Original article

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Development and validation of a novel prognostic score to predict survival in patients with metastatic colorectal cancer: the metastatic colorectal cancer score (mCCS)

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Abstract

Aim Published prognostic scores for metastatic colorectal cancer (mCRC) are based on data from highly selected patient subgroups with specified first-line treatments and may not be applicable to routine practice. We have therefore developed and validated the metastatic colorectal cancer score (mCCS) to predict overall survival (OS) for patients with mCRC.

Method A total of 1704 patients from the prospective, multicentre cohort study Tumour Registry Colorectal Cancer were separated into learning ($n = 796$) and validation ($n = 908$) samples. Using a multivariate Cox regression model, the six-factor mCCS was established.

Results The six independent prognostic factors for survival are as follows: two or more metastatic sites at the start of first-line treatment, tumour grading ≥ G3 at primary diagnosis, residual tumour classification ≥ R1/unknown, lymph node ratio (of primary tumour) ≥ 0.4, tumour stage ≥ III/unknown at primary diagnosis and *KRAS* status mutated/unknown. The mCCS clearly separated the learning sample into three risk groups: zero to two factors (low risk), three factors (intermediate risk) and four to six factors (high risk). The prognostic performance of the mCCS was confirmed in the validation sample and additionally stratified a large sample of patients with known *(K)RAS* mutation status.

Conclusion The novel prognostic score, mCCS, clearly defines three prognostic groups for OS at start of first-line therapy. For oncologists, the mCCS represents a simple and easy-to-apply tool for routine clinical use, as it is based on objective tumour characteristics and can assist with treatment decision-making and communication of the prognosis to patients.

Keywords Colorectal neoplasms, prognosis, cohort studies, risk assessment, survival

What does this paper add to the literature?
Prognostic scores for patients with metastatic colorectal cancer based on data from clinical trials are often not transferrable to routine practice. Therefore, we have developed and validated a prognostic score for patients in the 'real-world' setting, a simple and easy-to-apply tool for predicting survival regardless of first-line treatment.

Introduction

In Germany in 2014, 61 000 patients were diagnosed with CRC and 25 500 died from the disease, making CRC the third most frequent cause of cancer death in that country [1]. Over the last decade, the clinical outcome for patients with metastatic colorectal cancer (mCRC) has markedly improved, with median overall survival (OS) approaching 30 months in some clinical trials [2].

For most patients, treatment is palliative and consists of systemic chemotherapy; only those few with potentially resectable metastases (particularly those with isolated liver metastases) are treated with curative intent.

Current standard treatment is based on 5-fluorouracil (5-FU) combined with oxaliplatin or irinotecan or

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both [3]. The approval of molecular targeted therapies, such as antibodies targeting epidermal growth factor receptor (EGFR) or vascular endothelial growth factor (VEGF), has further increased treatment efficacy and led to the identification of the first, and so far only, predictive biomarker, the *RAS* mutation status [4,5]. However, the optimal combination of agents, and thus the best clinical management of patients with mCRC, remain controversial.

Identification of prognostic factors and the development of prognostic scores that can predict survival may help physicians in communication with patients and treatment decision-making. A number of laboratory and clinical factors predictive for OS have been identified in previous analyses [3,6–13] and two prognostic scores have been published [14,15]. Köhne and colleagues classified three risk groups for survival based on four baseline clinical parameters (performance status, white blood cell count, alkaline phosphatase and number of metastatic sites) in patients with mCRC receiving 5-FU monotherapy as first-line treatment [14]. The GERCOR study also classified three risk groups for survival based on three clinical parameters [performance status, lactate dehydrogenase (LDH) and number of metastatic sites, with LDH being the main prognostic factor] in patients with mCRC treated with an irinotecan- or oxaliplatin-based first-line chemotherapy [15]. Both prognostic scores focused on parameters evaluated at the start of first-line treatment. In addition, both scores were based on data from patients enrolled in randomized clinical trials, representing a selected population with few comorbidities and uniform treatment, limiting subsequent generalizability to all patients with mCRC.

In order to fill this gap, we have developed and validated a prognostic score to predict OS of patients with mCRC treated in German routine practice, based on information available before selection and the start of first-line treatment.

Method

Data source

The Tumour Registry Colorectal Cancer (TKK) is an ongoing, prospective, multicentre, longitudinal, nationwide cohort study which started in 2006. Since then, 269 medical oncologists from all over Germany have recruited more than 6000 patients. This study was reviewed by an ethics committee and is registered at ClinicalTrial.gov (NCT00910819). Eligible patients are aged 18 or over with histologically confirmed colorectal cancer and systemic chemo- or targeted therapy (e.g. antibodies). Written informed consent was obtained from all patients. The TKK has previously been described in detail [16]. Patients are treated according to physician choice and are followed for a minimum of 3 years (or until death, loss to follow-up or withdrawal of consent).

At the time of enrolment, data on patient and tumour characteristics are documented. From 2008 to 2013, the *KRAS* mutation status was collected without further information on the tested/mutated exon(s). Since 2014, data on the extended *RAS* testing routine have been documented (*KRAS* exons 2, 3 and 4 and *NRAS* exons 2, 3 and 4), further referred to as '*(K)RAS*' mutation testing.

Cohort definition

For the present analysis, all patients who had started first-line treatment for Stage IV disease and who had signed informed consent no more than 4 weeks after the start of treatment were chosen. The database cutoff was 31 March 2012. Up until then, 4593 patients had been recruited into the TKK: 2535 patients were recruited with Stage IV disease, and of these 1704 signed their informed consent no more than 4 weeks after start of first-line therapy and were thus eligible for the present analysis. This cohort was split up, resulting in a learning and a validation sample. The learning sample consisted of patients who started first-line treatment between 1 January 2006 and 31 March 2009 ($n = 796$). The validation sample consisted of patients who started first-line treatment between 1 April 2009 and 31 March 2012 ($n = 908$). Stratification of the prognostic score was further tested on a large sample of patients with either *(K)RAS* wild-type tumours ($n = 1504$) or *(K)RAS* mutated tumours ($n = 1085$) recruited from September 2006 until April 2017 and followed-up for at least 1 year. The database cutoff for survival follow-up data of this patient sample was April 2018.

Development of the prognostic score mCCS

Twenty-five variables documented in the TKK that could potentially serve as prognostic factors were identified by an expert panel of medical oncologists from Germany: gender, body mass index (BMI), age, presence of comorbidities (yes or no), Charlson Comorbidity Index (CCI), most frequent comorbidities, site of primary tumour (colon or rectum), tumour stage at primary diagnosis (I–IV), TNM classification, grading of primary tumour, number of resected lymph nodes, number of affected lymph nodes, lymph node ratio (number of lymph nodes involved to the number of examined lymph nodes), *KRAS* status, resection of

primary tumour (yes or no), type of resection of primary tumour, outcome of resection of primary tumour, number of metastatic sites at start of first-line treatment, single metastatic sites, pattern of metastasis, prior adjuvant treatment (yes or no), time from initial diagnosis to start of first-line therapy, type of insurance (statutory health insurance or private medical insurance), educational qualification, professional qualification.

Variables were categorized in accordance with suggestions from a previous study [17]. Additionally, infrequent categories were combined. Missing or unknown values were regarded as separate categories or combined. To simplify the score for clinical use, variables were dichotomized before entering the score. Cutoff points for dichotomization were selected based on literature or categories previously proposed by the expert panel [17].

For the construction of a simple classification rule, the following steps were performed: the relationship between the covariates and survival as well as the relationships among the covariates were analysed via exploratory data analysis. Covariates were excluded if there was a large proportion of missing data. For multivariate analysis (Cox regression), prognostic factors were identified using manual backward selection via model comparison (likelihood ratio test), allowing for one fallback per parameter. After dichotomization, the relationship between prognostic factor and survival was confirmed using Cox analysis. Based on the identified prognostic factors, a sum score (number of risk factors) was built. For practical reasons, prognostic factors were not weighted and each factor contributed one unit. Based on the number of prognostic factors, patients were stratified into three risk groups having approximately the same sample size. The predictive performance of the identified risk groups was tested in the validation sample using log-rank test and Kaplan–Meier method to compare both low *vs* intermediate and intermediate *vs* high risk groups. Adjustment for multiplicity was done for both comparisons according to Bonferroni.

Statistical analysis

Analyses were performed using STATISTICA (StatSoft, Inc.) version 10.0 and R version 2.15.1. Survival distributions were estimated using the Kaplan–Meier method [18]. Overall survival was defined as the interval between the start of first-line chemotherapy and date of death from any cause. Patients alive or lost to follow-up were censored at last contact. Follow-up time was estimated using the inverse Kaplan–Meier method [19].

Results

Patient characteristics

Table 1 presents the patient and tumour characteristics of the learning sample ($n = 796$) and the validation sample ($n = 908$). The samples were comparable with regard to patient and tumour characteristics. Due to updated guidelines regarding *(K)RAS* mutation status testing, the proportion of patients tested for *KRAS* mutation status was higher in the validation sample (start of first-line treatment 2009–2012) than in the learning sample (start of treatment 2006–2009). Similarly, first-line targeted therapies were used more often in the validation sample, probably reflecting changes over time in the choice of therapy.

Median follow-up time was 43.8 months [95% confidence interval (CI) 41.4–46.3] for the learning sample and 21.3 months (95% CI 19.6–23.3) for the validation sample. Median OS was 22.8 months (95%-CI 20.8–25.7) in the learning sample and 22.4 months (95%-CI 20.9–24.7) in the validation sample.

The mCCS prognostic score

A prognostic score was developed using patient data from the learning sample. Fifteen variables with sufficient numbers of documented data were included in the exploratory analysis and further tested in the multivariate analysis: gender, BMI, age, presence of comorbidities (yes or no), CCI, site of primary tumour (colon or rectum), tumour stage at initial diagnosis (I–IV), grading of primary tumour, lymph node ratio, *KRAS* status, number of metastatic sites at the start of first-line treatment, prior adjuvant treatment (yes or no), time from initial diagnosis to the start of first-line therapy, residual tumour classification (R0, R1, R2, RX), type of insurance (statutory *vs* private).

Six factors remained as independent prognostic factors for survival in the final model: number of metastatic sites, grading of primary tumour, residual tumour classification, lymph node ratio, tumour stage and *KRAS* mutation status. The hazard ratios for each parameter in univariate and multivariate analysis are shown in Table 2.

These six factors were dichotomized and a multivariate model with the resulting binary variables was calculated (Table 3). The cutoff points were as follows: two or more metastatic sites at start of first-line treatment, tumour grading $\geq$ G3 at primary diagnosis, residual tumour classification (of primary tumour) $\geq$ R1 or unknown, lymph node ratio (of primary tumour) ≥ 0.4,

Table 1 Patient and tumour characteristics (n = 1704).

Parameter		Learning sample 2006–2009	Validation sample 2009–2012
N. of patients (n)		796	908
Gender (n, %)	Male	501 (62.9)	581 (64.0)
	Female	295 (37.1)	327 (36.0)
Median age (years, SD)‡		67.4 (10.6)	67.0 (11.1)
Body mass index (kg/m^2) (mean, SD)		25.9 (4.9)	25.8 (4.9)
Charlson Comorbidity Index (mean, SD)		0.6 (1.2)	0.8 (1.5)
Patients with comorbidities (n, %)		546 (68.6)	629 (69.3)
Site of primary tumour (n, %)	Colon	490 (61.6)	560 (61.7)
	Rectum	306 (38.4)	344 (37.9)
	Missing/unknown	0 (0)	4 (0.4)
Stage at primary diagnosis (n, %)	I	30 (3.8)	28 (3.1)
	II	70 (8.8)	70 (7.7)
	III	122 (15.3)	128 (14.1)
	IV	469 (58.9)	589 (64.9)
	Missing/unknown	105 (13.2)	93 (10.2)
Tumour grading (n, %)	G1	17 (2.1)	18 (2.0)
	G2	476 (59.8)	496 (54.6)
	G3	196 (24.6)	248 (27.3)
	G4	3 (0.4)	3 (0.3)
	Gx	104 (13.1)	129 (14.2)
	Missing	0 (0)	14 (1.5)
KRAS (n, %)	Mutation	87 (10.9)	186 (20.5)
	Wild type	198 (24.9)	312 (34.4)
	Unknown	503 (63.2)	404 (44.5)
	Missing	8 (1.0)	6 (0.7)
Resection of primary tumour (n, %)		730 (91.7)	774 (85.2)
Residual tumour classification (n, %)	R0	453 (56.9)	502 (55.3)
	R1	51 (6.4)	60 (6.6)
	R2	71 (8.9)	73 (8.0)
	Rx	219 (27.5)	255 (28.1)
	Missing	2 (0.3)	18 (2.0)
Lymph node ratio* (n; median [Quartile])		444; 0.31 [0.14,0.51]	476; 0.26 [0.13,0.50]
Synchronous metastasis (n, %)		469 (58.9)	589 (64.9)
No. of metastatic sites‡ (mean, SD)		1.0 (0.7)	1.0 (0.7)
Metastatic sites (n, %)	Liver	514 (64.6)	526 (57.9)
	Lung	182 (22.9)	249 (27.4)
	Peritoneum	108 (13.6)	125 (13.8)
	Other	57 (7.2)	92 (10.1)
First-line chemotherapy (n, %)	FOLFIRI/CAPIRI	314 (39.4)	330 (36.3)
	FOLFOX/CAPOX	333 (41.8)	377 (41.5)
	FU mono/CAP mono	125 (15.7)	147 (16.2)
	None	3 (0.4)	3 (0.3)
	Other/unknown†	21 (2.6)	51 (5.6)
First-line targeted therapy (n, %)	Anti-VEGF	309 (38.8)	434 (47.8)
	Anti-EGFR	39 (4.9)	89 (9.8)
	None	448 (56.3)	350 (38.5)
	Other/unknown†	0 (0)	35 (3.9)

Missing data are labelled as 'unknown' when documented as such by the study site and 'missing' when not documented at all.
CAP, capecitabine; CAPIRI, capecitabine + irinotecan; CAPOX, capecitabine + oxaliplatin; EGFR, epidermal growth factor receptor; FU, fluorouracil; FOLFIRI, folinic acid + 5-fluorouracil + irinotecan; FOLFOX, folinic acid + 5-fluorouracil + oxaliplatin; SD, standard deviation, VEGF, vascular endothelial growth factor.
*Ratio of number of lymph nodes involved to number of examined lymph nodes.
†Including experimental first-line therapies that were not further specified to ensure trial confidentiality.
‡At the start of first-line therapy.

Table 2 Univariate and multivariate analysis (learning sample, $n = 796$).

	Univariate analysis			Multivariate analysis		
Parameter	Hazard ratio	95% CI	*P*	Hazard ratio	95% CI	*P*
Number of metastatic sites (reference 0)						
1	0.91	0.74–1.11	0.337	0.94	0.76–1.15	0.557
2	1.42	1.09–1.84	0.009	1.42	1.09–1.86	0.009
≥ 3	1.94	1.05–3.57	0.034	1.95	1.04–3.65	0.036
Tumour grading (reference G1/G2)						
G3/G4	1.43	1.17–1.76	< 0.001	1.35	1.09–1.66	0.005
GX/missing	1.44	1.11–1.87	0.006	1.11	0.83–1.49	0.457
Residual tumour classification (reference R0)						
R1	1.40	0.97–2.03	0.071	1.21	0.82–1.77	0.333
R2	1.84	1.37–2.49	< 0.001	1.74	1.26–2.39	< 0.001
RX/missing	1.65	1.35–2.01	< 0.001	1.50	1.20–1.88	< 0.001
Lymph node (LN) ratio (reference ratio ≥ 0.4)						
LN ratio ≥ 0.2, < 0.4	0.59	0.44–0.80	< 0.001	0.62	0.46–0.85	0.002
LN ratio < 0.2	0.65	0.50–0.86	0.002	0.69	0.52–0.92	0.010
LN ratio unknown/missing	0.72	0.58–0.90	0.004	0.87	0.67–1.13	0.298
Tumour stage (reference Stage IV)						
Stage III	1.20	0.94–1.52	0.141	1.49	1.15–1.92	0.002
Stage II	0.69	0.49–0.96	0.030	0.71	0.49–1.03	0.075
Stage I	0.49	0.28–0.85	0.011	0.55	0.31–0.99	0.046
Unknown/missing	1.28	0.99–1.65	0.064	1.39	1.06–1.81	0.017
KRAS status (reference wild type)						
KRAS mutated	1.29	0.95–1.74	0.104	1.32	0.96–1.80	0.083
KRAS unknown/missing	1.58	1.28–1.94	< 0.001	1.65	1.33–2.03	< 0.001

Table 3 Cutoff points and multivariate analysis with binary variables (learning sample, $n = 796$).

	Multivariate analysis		
Parameter	Hazard ratio	95% CI	*P*
Two or more metastatic sites at the start of first-line treatment	1.49	1.19–1.85	< 0.001
Tumour grading ≥ G3*	1.30	1.08–1.55	0.005
Residual tumour classification ≥ R1/unknown†	1.49	1.24–1.78	< 0.001
Lymph node ratio ≥ 0.4†	1.29	1.05–1.59	0.016
Tumour stage ≥ III/unknown*	1.44	1.07–1.93	0.016
KRAS mutated/unknown	1.51	1.23–1.85	< 0.001

*At primary diagnosis.
†Of primary tumour.

tumour stage ≥ III or unknown at primary diagnosis and *KRAS* status mutated or unknown (Table 3).

Based on these six prognostic factors a prognostic scoring system was developed. The existence of each of the risk factors was counted as one unit. These six factors constitute the mCCS. A score of 0–6 was calculated per patient and three risk groups for survival were identified: zero to two risk factors (low risk), three risk factors (intermediate risk) and four to six risk factors (high risk). For each of these risk groups, median OS was calculated for the learning sample (Fig. 1a). For patients with low risk, median OS was 31.2 months (95% CI 28.7–35.4), for patients with intermediate risk 20.9 months (95% CI 18.0–25.3) and for patients with high risk 14.6 months (95% CI 12.5–16.6).

The validity of the prognostic score was tested in the validation sample. Median OS for patients in the validation sample is shown in Fig. 1b. Median OS was 26.5 months for patients with low risk (95% CI 22.9–36.0), 22.2 months for patients with intermediate risk (95% CI 19.7–26.0) and 16.8 months for patients with high risk (95% CI 15.7–19.7). The differences were

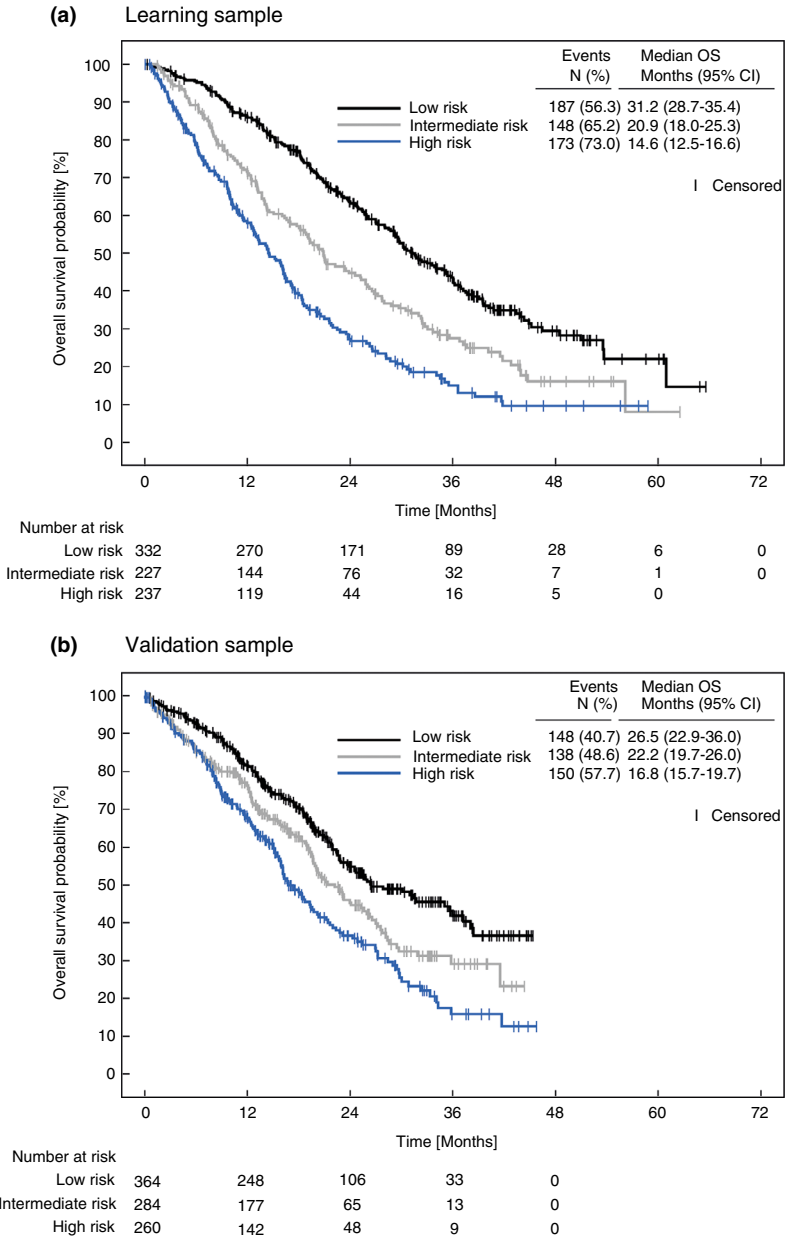

Figure 1 Overall survival according to risk group. Survival analysis according to risk group for (a) the learning sample and (b) the validation sample. Low risk, one or two risk factors; intermediate risk, three risk factors; high risk, four to six risk factors.

statistically significant ($P < 0.05$, adjusted for multiplicity). In the group with the good prognosis, median OS was more than one and a half times better than that observed in the poor prognosis group. In our sample, about 40% of patients were of low risk and 30% of patients were of either intermediate or high risk.

First-line treatment

The type of first-line chemotherapy was balanced between the three risk groups (Table 4). As described before, molecular targeted therapies were used more often in the validation sample. In both samples, patients in the low-risk group received anti-EGFR therapy more frequently than patients in the intermediate and high-risk groups (7.5/15.7% compared with 3.1/6.7% in the learning sample and 3.0/5.0% in the validation sample). A sensitivity analysis excluding these patients from the sample confirmed that the score separates patients into three distinct risk groups and indicated that treatment with EGFR inhibitor did not solely account for the good prognosis of patients in

Table 4 First-line treatment according to prognostic score.

	Learning sample			Validation sample		
Parameter	Low risk	Intermed. risk	High risk	Low risk	Intermed. risk	High risk
No. of patients (*n*, %)	332 (41.7)	227 (28.5)	237 (29.8)	364 (40.1)	284 (31.3)	260 (28.6)
Type of chemotherapy (*n*, %)						
FOLFIRI/CAPIRI	137 (41.3)	84 (37.0)	93 (39.2)	135 (37.1)	101 (35.6)	94 (36.2)
FOLFOX/CAPOX	140 (42.2)	92 (40.5)	101 (42.6)	142 (39.0)	114 (40.1)	121 (46.5)
FU mono/CAP mono	46 (13.9)	45 (19.8)	34 (14.3)	60 (16.5)	51 (18.0)	36 (13.8)
None	3 (0.9)	0 (0)	0 (0)	3 (0.8)	0 (0)	0 (0)
Other/unknown*	6 (1.8)	6 (2.6)	9 (3.8)	24 (6.6)	18 (6.3)	9 (3.5)
Type of molecular targeted therapy (*n*, %)						
Anti-VEGF	127 (38.3)	93 (41.0)	89 (37.6)	176 (48.4)	132 (46.5)	126 (48.5)
Anti-EGFR	25 (7.5)	7 (3.1)	7 (3.0)	57 (15.7)	19 (6.7)	13 (5.0)
None	180 (54.2)	127 (55.9)	141 (59.5)	116 (31.9)	120 (42.3)	114 (43.8)
Other/unknown*	0 (0)	0 (0)	0 (0)	15 (4.1)	13 (4.6)	7 (2.7)
Top three regimens (*n*, %)						
FOLFIRI + BEV	79 (23.8)	55 (24.2)	65 (27.4)	83 (22.8)	65 (22.9)	50 (19.2)
FOLFOX	90 (27.1)	58 (25.5)	68 (28.7)	56 (15.4)	48 (16.9)	52 (20.0)
FOLFIRI	47 (14.2)	22 (14.2)	25 (10.5)	17 (4.6)	20 (7.0)	27 (10.4)

BEV, bevacizumab; CAP, capecitabine; CAPIRI, capecitabine + irinotecan; CAPOX, capecitabine + oxaliplatin; EGFR, epidermal growth factor receptor; FU, fluorouracil; FOLFIRI, folinic acid + 5-fluorouracil + irinotecan; FOLFOX, folinic acid + 5-fluorouracil + oxaliplatin; VEGF, vascular endothelial growth factor.
*Including experimental first-line therapies that were not further specified to ensure trial confidentiality.

the low-risk group compared with the other groups (data not shown).

Adapted prognostic score

Since there has been an increase in *RAS* testing and *RAS*-targeted treatments in recent years, we tested whether the validated six-factor prognostic score still stratified patients if the *KRAS* status was excluded as a prognostic factor. Based on the five remaining prognostic factors (two or more metastatic sites, tumour grading ≥ G3 or unknown, residual tumour classification ≥ R1 or unknown, lymph node ratio ≥ 0.4 and tumour stage ≥ III or unknown), three risk groups could be defined: zero to one risk factor (low risk), two risk factors (intermediate risk), three to five risk factors (high risk). This adapted five-factor score was applied to a large cohort of patients with known *(K)RAS* mutation status recruited between September 2006 and April 2017. Looking at the survival of the patients with *(K)RAS* wild-type status according to these modified risk groups, median OS was still markedly different for patients with low (31.1 months, 95% CI 28.0–35.1), intermediate (26.5 months, 95% CI 23.6–29.5) and high risk (19.8 months, 95% CI 17.8–21.6; Fig. 2a). This modified score was also able to stratify the patients with *(K)RAS* mutations for median OS: low risk (27.0 months, 95% CI 25.4–30.3), intermediate risk (22.4 months, 95% CI 20.2–25.7) and high risk (16.7 months, 95% CI 15.0–18.6). A project to validate this five-factor score in an independent cohort is ongoing (VALIDATE, NCT03043950).

Discussion

The clinical management of mCRC patients remains a subject of debate, and better stratification of patients by prognostic risk is needed to improve clinical research and quality of care. We have developed and validated a prognostic mCCS for OS for patients with mCRC in a real-world setting, regardless of the first-line treatment. The mCCS comprises six tumour characteristics as independent prognostic factors for OS: number of metastatic sites, grading of primary tumour, residual tumour classification, lymph node ratio, tumour stage and *KRAS* mutation status. These prognostic factors are objective parameters that are routinely available at the start of treatment for mCRC and efficiently segregate the patients into three survival risk groups. The prognostic performance of the mCCS could be confirmed in a validation sample and also stratified patients with either *(K)RAS* wild-type or mutated tumours.

A limitation of this study could be the differences in the types of treatments received between patients in the

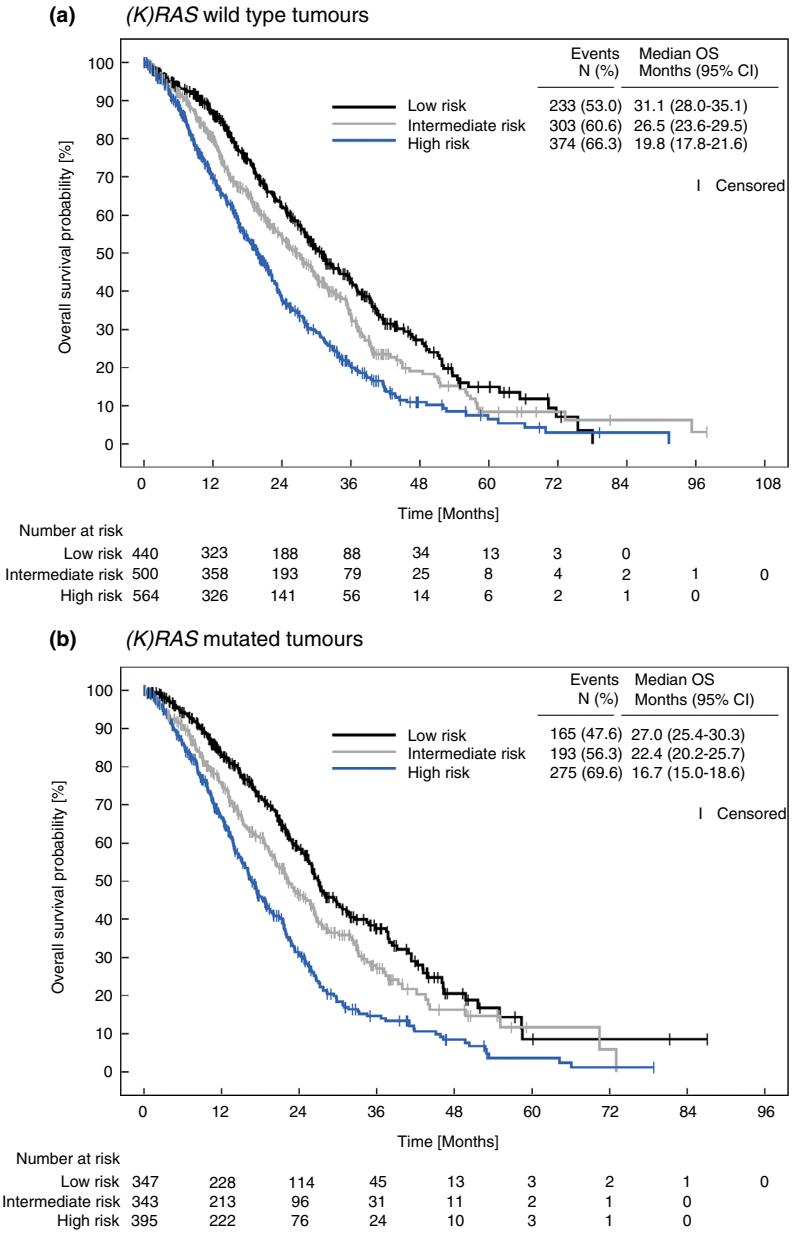

Figure 2 Overall survival according to risk group of the adapted prognostic score. Survival analysis according to risk group of the adapted prognostic score for (a) patients with *(K)RAS* wild-type status, recruited from 2006 to 2017 (n = 1504) and (b) patients with *(K)RAS* mutation status recruited from 2006 to 2017 (n = 1085). Low risk, zero or one risk factor; intermediate risk, two risk factors; high risk, three to five risk factors.

three allocated risk groups. However, patients received comparable treatment in terms of (a) use of oxaliplatin- *vs* irinotecan-based chemotherapy, (b) use of mono- *vs* combination therapy, (c) use of molecular targeted therapies, (d) the most frequently used regimens. A further limitation might be that the mCCS was kept as simple as possible in order to be easily applicable in routine care. We could have weighted the parameters differently in order to receive a more precise score but this would have meant that use of the mCCS would be more time-consuming.

At the time of recruitment for this prospective study, data on recently published prognostic markers like *NRAS* or *BRAF* mutation status, as well as sidedness, were not yet documented because they were not clinically relevant at the time. However, we do not believe that this limits the usability of the score. Firstly, we show that the *KRAS* mutation status can be omitted as

a prognostic factor and the score stratified patients with *RAS* wild-type or mutated tumours. Secondly, *BRAF* mutation status is rarely determined in routine practice and even more rarely are patients found to harbour *BRAF* mutations.

Prognostic scores are a valuable tool, combining as they do multiple prognostic factors. For patients with mCRC, the most frequently reported factors are performance status, laboratory parameters (such as lactate dehydrogenase or white blood cell count [3,10,14,15]) and tumour characteristics like the number of metastatic sites at the start of first-line treatment [14,15,20–24]. Besides the fact that the published scores are mostly based on data from clinical trials, and can therefore not be directly translated to routine care, multiple other factors have to be kept in mind: The use of laboratory parameters in prognostic models is common but complicated in routine practice by differing time points of testing, cut-off values, testing methods and reporting standards between laboratories. A major limitation of performance status as a prognostic factor is its reliance on subjective clinical assessment. Our mCCS is based on objective tumour characteristics usually available as standard information when the patient starts first-line treatment. Five of the factors reflect the status of the primary tumour even though about a third of the patients in our sample had been initially diagnosed with M0 stage disease and later relapsed and started first-line treatment; therefore characteristics of the primary tumour still determined prognosis after relapse in these patients.

In a recent publication, Desot *et al.* pointed out that a statistical difference between low- and intermediate-risk groups is sometimes lacking in several existing scores [23]. Our score separates three risk groups with a significant difference in OS between high- and intermediate-risk groups as well as between low- and intermediate-risk groups, and can identify patients with an intermediate risk.

During development and validation of the score, *KRAS* and later *RAS* mutation status became a key factor affecting the prognosis and the choice of first-line treatment in patients with mCRC. While patients with *(K)RAS* wild-type tumours generally have a better prognosis and can be treated with either EGFR or VEGF inhibitors, the prognosis of patients with *(K)RAS* mutant tumours is worse and the choice of treatment is more restricted. The question was raised whether our score would also separate three risk groups of patients if *(K)RAS* mutation status was excluded as a prognostic factor and whether it was also applicable to patients dependent on *(K)RAS* mutation status. We demonstrated that a five-factor score excluding the *(K)RAS* mutation status still clearly separates patients into three risk groups that differ significantly in OS.

Prognostic scores play an important role in reaching an optimized and individualized treatment and can help to set up appropriate treatment recommendations. It will be interesting to see a clinical trial stratifying the patients according to the mCCS and finding the optimal treatment recommendation for each risk group. Such risk-group-adapted treatment is already recommended in prostate cancer and is a big step towards personalized treatment [25,26].

Conclusion

We developed and validated a new prognostic score, the metastatic colorectal cancer score (mCCS), to predict survival in patients with mCRC based on tumour characteristics typically available in clinical practice at the start of first-line treatment. The mCCS is a powerful prognostic score that clearly defines three prognostic groups for survival at start of first-line therapy. For oncologists, the score represents a simple and easy-to-apply tool for routine clinical use. In the future, the mCCS may well help communicate prognosis, guide treatment decisions and stratify patients within clinical trials. Further studies on the clinical applicability of the mCCS as well as on the benefit of different treatment strategies for patients in the three risk groups will be of great interest.

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Conflicts of interest

The authors declare that they have no competing interests.

Ethics approval and consent to participate

The registry was reviewed by the ethics committee of the medical association (Landesärztekammer) Baden-Württemberg in Germany (ref. no. 078-06-f, 11 August 2006) and written informed consent was given by all participating patients.

References

1 Robert Koch-Institut, Gesellschaft der epidemiologischen Krebsregister in Deutschland e.V., editors. Krebs in Deutschland 2013/2014. Häufigkeiten und Trends [Internet]. 11. Ausgabe. Berlin: Robert Koch-Institut; 2017. Available from: https://www.krebsdaten.de/Krebs/DE/Content/Publikationen/Krebs_in_Deutschland/kid_2017/krebs_in_deutschland_2017.pdf?__blob=publicationFile

2 Fakih MG. Metastatic colorectal cancer: current state and future directions. *J Clin Oncol Off J Am Soc Clin Oncol* 2015; **33:** 1809–24.

3 Tournigand C, André T, Achille E *et al.* FOLFIRI followed by FOLFOX6 or the reverse sequence in advanced colorectal cancer: a randomized GERCOR study. *J Clin Oncol* 2004; **22:** 229–37.

4 Saltz LB, Clarke S, Díaz-Rubio E *et al.* Bevacizumab in combination with oxaliplatin-based chemotherapy as first-line therapy in metastatic colorectal cancer: a randomized phase III study. *J Clin Oncol* 2008; **26:** 2013–9.

5 Van Cutsem E, Köhne C-H, Láng I *et al.* Cetuximab plus irinotecan, fluorouracil, and leucovorin as first-line treatment for metastatic colorectal cancer: updated analysis of overall survival according to tumor KRAS and BRAF mutation status. *J Clin Oncol Off J Am Soc Clin Oncol* 2011; **29:** 2011–9.

6 Rougier P, Milan C, Lazorthes F *et al.* Prospective study of prognostic factors in patients with unresected hepatic metastases from colorectal cancer. Fondation Française de Cancérologie Digestive. *Br J Surg* 1995; **82:** 1397–400.

7 de Gramont A, Figer A, Seymour M *et al.* Leucovorin and fluorouracil with or without oxaliplatin as first-line treatment in advanced colorectal cancer. *J Clin Oncol Off J Am Soc Clin Oncol* 2000; **18:** 2938–47.

8 Saltz LB, Cox JV, Blanke C *et al.* Irinotecan plus fluorouracil and leucovorin for metastatic colorectal cancer. Irinotecan Study Group. *N Engl J Med* 2000; **13:** 905–14.

9 Van Cutsem E, Twelves C, Cassidy J *et al.* Oral capecitabine compared with intravenous fluorouracil plus leucovorin in patients with metastatic colorectal cancer: results of a large phase III study. *J Clin Oncol Off J Am Soc Clin Oncol* 2001; **19:** 4097–106.

10 Tournigand C, Cervantes A, Figer A *et al.* OPTIMOX1: a Randomized Study of FOLFOX4 or FOLFOX7 With Oxaliplatin in a Stop-and-Go Fashion in Advanced Colorectal Cancer—A GERCOR Study. *J Clin Oncol* 2006; **24:** 394–400.

11 Rosenberg R, Engel J, Bruns C *et al.* The prognostic value of lymph node ratio in a population-based collective of colorectal cancer patients. *Ann Surg* 2010; **251:** 1070–8.

12 Alonso-Orduna V, Marmol M, Escudero P *et al.* 599pa validation of current prognostic scores in metastatic colorectal cancer (mcrc) and a new prognostic score (a Gemcad Study). *Ann Oncol* 2014; **25(suppl 4):** iv204.

13 Diouf M, Chibaudel B, Filleron T *et al.* Could baseline health-related quality of life (QoL) predict overall survival in metastatic colorectal cancer? The results of the GERCOR OPTIMOX 1 study. *Health Qual Life Outcomes* 2014; **12:** 69.

14 Köhne CH, Cunningham D, Di Costanzo F *et al.* Clinical determinants of survival in patients with 5-fluorouracil-based treatment for metastatic colorectal cancer: results of a multivariate analysis of 3825 patients. *Ann Oncol* 2002; **13:** 308–17.

15 Chibaudel B, Bonnetain F, Tournigand C *et al.* Simplified prognostic model in patients with oxaliplatin-based or irinotecan-based first-line chemotherapy for metastatic colorectal cancer: a GERCOR study. *Oncologist* 2011; **16:** 1228–38.

16 Marschner N, Arnold D, Engel E *et al.* Oxaliplatin-based first-line chemotherapy is associated with improved overall survival compared to first-line treatment with irinotecan-based chemotherapy in patients with metastatic colorectal cancer - Results from a prospective cohort study. *Clin Epidemiol* 2015; **7:** 295–303.

17 Noura S, Ohue M, Kano S *et al.* Impact of metastatic lymph node ratio in node-positive colorectal cancer. *World J Gastrointest Surg* 2010; **2:** 70–7.

18 Kaplan EL, Meier P. Nonparametric estimation from incomplete observations. *Am Stat Assoc* 1958; **53:** 457–81.

19 Schemper M, Smith TL. A note on quantifying follow-up in studies of failure time. *Control Clin Trials* 1996; **17:** 343–6.

20 Kemeny N, Braun DW. Prognostic factors in advanced colorectal carcinoma. Importance of lactic dehydrogenase level, performance status, and white blood cell count. *Am J Med* 1983; **74:** 786–94.

21 Steinberg J, Erlichman C, Gadalla T, Fine S, Wong A. Prognostic factors in patients with metastatic colorectal cancer receiving 5-fluorouracil and folinic acid. *Eur J Cancer Oxf Engl 1990* 1992; **28A:** 1817–20.

22 Shitara K, Matsuo K, Yokota T *et al.* Prognostic factors for metastatic colorectal cancer patients undergoing irinotecan-based second-line chemotherapy. *Gastrointest Cancer Res GCR* 2011; **4:** 168–72.

23 Desot E, de Mestier L, Volet J *et al.* Prognostic factors in patients with non resectable metastatic colorectal cancer in the era of targeted biotherapies: relevance of Köhne's risk classification. *Dig Liver Dis* 2013; **45:** 330–5.

24 Chau I, Joulain F, Iqbal SU, Bridgewater J. A VELOUR post hoc subset analysis: prognostic groups and treatment outcomes in patients with metastatic colorectal cancer treated with aflibercept and FOLFIRI. *BMC Cancer* 2014; **14:** 605.
25 Serrano NA, Anscher MS. Favorable vs unfavorable intermediate-risk prostate cancer: a review of the new classification system and its impact on treatment recommendations. *Oncol Williston Park N* 2016; **30:** 229–36.
26 Zumsteg ZS, Spratt DE, Pei I et al. A new risk classification system for therapeutic decision making with intermediate-risk prostate cancer patients undergoing dose-escalated external-beam radiation therapy. *Eur Urol* 2013; **64:** 895–902.

