Antiangiogenic Drug-induced Proteinuria as a Predictive Factor in Metastatic Colorectal Cancer (mCRC)

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Abstract

Background: Treatment with bevacizumab is known to cause adverse effects such as proteinuria, hypertension, fistulas which, in addition to chemotherapy-induced toxicity, affect the quality of life. However, while bevacizumab-induced hypertension has been linked to increased overall survival, data on proteinuria are controversial.

Patients and methods: We performed a retrospective analysis to observe the influence of adverse effects on the results of treatment with bevacizumab and chemotherapy in patients with mCRC.

Results: Out of the 3497 mCRC patients admitted to our center between 2014 and 2019, 150 met the criteria for inclusion in our analysis. Of these, 50.7% experienced proteinuria and had reached a longer overall survival (40 versus 25 months, p=0.015) and progression free survival (15 versus 12 months, p=0.039). Patients with anemia during treatment, regardless of grade, had a 20-month shorter survival. The following groups were identified as having a lower risk of death: patients with proteinuria (HR 0.630; 95% CI 0.424-0.935; p=0.022), disease control (HR 0.436; 95% CI 0.291-0.653; p<0.001) and non-metastatic stage at diagnosis (HR 0.477; 95% CI 0.300-0.757; p=0.002). Anemia was a negative prognostic factor (HR 2.153; 95% CI 1.343-3.454; p=0.001).

Conclusions: Proteinuria seems to be a useful predictive factor in mCRC patients undergoing bevacizumab-based systemic therapy. Since it is already routinely assessed in this clinical setting, proteinuria could be easily integrated in the decision-making process and thus allow physicians to further individualize systemic treatments.

Introduction

Colorectal cancer (CRC) has an increased incidence in both men and women.[1] If diagnosed at an early stage, it is associated with a good prognosis. However, 20–25% of patients already have metastases at the time of diagnosis and about half of those diagnosed at an early stage will eventually develop metastatic disease.[2] Surgery and fluoropyrimidine-based chemotherapy continue to represent the treatment backbone of CRC, but the advent of molecular targeted therapy has changed the treatment landscape and greatly influenced prognosis of metastatic disease over the last 15 years.

One of the major targets of the biological therapy is the cell proliferation pathway, which in CRC depends on Epidermal Growth Factor Receptor signaling. Monoclonal antibodies such as cetuximab or panitumumab have been successfully used, in conjunction with chemotherapy, for the treatment of patients not harboring mutations in the *RAS* oncogenes (i.e., wild-type *KRAS* and *NRAS*). Also, the *BRAF* mutations such as V600E or V600K have shown prognostic, but not predictive significance for this group of patients in various studies.

Angiogenesis has an important role in tumor proliferation and metastasis. Vascular Endothelial Growth Factor (VEGF) is a key mediator of this process, and, as such, it is also a major target for many biological

therapies. Inhibition of angiogenesis has become the standard care in certain types of cancers such as colorectal, bronchopulmonary, ovarian, renal, breast and cervical cancer.[3–5] However, despite extensive research, one of the major drawbacks of antiangiogenic therapy continues to be the lack predictive biomarkers.

A current global issue is the cost of anticancer drugs. More than US $100 billion is spent annually worldwide.[6] The cost-effectiveness ratio of bevacizumab for mCRC is $571.240 per quality-adjusted life years in first line setting.[7]

Identifying a predictive marker for bevacizumab therapy would help individualize treatment and alleviate the burden of increased cost.

In combination with chemotherapy, bevacizumab (a humanized IgG monoclonal antibody that binds to VEGF-A and prevents activation of the tyrosine kinase domain of its receptors VEGFR1 and VEGFR2) has been shown to be effective in clinical trials by increasing overall survival (OS), progression free survival (PFS) and response rate.[4,8–12] However, adverse effects (AEs) of bevacizumab, in addition to those induced by chemotherapy, may negatively impact treatment outcomes. Hematological, digestive and neurological toxicity has been reported in patients with CRC treated with chemotherapy.[13–15] Bevacizumab is also associated with several particular side effect such as high blood pressure, risk of bleeding, proteinuria, fistulas, gastrointestinal perforations, thromboembolic events, impaired wound healing and heart failure.[8,16]

Bevacizumab was associated with the onset of proteinuria in 10 to 30% of the patients with CRC and up to 71% in patients with renal cancer.[17] Although studies have shown a relationship between bevacizumab and the risk of developing proteinuria,[18–20] the mechanism by which it occurs is not yet fully understood. Most of the time, AEs are reported in clinical trials rather to verify the safety of treatment and not to evaluate their influence on OS. Tanaka et al. have shown that the occurrence of proteinuria can be considered a predictive factor[21] but others have failed to demonstrate this relationship.[17]

Studies reported that febrile neutropenia may reduce dose intensity of chemotherapy, this leading to decreased OS in cancer patients.[22,23] Anemia is frequently observed in CRC patients due to tumor bleeding, especially in rectal cancer. In patients with squamous cell carcinoma of anal canal and anal margin, for example, hemoglobin concentration was an independent prognostic factor for OS, those with anemia having a poor prognosis.[24] Several studies investigated the impact of preoperative anemia in CRC patients[25,26] but, to the best of knowledge, there are no data regarding the impact of myleosupression induced anemia or other side effects of chemotherapy and bevacizumab.

The aim of this retrospective study is to analyze the influence of proteinuria, hematological, hepatic, renal, digestive and neurological toxicity on the results of treatment with bevacizumab and chemotherapy in patients with mCRC. Identifying a biomarker may help to select the mCRC patients subgroup who will have a favorable outcome following treatment with bevacizumab and chemotherapy.

Patients And Methods

Patients

We performed a retrospective analysis of patients diagnosed with mCRC treated with bevacizumab and chemotherapy in our center. Inclusion criteria were: age over 18 years, histologically confirmed colorectal cancer, first-line bevacizumab treatment and at least one urinalysis during treatment. Patients with incomplete data were excluded.

The study was approved by the Ethics Committee of the Regional Institute of Oncology Iasi and all procedures were performed in accordance with the ethical standards of the Ethics Committee of the Regional Institute of Oncology Iasi and the 1964 Helsinki Declaration and its later amendments. Informed consent was waived for the individual participants included in the study in accordance with the ethical standards of the Ethics Committee of the Regional Institute of Oncology Iasi.

For each case, several types of data were collected by reviewing patients' medical records: demographic characteristics, types of chemotherapy, pre-existing comorbidities, treatment-related AEs (including the onset of proteinuria), PFS and OS. Hematological toxicity (anemia, neutropenia, thrombocytopenia), hepatic and renal toxicity were classified according to Common Terminology Criteria for Adverse Events (CTCAE) v4.0 by analysis of complete blood count (CBC) and differential, liver function (GGT, gamma-glutamyl transpeptidase; ASAT, aspartate-aminotransferase; ALAT, alanine-aminotransferase) and creatinine. Proteinuria was assessed in the summary urine test and was noted to be present or absent, with a cut-off level of 30 mg/dL. Tumor response was evaluated after at least 6 month of treatment and interpreted according to the Response Evaluation Criteria in Solid Tumors (RECIST) v1.1 provisions[27]: complete response (CR, disappearance of all lesions), partial response (PR, at least a 30% decrease in the sum of diameters of target lesions), stationary disease (SD, decrease by less than 30% or increase by less than 20%), progressive disease (PD, at least a 20% increase in the sum of diameters of target lesions or the appearance of new lesions).

Statistical Analysis

For statistical analysis, we used the SPSS v.16.0 software (SPSS Inc., Chicago, IL, USA). The qualitative and quantitative variables were characterized by frequency, mean, median, and standard deviation, to describe the basic characteristics of the studied population. The Kaplan Meier curve was used to estimate PFS and OS and the log-rank test was used to compare groups, with a p-value of < 0.05 indicating statistical significance. A logistic regression analysis was performed using development of proteinuria as the dependent variable and the following factors as independent variables: previous hypertension, diabetes, other cardiovascular comorbidities, age, gender and first line chemotherapy regimen. To identify factors influencing survival, a Cox regression analysis was performed using OS as the dependent variable and the following as independent variables: proteinuria, anemia, neutropenia, thrombocytopenia, renal, hepatic, neurological, digestive toxicity, disease control rate (DCR, i.e., CR plus PR plus SD) with first-line treatment, stage at diagnosis (metastatic versus non-metastatic) and primary

tumor resection. Factors associated with OS with $p < 0.20$ in univariate analysis were included in the multivariate model.

Results

A total of 150 mCRC patients undergoing first-line chemotherapy concomitant with bevacizumab between 2014 and 2019 were included in the analysis. Median age of the patients was 64 ± 9.6 years. Most of the tumors (67%) were located on the descending colon. Mutations in *RAS* (*KRAS*, *NRAS*) and *BRAF* (V600E) genes were present in 60 patients out of the 107 for which these data were available. The liver was the most common site for metastasis (63%). Median follow up was 27 months. Baseline patient disposition and disease characteristics are summarized in Table 1.

Table 1
Patient disposition and disease characteristics

Characteristic	N	(%)
Median age, years (range)	64	(33–82)
Gender		
Male	86	(57)
Female	64	(43)
Pre-existing hypertension	39	(26)
Other cardiovascular comorbidities[a]	29	(19)
Diabetes	17	(11)
Tumor location		
Left colon	101	(67)
Right colon	49	(33)
Stage at diagnosis		
Metastatic	109	(73)
Non-metastatic		
DFS less than 12 months	15	(10)
DFS more than 12 months	26	(17)
Primary tumor resection	122	(81)
RAS and *BRAF* status		
Wild type	47	(31)
Mutant	60	(40)
Not tested	43	(29)
Chemotherapy regimen		
Oxaliplatin-based	107	(71)
Irinotecan-based	28	(19)

[a]chronic heart failure, ischemic heart disease, angina, atrial fibrillation, aortic or mitral regurgitation

[b]nonregional lymph nodes; brain; ovarian; adrenal;

DFS – disease free survival

Characteristic	N	(%)
Fluorouracil/Capecitabine-based	15	(10)
Tumor response		
CR	8	(5.3)
PR	35	(23.3)
SD	66	(44)
PD	41	(27.3)
Metastases		
Liver	94	(62.6)
Lung	25	(16.6)
Bone	8	(5.3)
Other[b]	9	(6)
[a]chronic heart failure, ischemic heart disease, angina, atrial fibrillation, aortic or mitral regurgitation		
[b]nonregional lymph nodes; brain; ovarian; adrenal;		
DFS – disease free survival		

We analyzed both bevacizumab- and chemotherapy-related toxicities. The most common side effects and the incidence of grade 3 or higher AEs during the treatment period are shown in Table 2. Hepatic toxicity and anemia were the most common AEs of any-grade; hepatic toxicity and neutropenia were the most common grade 3 and 4 AEs. Grade 3 or higher oxaliplatin-related neurological toxicity (peripheral neuropathy) occurred in 11 patients.

Table 2
Adverse effects of bevacizumab and chemotherapy

Event	All grades N (%)	Grade ≥ 3 N (%)
Any	143 (95)	57 (38)
Proteinuria	76 (50.7)	*
Anemia	108 (72)	8 (5.3)
Neutropenia	84 (56)	13 (8.7)
Thrombocytopenia	76 (50.6)	0
Renal toxicity	57 (38)	2 (1.3)
Hepatic toxicity	121 (80.6)	40 (26.6)
Neurological toxicity	69 (46)	11 (7.3)
Digestive toxicity[a]	44 (29)	3 (2)
*Evaluation of proteinuria was qualitative only		
[a]Digestive toxicity refers to nausea, vomiting, and/or diarrhea		

Proteinuria was present in 50.7% of patients. None of the factors analyzed using the logistic regression method was related to the development of proteinuria: pre-existing hypertension ($p = 0.08$), presence of diabetes ($p = 0.477$), other cardiovascular comorbidities ($p = 0.589$), gender ($p = 0.259$), age ($p = 0.383$), chemotherapy regimen (oxaliplatin-based, $p = 0.965$; irinotecan-based, $p = 0.835$; fluorouracil/capecitabine-based, $p = 0.976$).

Median PFS was 13 months (95% CI 11.9–14.0) in the entire study population, and median OS was 35 months (95% CI 30.9–39.0). Patients who developed proteinuria during treatment had a longer PFS (15 versus 12 months, $p = 0.039$) and OS (40 versus 25 months, $p = 0.015$) compared with those without proteinuria (Fig. 1). The DCR was also higher in patients with proteinuria (76.3% versus 68.9%) but the difference was not statistically significant ($p = 0.309$).

Patients who had anemia during treatment, regardless of grade, had a 20-month shorter survival (Fig. 2) compared with those not experiencing this AE (32 versus 52 months, $p < 0.001$). The DCR was higher in patients without anemia (73.8% versus 72.2%) but the difference did not reach statistical significance ($p = 0.84$).

Patients who achieved disease control with first-line chemotherapy plus bevacizumab treatment had a significantly longer survival: 40 versus 23 months (Fig. 3) compared to those with progressive disease ($p < 0.001$). Patients with the metastatic stage at diagnosis had a 31-month OS, while survival of those who

had progressed in less than 12 months after completion of adjuvant chemotherapy was 37 months; patients progressing at more than 12 months from completion of adjuvant treatment achieved the best OS, of 50 months ($p = 0.002$) (Fig. 4).

The following factors were significantly associated with OS in the univariate analysis: proteinuria, anemia, disease control and surgical resection of the primary tumor (Table 3). Factors considered to be associated with OS ($p < 0.20$) in univariate analysis were included in the multivariate model: proteinuria, anemia, thrombocytopenia, hepatic and renal toxicity, disease control, staging at diagnosis and surgical resection of the primary tumor.

Table 3
Univariate and multivariate prognostic factors for longer OS in metastatic colorectal patients treated with bevacizumab and chemotherapy

Characteristics	Univariate analysis			Multivariate analysis[a]		
	HR	95% CI	p	HR	95% CI	p
Proteinuria	0.635	0.437–0.923	0.017	0.630	0.424–0.935	0.022
Anemia	2.472	1.556–3.928	0.001	2.153	1.343–3.454	0.001
Neutropenia	0.865	0.596–1.256	0.446	-		
Thrombocytopenia	0.731	0.506–1.057	0.096	0.682	0.455–1.021	0.063
Hepatic toxicity	1.417	0.863–2.326	0.169	1.452	0.851–2.478	0.171
Renal toxicity	1.305	0.897–1.898	0.164	1.411	0.954–2.088	0.085
Neurological toxicity	1.191	0.817–1.736	0.364	-		
Digestive toxicity	1.279	0.860–1.092	0.224	-		
Disease control	0.436	0.294–0.647	< 0.001	0.436	0.291–0.653	< 0.001
Staging at diagnosis[b]	0.493	0.319–0.764	0.002	0.477	0.300-0.757	0.002
Surgical resection of the primary tumor	1.411	0.857–2.323	0.176	1.102	0.652–1.864	0.717
[a]Factors related to OS in univariate analysis ($p < 0.20$) were included in the multivariate model: proteinuria, anemia, thrombocytopenia, hepatic and renal toxicity, disease control, staging at diagnosis and surgical resection of the primary tumor;						
[b]Staging at diagnosis: metastatic versus non-metastatic;						

In the multivariate analysis, the following groups had a lower risk of death: patients with proteinuria (HR 0.630; 95% CI 0.424–0.935; $p = 0.022$), no tumor progression (HR 0.436; 95% CI 0.291–0.653; $p < 0.001$) and non-metastatic stage at diagnosis (HR 0.477; 95% CI 0.300-0.757; $p = 0.002$). Patients with low hemoglobin had an increased risk of death (HR 2.153; 95% CI 1.343–3.454; $p = 0.001$), anemia being a negative prognostic factor.

Discussions

Numerous studies and retrospective analysis have been performed to identify novel prognostic factors that can be readily used in the clinical setting for CRC patients. Factors such as location of the primary tumor, histologic grade, history of primary surgery, metastasectomy, performance status, peritoneal metastases, lactate dehydrogenase, PFS interval prior liver surgery, carcinoembryonic antigen levels, liver toxicity (transaminases), size of two largest lesions on CT scan have been evaluated in several prospective and retrospective studies.[28–30] However, no prognostic or predictive biomarkers specific to patients undergoing antiangiogenic systemic therapy have been identified to date. Although VEGF is one of the most studied biomarker in clinical trials,[31–33] available data are still contradictory.

The main purpose of this study was to analyze the putative relationship between the occurrence of treatment-related side effects, specifically bevacizumab-induced proteinuria, and OS. Results showed that the category of patients who developed proteinuria had a significantly better OS and PFS compared to those who did not experienced this AE.

Previous studies have shown a close correlation between the use of bevacizumab and the development of proteinuria.[18–20] Proteinuria has also been studied as a predictive factor, but no consensus was reached. Zee at al. reported significantly lower survival rates in patients with colorectal cancer treated with antiangiogenic therapy if they developed proteinuria grade 2 or higher, as opposed to grade 0–1 (OS 4.2 months versus 23.9 months).[34] In another study, no correlation was found between the severity of proteinuria and survival in patients with mCRC treated with bevacizumab.[17] However, Feliu et al. demonstrated that the occurrence of proteinuria is correlated with the response rate. They included only elderly patients in the study. Patients with moderate and severe proteinuria had a response rate of 56% and OS of 22 months compared to 37% and 20.1 months, respectively, in patients with grade 0–1 proteinuria; however, the survival advantage was not statistically significant.[35] Another study showed that the early development of both hypertension and proteinuria after initiation of bevacizumab in patients with breast cancer is associated with tumor response, and the authors suggested that these two side effects could be considered predictive.[21]

Other authors correlated the development of proteinuria with the cumulative dose of bevacizumab, the number of cycles administered,[35,36] systolic blood pressure values above 130 mmHg[37] or the presence of diabetes.[38] Of these, only the presence of diabetes was analyzed in the present study, but neither this, nor any other variable appeared to significantly influence the development of proteinuria; 10 of 17 diabetic patients included in our cohort developed proteinuria during treatment. A meta-analysis that included data from 16 studies showed that adding bevacizumab to chemotherapy increases 4.79-fold the median risk of grade 3–4 proteinuria. This increase varied with cancer type (e.g., 2.52 for colorectal cancer; 48.7 for kidney cancer) and showed a linear relationship with the dose of bevacizumab (e.g., 2.62 at a dose of 2.5 mg/kg and 8.56 at 5 mg/kg, compared to chemotherapy alone).[18]

Several potential angiogenesis-related mechanisms have been proposed for the induction of proteinuria. As a response to hypoxia and decreased proteasomal degradation of hypoxia-inducible factor 1-alpha

(HIF-1-alpha), both production of VEGF by podocytes and consecutive activation of the VEGF-2 receptor on glomerular capillary endothelial cells are increased. Conversely, VEGF/VEGFR-2 inhibition causes a loss of podocytes, endothelial fenestration, glomerulosclerosis and tubulointerstitial fibrosis.[39] In addition, inhibition of VEGF may cause glomerular thrombotic microangiopathy and membranoproliferative changes.[40]

In addition, correlation between bevacizumab-induced toxicity and outcome may have a genetic explanation. Studies identified genetic variants of VEGF and VEGFR having potentially predictive value for antiangiogenic therapy.[41,42] Hansen et al. reported that VEGFR-1 319 C/A single nucleotide polymorphism was associated with the response rate in mCRC patients treated with bevacizumab and chemotherapy.[43] Another study suggests that genetic variants of VEGF may be linked to the risk of toxicity. Breast cancer patients treated with bevacizumab and chemotherapy carrying *VEGF-634 CC* and *VEGF-1498 TT* genotypes had a lower incidence of grade 3 or 4 hypertension.[44] Nikzamir et al. reported that *VEGF + 405 GG* genotype was a predictive factor for albuminuria in patients with type 2 diabetes.[45] Patients developing proteinuria during bevacizumab treatment may be carriers of such variants. However, the role of genetic variants of VEGF in the development of bevacizumab-related proteinuria has not been studied yet.

No guidelines are currently available for the management of bevacizumab-induced proteinuria, although there is general consensus on the necessity to prevent subsequent renal failure, cardiovascular complications, as well as tumor progression due to permanent discontinuation of biologic therapy if proteinuria is greater than 2 g/24 h or nephrotic syndrome occurs, respectively.

In the present study, occurrence of at least one episode of anemia during treatment was a negative prognostic factor for OS in the uni- and multivariate analyses. Survival decreased significantly according to the grade of anemia (20 months for grade 3 versus 31 months for grade 2 versus 34 months for grade 1; no grade 4 or 5 anemia was reported). This is in accord with the conclusions of a meta-analysis reporting that anemia at any point during the course of the disease increases the risk of death in cancer patients. When presenting anemia, the relative risk of death was increased by 19% in lung cancer, by 75% in head and neck carcinomas, and by 47% in prostate cancer patients.[46] Anemia during chemotherapy also affects OS by the deriving necessity to delay or reduce the dose of chemotherapy. In addition, anemia produces tumor hypoxia that reduces the effectiveness of chemotherapy and bevacizumab. Although anemia can be corrected, there is no evidence that application of therapeutic methods improves long-term prognosis.

Another factor influencing both OS and disease free survival (DFS) is the tumor stage at diagnosis.[47,48] In uni- and multivariate analysis we have split our study population into 2 groups (upfront metastatic, n = 109; and non-metastatic, n = 41) and found that initially non-metastatic patients had a significant better survival.

In the current analysis, renal, hepatic, digestive and neurological toxicities have affected quality of life to various degrees, but did not influence OS.

Köhne et al. analyzed a panel of clinical, hematological and biochemical factors to identify prognostic markers of in CRC patients treated with fluorouracil-based chemotherapy. Platelets (> 400×10^9/L), alkaline phosphatase level (> 300 IU/L), white blood cell (WBC) count (> 10×10^9/L) and hemoglobin (< 11 g/dL) predicted an inferior survival probability; lactate dehydrogenase, bilirubin, ALAT, ASAT, total protein, albumin, carcinoembryonic antigen (CEA) levels were not significant. Also, an ECOG performance status > 1, presence of liver metastases or peritoneal carcinomatosis predicted a worse patient outcome.[49]

Another multivariate analysis concluded that primary tumor location, performance status, number of metastatic sites, baseline CEA level and platelets may be considered prognostic factors in patients with mCRC treated with oxaliplatin and bevacizumab.[50] In our study, thrombocytopenia during treatment with bevacizumab and chemotherapy did not affect OS.

Our research is subject to several limitations. The most important is relatively small population size, which precludes definitive conclusions or recommendations based on the results above. However, our results provide important data on predictive role of proteinuria and warrants more extensive prospective studies in order to validate the present findings.

Second, the study might have a potentially short follow-up bias. Studies reported a wide range time-to-onset of proteinuria, from 3 weeks to 37 months, with a median of 5.6 months from the start of bevacizumab. Median follow up for the present study was 27 months, so several additional cases of late proteinuria occurring in our population were not considered.

Another limitation refers to not accounting for baseline values of some parameters, such as blood pressure or anemia. It is common knowledge that hypertension influences the development of proteinuria through various mechanisms. In the logistic regression analysis, we included only pre-existing hypertension without considering whether blood pressure had been controlled by anti-hypertensive treatment. It is also possible that some patients might have developed hypertension during treatment and this might have influenced the occurrence of proteinuria. Similarly, low baseline hemoglobin values might have had an impact on OS; we only included in the analysis the cases of anemia occurring as side effects of systemic treatment. To correctly assess the prognostic value of treatment-related anemia, new studies with a different methodology are needed.

Conclusions

The results of our study suggest that, in addition to disease control achievement and non-metastatic stage at diagnosis, the development of proteinuria during first-line treatment with bevacizumab and chemotherapy of patients with mCRC correlates with a better prognosis. Despite the fact that literature data are controversial in terms of the predictive role of proteinuria, the results of our study argue in favor of it. The presence of diabetes, pre-existing hypertension and other cardiovascular conditions did not

increase proteinuria risk in the studied group. The presence of anemia during treatment was a negative prognostic factor.

Declarations

Data Availability

The datasets generated and analyzed during the current study are available from the corresponding author on request.

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Author contributions

DCM: methodology, data analysis and interpretation, writing original draft, final manuscript approval;

MVM: concept and design, writing, review and editing, final manuscript approval;

BG: collection and assembly of data, resources, final manuscript approval;

TAS: collection and assembly of data, design, final manuscript approval;

PC: supervision, data analysis and interpretation, writing, review and editing, final manuscript approval;

DCM and MVM Contributed equally as first authors;

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Competing Interests Statement

DCM has no competing financial interests.

MVM has received honoraria from and was an investigator in F. Hofmann-LaRoche-sponsored trials.

BG has received honoraria from and was an investigator in F. Hofmann-LaRoche-sponsored trials.

TAS has received honoraria from F. Hofmann-LaRoche.

PC has no competing financial interests.

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Figures

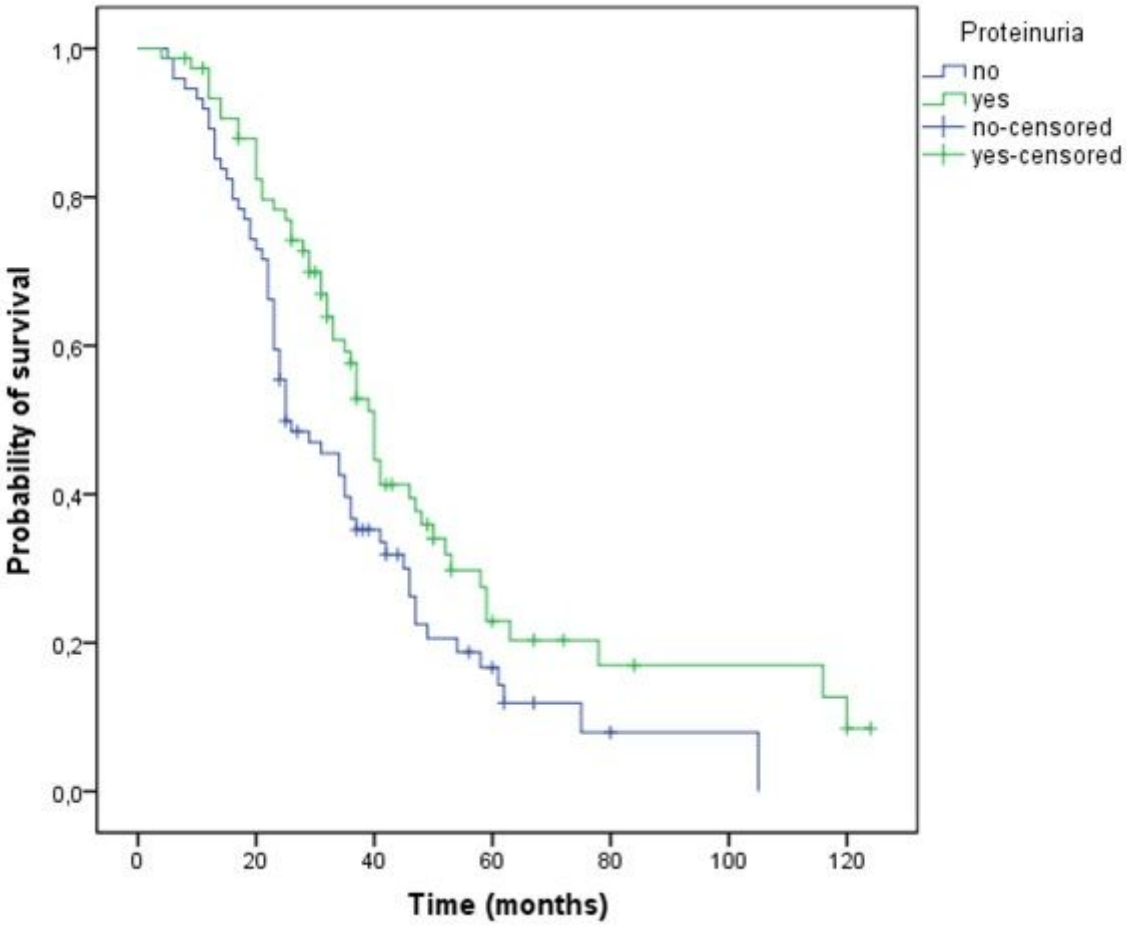

Figure 1

Kaplan-Meier curve of overall survival for patients who have or have not developed proteinuria during treatment (OS, 40 versus 25 months, p=0.015)

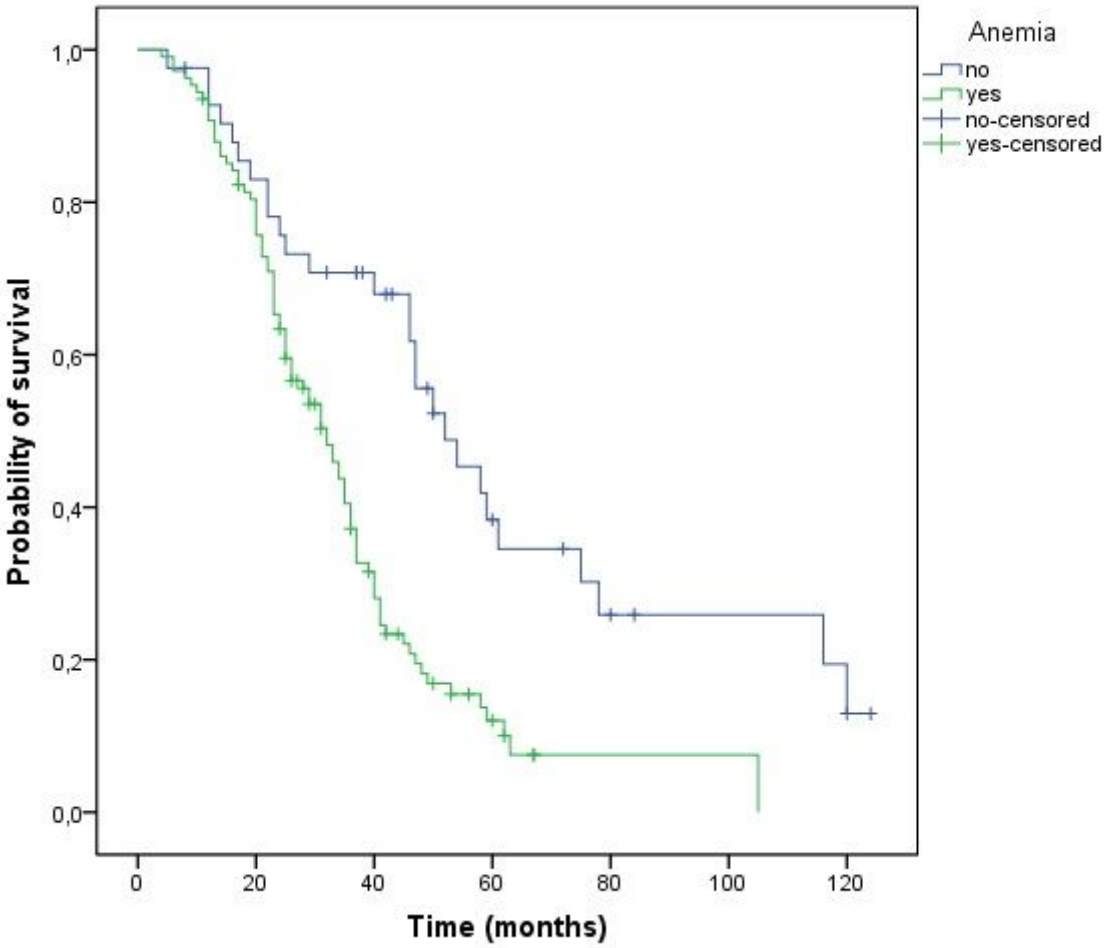

Figure 2

Kaplan-Meier curve of overall survival for patients who have or have not developed anemia during treatment (OS, 32 versus 52 months, p<0.001)

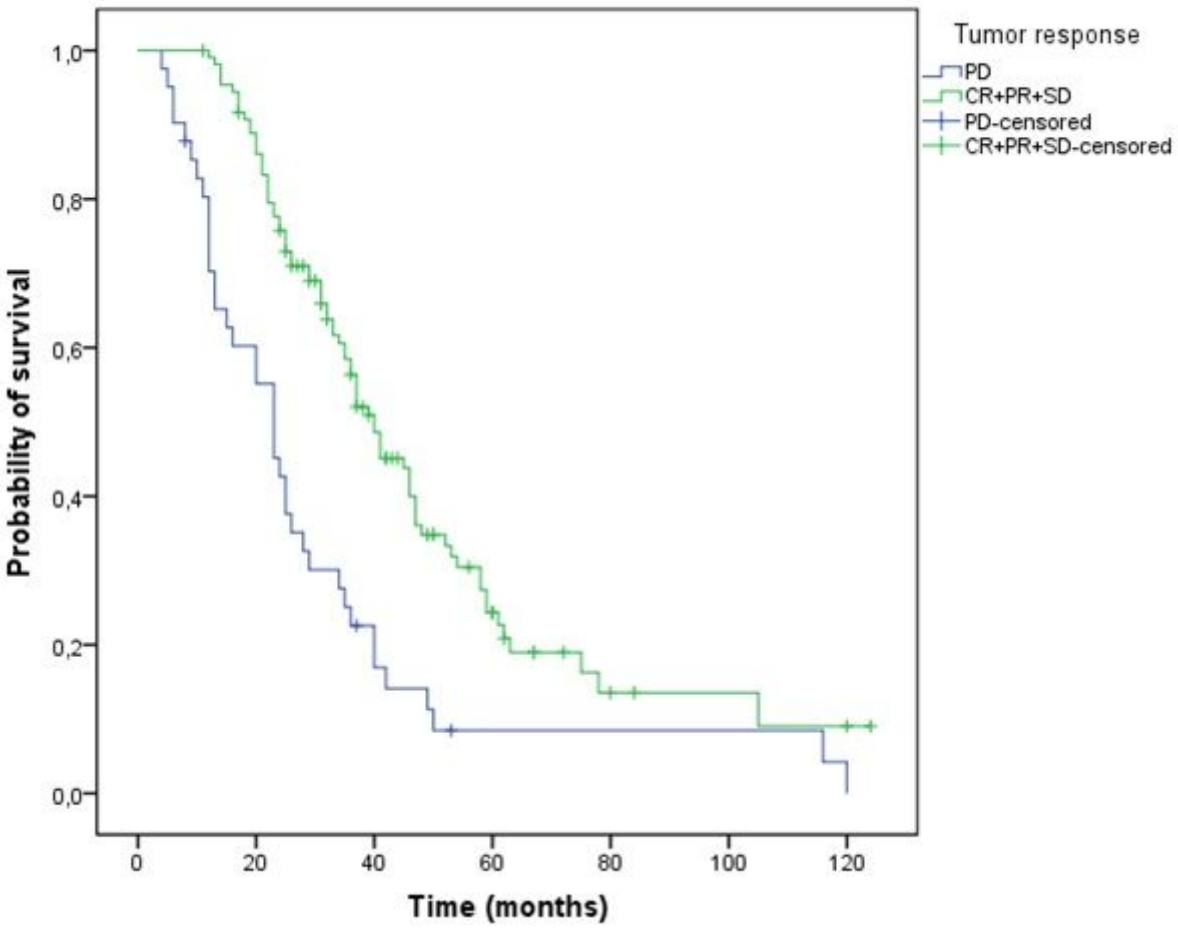

Figure 3

Kaplan-Meier curve of overall survival for patients who have or have not obtained a tumor response (OS, 40 versus 23 months, p<0.001)

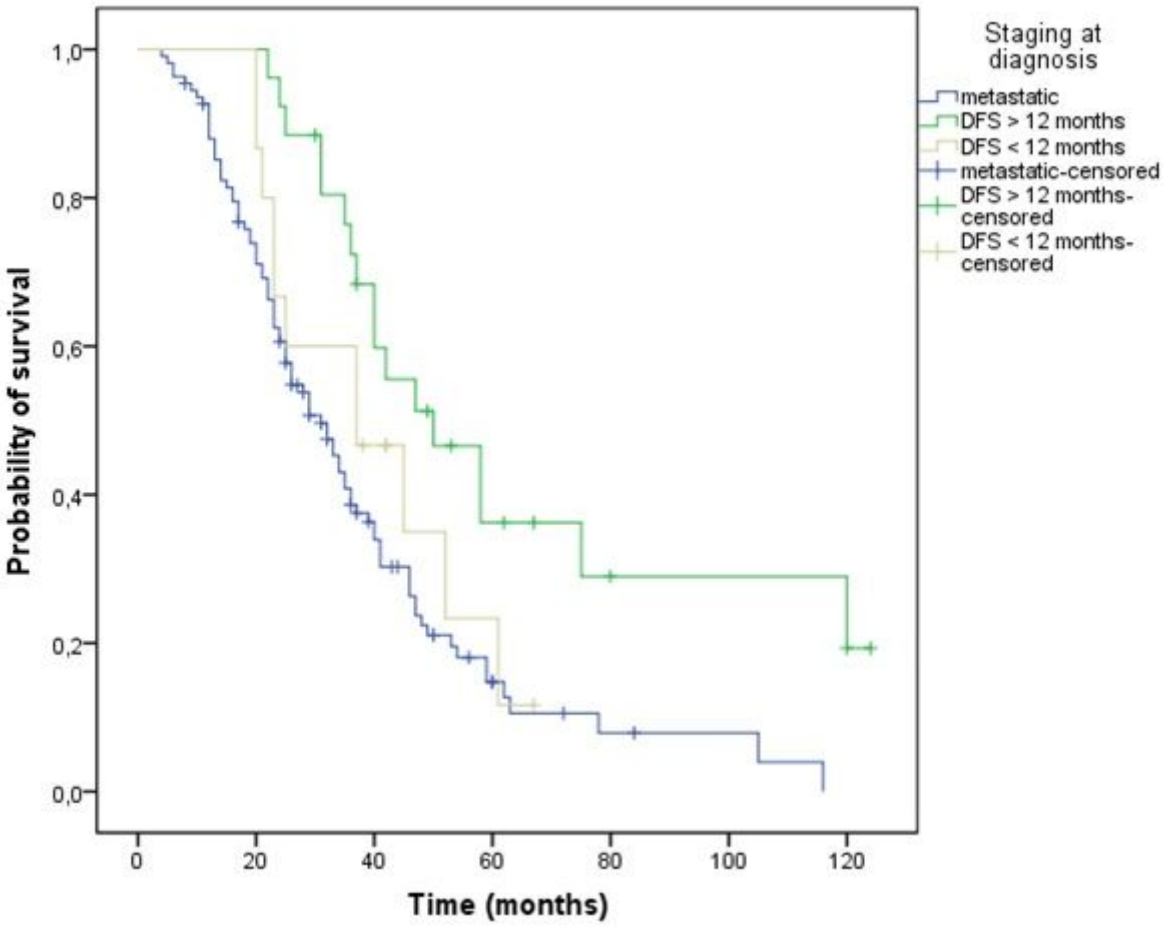

Figure 4

Kaplan-Meier curve of overall survival depending on the stage at diagnosis: metastatic or non-metastatic: DFS less or more than 12 months (OS, 31 versus 37 versus 50 months, p=0.002)