A prognostic score based on tumour characteristics to predict survival of patients with metastatic colorectal cancer: results from a prospective study.

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Background

Prognostic scores can be used to compare patient's characteristics between different clinical trials, to stratify patients and to assess whether patients with different risk profiles benefit from specific therapies. Several laboratory and clinical factors have been reported to predict survival of patients with metastatic colorectal cancer (mCRC, Köhne et al., 2002; Chibaudel et al., 2011). These results were based on data from clinical trials, which generally exclude specific groups of patients, e.g. those with comorbidities. Clinical tumour registries provide insight into real-life treatment of unselected patients. Here we present the development and validation of a prognostic score based on tumour characteristics of patients treated in routine practice.

Methods

The clinical Tumour Registry on Colorectal Cancer (TKK) prospectively collects data on patients with CRC treated by office-based medical oncologists in Germany. Patients receive standard treatments according to physician's choice. At time of enrolment, data on patients' demography, tumour characteristics, clinical parameters, comorbidities and previous treatments are documented. During the course of therapy, all systemic treatments as well as outcome parameters including date of progression(s) and death are documented. Patients are followed until death or for a maximum of five years.

Using the TKK, we split data from patients at the start of first-line treatment into a learning (796 patients; 2006-2008) and a validation sample (908 patients; 2009-2012). Overall survival (OS) was defined as the interval between first administration of first-line chemotherapy and death from any cause, and was estimated with the Kaplan-Meier method. Patients alive or lost to follow-up were censored at last contact or last documentation. Available baseline characteristics were analysed for interactions, their applicability as covariates and individual impact with regards to OS using univariate Cox regression models and descriptive statistics. Six prognostic factors for OS were identified in the learning sample based on multivariate Cox proportional hazards regressions. The six factors were dichotomised based on established criteria. A score was proposed stratifying patients into three prognostic groups. The predictive performance was validated in the independent validation sample.

Results

Learning sample

At the start of first-line treatment patients' median age was 67 years, 63% of patients were diagnosed with at least one comorbidity (Table 1). Median follow-up of all patients was 44 months and median OS was 23 months (64% events, Figure 1A).

Table 1 Patient characteristics

	Learning sample 2006-2008 (N = 796)	Validation sample 2009-2012 (N = 908)
Sex - male (%)	62.9	64.0
Median age at start of therapy (yrs)	67.4	67.0
Patients with comorbidities (%)	68.6	69.3
Type of cancer – colon (%)	61.6	61.7
Tumour characteristics at initial diagnosis		
Stage (%)		
I	3.8	3.1
II	8.8	7.7
III	15.3	14.1
IV	58.9	64.9
unknown	13.2	10.2
Tumour grading (%)		
G1	2.1	2.0
G2	59.8	54.6
G3	24.6	27.3
G4	0.4	0.3
Gx	13.1	14.2
Outcome of resection (%)		
R0	56.9	55.3
R1	6.4	6.6
R2	8.9	8.0
Rx	27.5	28.1
Lymph node ratio (median)	0.3	0.3
Tumour characteristics at start of first-line treatment		
KRAS status (%)		
Mutation	10.9	20.5
Wild type	24.9	34.4
Unknown	63.2	44.5
No. of metatastatic sites (mean±SD)	1.0 ±0.7	1.0 ±0.7

Table 2 Prognostic factors - multivariate Cox regression model

	Hazard Ratio	95% CI	p value
Initial diagnosis			
Tumour stage ≥ 3	1.44	1.07 - 1.93	0.02
Grading ≥ G3	1.30	1.08 - 1.55	0.005
Resection ≥ R1	1.49	1.24 - 1.78	<0.001
Lymph node ratio ≥ 0.4	1.29	1.05 - 1.59	0.02
Start of first-line treatment			
KRAS mutation status = mutated	1.51	1.23 - 1.85	<0.001
No. of metastatic sites ≥ 2	1.49	1.19 - 1.85	<0.001

Table 3 Prognostic risk groups - overall survival

	Learning sample			Validation sample		
	Low risk	Interm. risk	High risk	Low risk	Interm. risk	High risk
Patients	42 %	28 %	30 %	40 %	31 %	29 %
events	56 %	65 %	73 %	41 %	49 %	55 %
Overall survival (median, months)	31	21	14	26	22	17

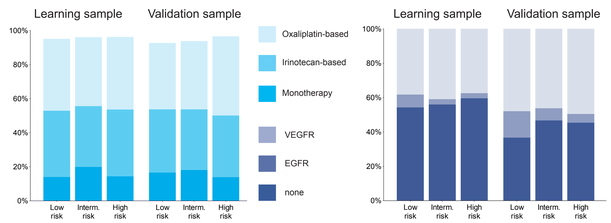

Figure 1 First-line treatment - chemotherapy backbone and targeted therapies

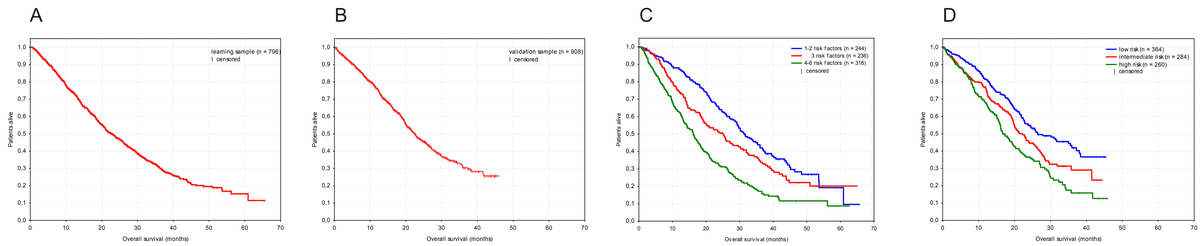

Figure 2 Overall survival - all patients and prognostic risk groups - learning and validation sample

KRAS mutation status (mutated) and number of metastatic sites at start of palliative treatment (≥ 2); tumour stage (≥ 3) and grading (≥ G3) at initial diagnosis; and resection (≥ R1) and lymph node ratio (≥ 0.4) of primary tumour were identified as prognostic risk factors (Table 2). Patients were stratified into three groups according to the proposed risk factors.

First-line treatments were comparable between the three groups (Figure 1). Overall 42% of patients received an oxaliplatin-based, 39% an irinotecan-based combination chemotherapy, and 16% of patients received a mono-chemotherapy as first-line treatment. 44% of patients received targeted therapies as first-line treatment.

Median OS was 31 months for patients with low risk (1-2 risk factors, 42 %), 21 months for patients with intermediate risk (3 risk factors, 28 % of pts, HR 1.6) and 14 months for patients with poor risk (4-6 risk factors, 30 % of pts, HR 2.5, Figure 2C, Table 3). The difference in OS was statistically significant ($p < .02$, adjusted for multiplicity).

Validation sample

Results were confirmed in the validation sample. Patient characteristics were similar to the learning sample, except for more patients being diagnosed with stage IV disease and being tested for KRAS mutation status (Table 1). First-line chemotherapy treatment was comparable to the learning sample (Figure 1), while targeted therapies were used more often in the validation than in the learning sample (58% and 44% respectively).

After a median follow-up of 25 months, median OS was 23 months (52% events, Figure 1B). Median survival for the low, intermediate and high risk group was 26 (n=364, 40%), 22 (n=284, 31%), and 17 months (n=260, 29%), respectively (Figure 2D, Table 3).

Conclusions

At the start of first-line treatment, patients with mCRC can be stratified into three risk groups based on six tumour characteristics, with patients with low risk having the longest OS. The three risk groups were confirmed in patients treated between 2009 and 2012 receiving mostly targeted therapies and combinational chemotherapies.

Four out of six risk factors represent the primary tumour indicating that characteristics of the primary tumour significantly affect prognosis, even in patients with metastatic disease.

This score could be used to stratify patients in RCTs, and to compare the risk profile of patients recruited in different clinical trials. Furthermore, it will be interesting to analyse the effectiveness of treatments as published in RCTs with regards to the three risk groups to assess which patients benefit from specific therapeutic strategies.

Collaborators

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