2 | | | | | | | |
| 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 | 0.6 | | | | | | | 1.0 | 0.5-2.1 | 0.3 | | | | | | | |
| 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 | 0.3 | | | | | | | 1.8 | 1.1-2.9 | 0.01 * | | | | | | | |
| Nutritional intervention | 1.7 | 0.6-4.4 | 0.3 | 0.5 | 0.1-1.9 | 0.3 | | | | 1.6 | 1.0-2.5 | 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 | |
| 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 | 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 | |
| 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 | 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 | |

| | | | | | | | | | | | | | | | | | | | | | | | | | | |
|--|-----|---------|--------|-----|----------|--------|-----|---------|--------|---------|---------------------|--------|---------|---------|-----|---------|-------|-----|---------|---------------------|-----|---------|--------|-----|---------|--------|
| 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 | <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* |
| 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 | <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 |
| 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 | 0.2 | | | | | | | 1.4 | 0.9-2.2 | 0.1 | | | | | | |
| Lymphocytes < 1000/mm ³ | 1 | 0.3-3.4 | 1 | 2.6 | 0.9-8.0 | 0.085 | | | 1.9 | 1.1-3.3 | 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 | | | | | | |
| 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 | <10 ⁻⁴ * | | | | | | | 2.5 | 1.6-3.8 | <10 ⁻⁴ * | | | | | | |
| 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 | 0.002* | 1.5 | 0.8-2.6 | 0.2 | | | 2.0 | 1.3-3.1 | 0.001* | 2.6 | 1.3-5.3 | 0.006* | | | |
| 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 | 0.004* | | | | | | | 2.2 | 1.5-3.5 | <10 ⁻⁴ * | | | | | | |
| 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 | 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 |
| 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 | 0.2 | | | | | | | 2.3 | 1.3-4.2 | 0.004* | | | | | | |
| 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 | 0.02* | | | | | | | 2.5 | 1.3-4.8 | 0.008* | | | | | | |

OR: odds ratio; 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 < 0.05*

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

| | PFS | OS |
|--|--|--|
| | C-index (95% bootstrap percentile CI) | C-index (95% bootstrap percentile CI) |
| Multivariate models including PGSGA | 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; PFS: progression-free survival; OS: overall survival;

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

Figure 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 NRI

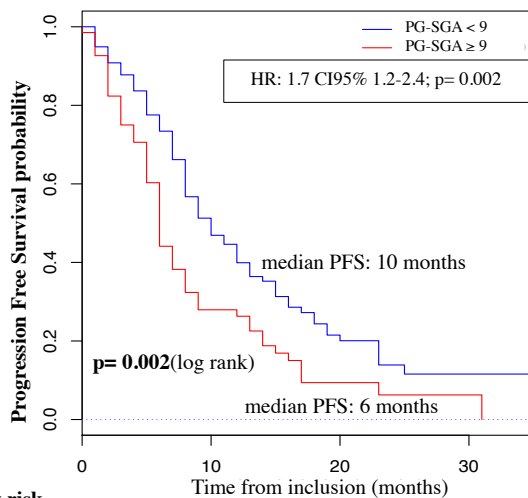
D. OS according to nutritional status defined by NRI

HR: hazard ratio; CI95%: confidence interval 95%; PG-SGA: PG-SGA : Patient-Generated

Subjective Global Assessment ; NRI: Nutritional Risk Index; PFS : progression-free survival ;

OS : overall survival

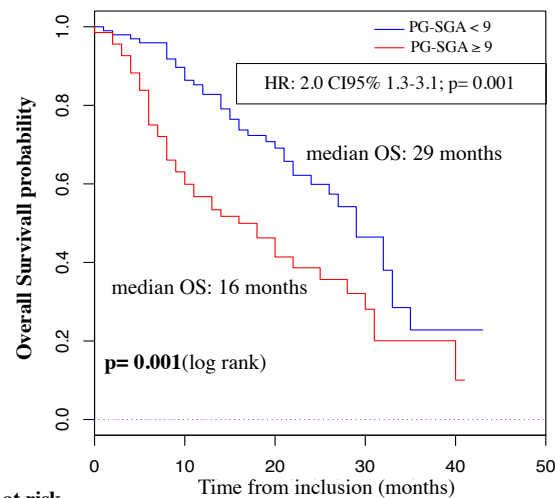
A



Number at risk

| | | | | |
|------------|----|----|----|---|
| PG-SGA < 9 | 98 | 47 | 15 | 2 |
| PG-SGA ≥ 9 | 68 | 17 | 3 | 1 |

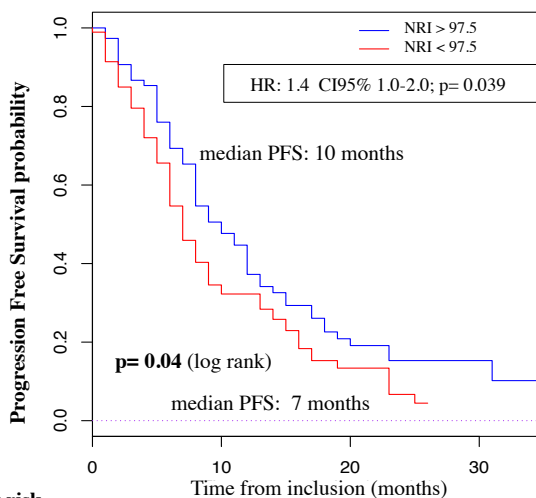
B



Number at risk

| | | | | | | |
|------------|----|----|----|----|---|---|
| PG-SGA < 9 | 98 | 82 | 43 | 11 | 3 | 0 |
| PG-SGA ≥ 9 | 68 | 40 | 19 | 8 | 2 | 0 |

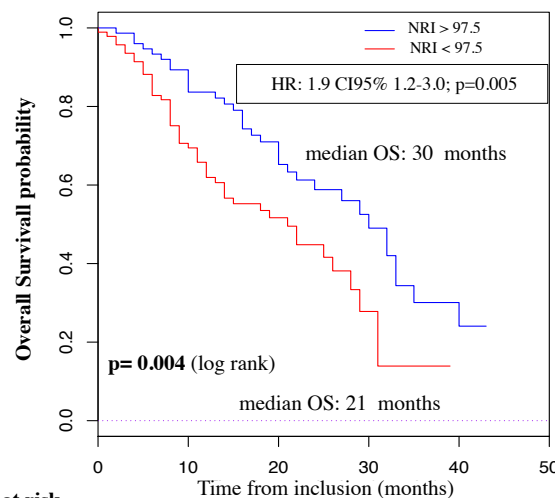
C



Number at risk

| | | | | |
|------------|----|----|----|---|
| NRI > 97.5 | 75 | 35 | 12 | 3 |
| NRI < 97.5 | 93 | 30 | 6 | 0 |

D



Number at risk

| | | | | | | |
|------------|----|----|----|----|---|---|
| NRI > 97.5 | 75 | 63 | 37 | 15 | 5 | 0 |
| NRI < 97.5 | 93 | 61 | 25 | 4 | 0 | 0 |