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ORIGINAL ARTICLE

# ECOG performance score 0 versus 1: impact on efficacy and safety of first-line 5-FU-based chemotherapy among patients with metastatic colorectal cancer included in five randomized trials

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## Abstract

**Background** Within the context of metastatic colorectal cancer, patients with Eastern Cooperative Oncology Group (ECOG) performance score 0–1 are usually pooled together in clinical practice guidelines and clinical trials' reports. The current study aims to delineate potential differences in outcomes between metastatic colorectal cancer patients with ECOG score 0 versus 1 who are treated with currently accepted first-line fluorouracil (5FU)-based chemotherapy.

**Methods** The current study is based on a pooled dataset from five clinical trials of 5FU-based treatment for metastatic colorectal cancer (NCT00272051; NCT00115765; NCT00305188; NCT00364013; and NCT00384176). Patients with metastatic colorectal cancer and ECOG score of 0–1 were eligible for the current study. Multivariable logistic regression analysis was used to assess the relationship between ECOG performance status and the development of different toxicities. Kaplan-Meier survival estimates were used to clarify the impact of the ECOG score on overall and progression-free survivals. Multivariable Cox regression analysis was then used to evaluate the impact of ECOG score on overall and progression-free survivals.

**Results** A total of 3143 patients were included in the current analysis. Within multivariable logistic regression analysis, patients with an ECOG score of 0 have a lower probability of serious adverse events (OR 0.678; 95% CI 0.583–0.788; $P < 0.001$), fatal adverse events (OR 0.552; 95% CI 0.397–0.766; $P < 0.001$), high-grade anemia (OR 0.426; 95% CI 0.252–0.721; $P = 0.001$), and high-grade nausea/vomiting (OR 0.697; 95% CI 0.509–0.955; $P = 0.024$). Through Kaplan-Meier survival analysis, patients with an ECOG score of 0 have better overall and progression-free survivals ($P < 0.001$ for both endpoints). Median overall survival was 27.63 months among patients with an ECOG score of 0 versus 20.00 months among patients with an ECOG score of 1. Within multivariable Cox regression analysis, patients with ECOG score of 0 were associated with better overall and progression-free survivals (HR for overall survival 0.613; 95% CI 0.556–0.676; $P < 0.001$); (HR for progression-free survival 0.765; 95% CI 0.705–0.829; $P < 0.001$).

**Conclusion** Compared with patients with ECOG score of 1, patients with ECOG score of 0 have better overall and progression-free survival, and less probability of serious and fatal adverse events. This distinction in outcomes should be noted when choosing appropriate therapeutic strategies and when designing/reporting the results of clinical trials.

**Keywords** ECOG · Performance · Efficacy · Toxicity · Outcomes

## Introduction

Prognostic stratification of patients with metastatic colorectal cancer is determined by a multitude of disease-related and patient-related factors. Disease-related factors include disease stage, location, biology, and response to treatment [1]. Patient-related factors include biological age, comorbidity, and performance status [2, 3]. While the impact of performance status on the safety and efficacy of different treatments for metastatic colorectal cancer have been evaluated before, most of the studies evaluating this parameter classify patients into those with Eastern Cooperative Oncology Group (ECOG) performance score 0–1 versus those with score ≥ 2 [4]. Few studies have explored the impact of score 0 versus 1 on the outcomes of this group of patients, and these studies used chemotherapy regimens that are considered suboptimal by today's standards [5, 6].

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Most cancer registries and population-based studies do not accurately capture performance status, comorbidity, or side effects of systemic treatment. Thus, they are not suitable to evaluate the impact of performance status on efficacy and toxicity of treatment. A better way to answer this question is to tackle it in the context of a secondary analysis of clinical trial datasets (which accurately capture performance, medical profile, efficacy, toxicity as well as other prognostically relevant information).

## Objective

To evaluate the efficacy and toxicity outcomes of patients with metastatic colorectal cancer with ECOG performance score 0 versus 1.

## Methodology

### Sources of study population

Project Data Sphere (PDS) is a recent initiative of multiple stakeholders who are interested in data sharing of clinical trial datasets. Through this platform, de-identified datasets of several clinical trials were made available [7]. De-identified datasets of five randomized studies evaluating patients with metastatic colorectal cancer receiving first-line fluorouracil (5FU)-based chemotherapy were extracted from the PDS platform (NCT00272051; NCT00115765; NCT00305188; NCT00364013; and NCT00384176). These studies were then pooled together. Additional details about each included trial and chemotherapy regimens used were provided in Table 1. Results of three of these included trials are available elsewhere [8–10].

### Study eligibility

Inclusion criteria in the current study included the following: (1) patients with metastatic colorectal cancer treated with first-line 5FU-based chemotherapy; (2) ECOG performance score of 0 or 1.

Cases with unknown ECOG performance as well as cases with score > 1 were excluded from the current analysis.

### Collection of data

The following data were collected from each included participant where applicable: site of primary tumor, M sub-stage (according to AJCC 7th staging system), age at diagnosis, ECOG score, race, body mass index (BMI), sex, co-treatment with oxaliplatin, co-treatment with bevacizumab and co-treatment with panitumumab, and comorbidities (diabetes mellitus or hypertension). M sub-stage was constructed through the information about the number of metastatic deposits as well as the presence or absence of peritoneal metastases.

Rates of different adverse events were reviewed. These include the following: cardiac adverse events (including arrythmia and ischemic events), diarrhea (all- and high-grade), nausea/vomiting (all- and high-grade), stomatitis (all- and high-grade), neutropenia (all- and high-grade), anemia (all- and high-grade), thrombocytopenia (all- and high-grade), febrile neutropenia, serious adverse events, and fatal adverse events. Information about biological characteristics of the tumor (e.g., RAS, BRAF, and MSI statuses) as well as the

**Table 1** Description of different cohorts included in the current analysis

| Study | Number of patients from each study | Study details |
|---|---|---|
| (NCT00115765) (PACCE) | 842 (26.8%) | Arms:<br>Investigational arm: chemotherapy and bevacizumab and panitumumab<br>Control arm: chemotherapy and bevacizumab<br>Date of conduct:<br>June 2005 to December 2009 |
| (NCT00364013) (PRIME) | 888 (28.4%) | Arms:<br>Investigational arm: FOLFOX and panitumumab<br>Control arm: FOLFOX alone<br>Date of conduct:<br>August 2006 to March 2013 |
| (NCT00272051)* | 303 (9.5%) | Control arm: FOLFOX and placebo<br>Date of conduct: July 2002 to May 2004 |
| (NCT00305188)* | 432 (13.7%) | Control arm: FOLFOX and placebo<br>Date of conduct:<br>December 2005 to October 2009 |
| (NCT00384176) (Horizon III)* | 679 (21.6%) | Control arm: FOLFOX and bevacizumab<br>Date of conduct: August 2006 to August 2015 |

*In these three studies, only comparator arms were included

sidedness of the colon cancer (right- versus left-sided) were not available in the study cohort.

The following endpoints were considered in the current study: safety (rates of different adverse events), overall survival, and progression-free survival.

### Statistical analysis

In order to assess differences in baseline categorical variables as well as different toxicities between patients with ECOG score 0 versus 1, chi-square testing was used. Likewise, independent *t*-test was employed to assess differences in baseline continuous variables between both groups of patients.

The impact of ECOG score on the occurrence of selected toxicities (which were significantly different between both ECOG groups in the chi-square testing) was then further assessed in a multivariable logistic regression analysis. This model was adjusted for M sub-stage (M1a versus M1b), primary tumor location, age, sex, BMI, race, bevacizumab-containing treatment, panitumumab-containing treatment, hypertension, and diabetes mellitus.

Overall and progression-free survival differences according to the ECOG score were then evaluated through Kaplan-Meier survival analysis. The impact of ECOG performance status on overall and progression-free survival was further assessed through multivariable Cox regression analysis. This model was adjusted for the same factors as in the logistic regression model. SPSS statistics (version 20.0, IBM) was then used to conduct all statistical analyses.

## Results

### Patients' characteristics

A total of 3223 patients were available from the five included clinical trials. After excluding 80 patients with unknown ECOG score or ECOG score > 1, a total of 3143 patients were included in the current analysis. Comparing patients with the two ECOG scores together, patients with a score of 1 were more likely to have older age ($P = 0.011$), lower BMI ($P < 0.001$), female sex ($P = 0.032$), and M1b stage ($P < 0.001$). There was no difference between both categories with regard to race ($P = 0.446$), primary tumor site ($P = 0.458$), co-treatment with bevacizumab ($P = 0.695$), panitumumab ($P = 0.228$), or oxaliplatin ($P = 0.648$). There was no difference with regard to co-diagnosis with diabetes mellitus ($P = 0.684$) or hypertension ($P = 0.798$) (Table 2). Mean follow-up duration is 17.87 months (SD 10.89).

### Probability of different adverse events according to ECOG score

Comparing patients with the two ECOG scores together, patients with an ECOG score of 1 were more likely to have serious adverse events ($P < 0.001$), fatal adverse events ($P < 0.001$), high-grade nausea and vomiting ($P = 0.012$), all-grade anemia ($P = 0.017$), and high-grade anemia ($P < 0.001$). They are less likely, however, to have all-grade thrombocytopenia ($P = 0.045$) and peripheral neuropathy ($P = 0.036$) (Table 3). There was no difference between both patient categories with regard to other side effects (as detailed in Table 3).

Multivariate logistic regression analyses were then conducted to validate the impact of performance score on the above described adverse events. Patients with an ECOG score of 0 have a lower probability of serious adverse events (OR 0.678; 95% CI 0.583–0.788; $P < 0.001$), fatal adverse events (OR 0.552; 95% CI 0.397–0.766; $P < 0.001$), high-grade anemia (OR 0.426; 95% CI 0.252–0.721; $P = 0.001$), and high-grade nausea/vomiting (OR 0.697; 95% CI 0.509–0.955; $P = 0.024$). They are more likely, however, to have all-grade thrombocytopenia (OR 1.241; 95% CI 1.024–1.505; $P = 0.028$) (Table 4).

### Survival outcomes according to ECOG performance status

Kaplan-Meier survival estimates/log-rank testing was used to compare overall with progression-free survival according to ECOG performance status. Patients with an ECOG score of 0 have better overall and progression-free survivals ($P < 0.001$ for both endpoints) (Fig.1a, b). Median overall survival was 27.63 months among patients with an ECOG score of 0 versus 20.00 months among patients with an ECOG score of 1.

Multivariate Cox regression analysis was then conducted to further assess the impact of performance status on both overall and progression-free survival. For both endpoints, patients with an ECOG score of 0 were associated with better outcomes (HR for overall survival 0.613; 95% CI 0.556–0.676; $P < 0.001$); (HR for progression-free survival 0.765; 95% CI 0.705–0.829; $P < 0.001$) (Table 5).

## Discussion

The current study evaluates the impact of ECOG performance score of 0 versus 1 on the outcomes of metastatic colorectal cancer treated in five randomized trials. It shows that compared with patients with an ECOG score of 1, patients with an ECOG score of 0 have better overall survival, progression-free survival, and less probability of serious and fatal adverse events. The current approach grouping patients with ECOG

**Table 2** Baseline characteristics of included patients (3143 patients)

| Parameter | Patients with ECOG = 0 (1848 patients) | Patients with ECOG = 1 (1295 patients) | *P* value |
|---|---|---|---|
| Age | | | 0.011 |
| Mean (SD) | 60.26 (10.95) | 61.28 (11.22) | |
| BMI | | | < 0.001 |
| Mean (SD) | 26.67 (5.05) | 25.83 (4.97) | |
| Race | | | 0.446 |
| Caucasian | 1683 (91.1%) | 1169 (90.3%) | |
| Others | 165 (9.8%) | 126 (9.7%) | |
| Sex | | | 0.032 |
| Male | 1132 (61.3%) | 744 (57.5%) | |
| Female | 716 (38.7%) | 551 (42.5%) | |
| Primary tumor site | | | 0.458 |
| Colon | 1244 (67.3%) | 888 (68.6%) | |
| Rectum | 604 (32.7%) | 407 (31.4%) | |
| Number of organs with distant metastases | | | < 0.001 |
| 1 | 805 (43.6%) | 463 (35.8%) | |
| ≥ 2 | 1040 (56.3%) | 831 (64.1%) | |
| Unknown | 3 (0.2%) | 1 (0.1%) | |
| M stage (TNM 7th) | | | < 0.001 |
| M1a | 785 (42.5%) | 446 (34.4%) | |
| M1b | 1061 (57.4%) | 848 (65.5%) | |
| Unknown | 2 (0.1%) | 1 (0.1%) | |
| Panitumumab-containing chemotherapy | | | 0.228 |
| Yes | 527 (28.5%) | 344 (26.6%) | |
| No | 1321 (71.5%) | 951 (73.4%) | |
| Bevacizumab-containing chemotherapy | | | 0.695 |
| Yes | 913 (49.4%) | 649 (50.1%) | |
| No | 935 (50.6%) | 646 (49.9%) | |
| Oxaliplatin-containing chemotherapy | | | 0.648 |
| Yes | 1745 (94.4%) | 1225 (94.6%) | |
| No | 97 (5.2%) | 68 (5.3%) | |
| Unknown | 6 (0.3%) | 2 (0.2%) | |
| Diabetes mellitus | | | 0.684 |
| Yes | 150 (8.1%) | 116 (9%) | |
| No | 1177 (63.7%) | 367 (28.3%) | |
| Unknown | 521 (28.2%) | 812 (62.7%) | |
| Hypertension | | | 0.798 |
| Yes | 480 (26%) | 323 (24.9%) | |
| No | 847 (45.8%) | 605 (46.7%) | |
| Unknown | 521 (28.2%) | 367 (28.3%) | |

score 0 and 1 together in describing the outcomes of metastatic colorectal cancer clinical trials needs to be reviewed.

Numerous retrospective studies have evaluated the impact of performance status on the prognosis and outcomes of metastatic colorectal cancer [11]. However, most of these studies pool patients with ECOG score 0 and 1 together, and very few (if any) studies evaluated the differences in outcomes between patients with ECOG score 0 versus score 1. A previously published pooled analysis by the North Central Cancer Treatment Group has evaluated the outcomes of patients with metastatic colorectal cancer treated with 5FU-based treatment, and it also showed worse survival and higher adverse events with higher performance status [5]. This pooled analysis is, however, different from the current analysis in including patients with score 2/3 as well as use of chemotherapy regimens that can be considered suboptimal by today's standards.

**Table 3** Distribution of toxicities according to ECOG score:

| Parameter | Patients with ECOG = 0 | Patients with ECOG = 1 | *P* value |
|---|---|---|---|
| Serious adverse events | | | < 0.001 |
| Yes | 643 (34.8%) | 565 (43.6%) | |
| No | 1205 (65.2%) | 730 (56.4%) | |
| Fatal adverse events | | | < 0.001 |
| Yes | 73 (4%) | 92 (7.1%) | |
| No | 1775 (96%) | 1203 (92.9%) | |
| Any cardiac adverse events | | | 0.447 |
| Yes | 139 (7.5%) | 107 (8.3%) | |
| No | 1709 (92.5%) | 1188 (91.7%) | |
| Arrhythmias | | | 0.148 |
| Yes | 78 (4.2%) | 69 (5.3%) | |
| No | 1770 (95.8%) | 1226 (94.7%) | |
| Ischemic events | | | 0.471 |
| Yes | 38 (2.1%) | 22 (1.7%) | |
| No | 1810 (97.9%) | 1273 (98.3%) | |
| Alopecia | | | 0.192 |
| Yes | 252 (13.6%) | 156 (12%) | |
| No | 1596 (86.4%) | 1139 (88%) | |
| Peripheral neuropathy* | | | 0.036 |
| Yes | 920 (52.7%) | 598 (48.8%) | |
| No | 825 (47.3%) | 627 (51.2%) | |
| Diarrhea-all grade | | | 0.531 |
| Yes | 1071 (58%) | 765 (59.1%) | |
| No | 777 (42%) | 530 (40.9%) | |
| Diarrhea- high grade | | | 0.261 |
| Yes | 226 (12.2%) | 176 (13.6%) | |
| No | 1622 (87.8%) | 1119 (86.4%) | |
| Stomatitis-all grade | | | 0.156 |
| Yes | 466 (25.2%) | 298 (23%) | |
| No | 1382 (74.8%) | 997 (77%) | |
| Stomatitis-high grade | | | 0.471 |
| Yes | 38 (2.1%) | 22 (1.7%) | |
| No | 1810 (97.9%) | 1273 (98.3%) | |
| Nausea/vomiting-all grade | | | 0.398 |
| Yes | 1152 (62.3%) | 788 (60.8%) | |
| No | 696 (37.7%) | 507 (39.2%) | |
| Nausea/vomiting-high grade | | | 0.012 |
| Yes | 86 (4.7%) | 87 (5.7%) | |
| No | 1762 (95.3%) | 1208 (93.3%) | |
| Anemia-all grade | | | 0.017 |
| Yes | 279 (15.1%) | 237 (18.3%) | |
| No | 1569 (84.9%) | 1058 (81.7%) | |
| Anemia-high grade | | | <0.001 |
| Yes | 24 (1.3%) | 40 (1.3%) | |
| No | 1824 (98.7%) | 1255 (96.9%) | |
| Thrombocytopenia-all grade | | | 0.045 |
| Yes | 354 (19.2%) | 212 (16.4%) | |
| No | 1494 (80.8%) | 1083 (83.6%) | |
| Thrombocytopenia-high grade | | | 0.755 |

**Table 3** (continued)

| Parameter | Patients with ECOG = 0 | Patients with ECOG = 1 | *P* value |
|---|---|---|---|
| Yes | 48 (2.6%) | 36 (2.8%) | |
| No | 1800 (97.4%) | 1259 (97.2%) | |
| Neutropenia-all grade | | | 0.504 |
| Yes | 777 (42%) | 560 (43.2%) | |
| No | 1071 (58%) | 735 (56.8%) | |
| Neutropenia-high grade | | | 0.621 |
| Yes | 540 (29.2%) | 389 (30%) | |
| No | 1308 (70.8%) | 906 (70%) | |
| Febrile neutropenia | | | 0.615 |
| Yes | 46 (2.5%) | 36 (2.8%) | |
| No | 1802 (97.5%) | 1259 (97.2%) | |

*Only for patients receiving oxaliplatin-based treatment

As this study represents a pooled analysis of clinical trial datasets, almost all of the included patients have limited comorbidities. Thus, comorbidities are not expected to significantly impact the outcomes of the current study. That said, diabetes mellitus and hypertension were evaluated in multivariable logistic and Cox regression analyses in order to neutralize any possible effect of these comorbidities on the outcomes of those patients. A prior study—based also on the PDS platform—suggested that diabetes mellitus does not affect overall or progression-free survival of metastatic colorectal cancer patients treated with first-line FOLFOX chemotherapy. Moreover, it does not influence the incidence or severity of oxaliplatin-related paresthesia, but it might be associated with a shorter time to develop oxaliplatin-induced paresthesia compared to patients without diabetes mellitus [12].

There is also an observed imbalance in the baseline characteristics between both ECOG groups with regard to M substage and BMI. Previous studies have suggested that lower BMI might be associated with worse outcomes among metastatic colorectal cancer patients [13]. In order to mitigate the impact of this imbalance, overall and progression-free survival analyses were assessed in multivariable Cox regression models which were adjusted for relevant baseline characteristics, and these models have confirmed the prognostic impact of ECOG score on overall and progression-free survival.

The current study has suggested that patients with an ECOG score of 1 not only have poorer survival but also have higher probability of serious and fatal adverse events. These findings are in line with numerous prior studies in solid tumors suggesting that the higher the performance score is the more likely the patients will

**Table 4** Multivariate logistic regression analysis for the impact of ECOG status on the probability of selected toxicities*

| Selected toxicities | ECOG score | OR (95% CI) | *P* value |
|---|---|---|---|
| SAEs | Score 1 | Reference | < 0.001 |
| | Score 0 | 0.678 (0.583–0.788) | |
| FAEs | Score 1 | Reference | < 0.001 |
| | Score 0 | 0.552 (0.397–0.766) | |
| All-grade anemia | Score 1 | Reference | 0.062 |
| | Score 0 | 0.828 (0.679–1.009) | |
| High-grade anemia | Score 1 | Reference | 0.001 |
| | Score 0 | 0.426 (0.252–0.721) | |
| All-grade thrombocytopenia | Score 1 | Reference | 0.028 |
| | Score 0 | 1.241 (1.024–1.505) | |
| High-grade nausea/vomiting | Score 1 | Reference | 0.024 |
| | Score 0 | 0.697 (0.509–0.955) | |
| Peripheral neuropathy | Score 1 | Reference | 0.138 |
| | Score 0 | 1.127 (0.962–1.319) | |

*Each of which is adjusted for age, BMI, sex, race, M substage (M1a versus M1b), primary tumor location, hypertension, diabetes mellitus, bevacizumab-containing treatment, and panitumumab-containing treatment

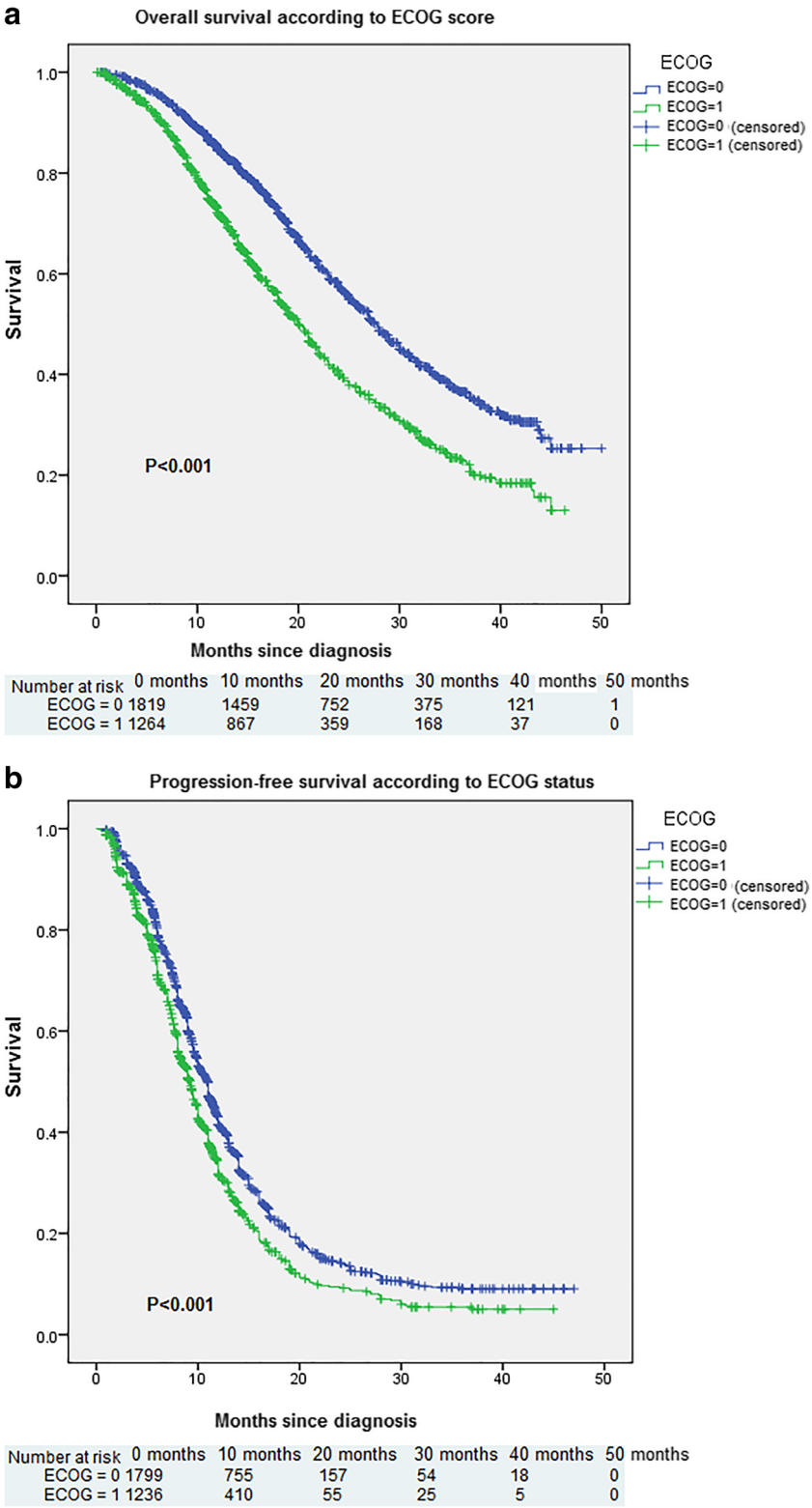


**Fig.1** **a** Overall survival and **b** progression-free survival (according to ECOG performance score)

experience life-threatening adverse events. This information should be incorporated into the counseling process of newly diagnosed patients when discussing the potential for life-threatening side effects with chemotherapy.

Clinical trials for patients with metastatic colorectal cancer used to report patients with ECOG score 0 and 1 as one category (versus patients with performance score > 1). The current study suggests that outcomes should be stratified between

**Table 5** Multivariate Cox regression analysis for the impact of ECOG score on overall and progression-free survival

| Parameter* | HR (95% CI) | *P* value |
|---|---|---|
| i. Overall survival | | |
| ECOG score | | < 0.001 |
| Score 1 | Reference | |
| Score 0 | 0.613 (0.556–0.676) | |
| ii. Progression-free survival | | |
| ECOG score | | < 0.001 |
| Score 1 | Reference | |
| Score 0 | 0.765 (0.705–0.829) | |

*Each of these analyses is adjusted for age, BMI, sex, race, M substage (M1a versus M1b), primary tumor location, hypertension, diabetes mellitus, bevacizumab-containing treatment, and panitumumab-containing treatment

ECOG score 0 and 1. Likewise, most of the international guidelines discussing therapeutic decision-making for metastatic colorectal cancer deal with ECOG score 0–1 as a single prognostic category in terms of treatment selection. The current study suggests that this approach needs to be reviewed, and appropriate distinction between patients with score 0 versus score 1 should be performed.

The current study is associated with several limitations that need to be discussed. First, although the current study dataset is based on prospectively collected clinical trial datasets, the question of the impact of the ECOG score on the outcomes was not the primary research question for any of the included clinical trials. Thus, the nature of this study is a retrospective analysis of prospectively collected datasets (with all the potential biases that might be associated with a retrospective analysis). Second, the current study did lack some information about the biological phenotype of colorectal cancer (including RAS, BRAF, and MSI statuses). This might have affected overall prognostic assessment of the study cohort. These limitations need to be viewed in light of the strengths of the current analysis; most notably, the credibility of data collection in the context of prospectively collected clinical trial datasets.

In conclusion, compared with patients with an ECOG score of 1, patients with an ECOG score of 0 have better overall and progression-free survival, and less probability of serious and fatal adverse events. This distinction in outcomes should be noted when choosing appropriate therapeutic strategies and when designing/reporting the results of clinical trials.

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