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Original Research

Predicting 10-year survival after resection of colorectal liver metastases; an international study including biomarkers and perioperative treatment

Florian E. Buisman [a], Daniele Giardiello [b,c], Nancy E. Kemeny [d], Ewout W. Steyerberg [b,e], Diederik J. Höppener [a], Boris Galjart [a], Pieter M.H. Nierop [a], Vinod P. Balachandran [f], Andrea Cercek [d], Jeffrey A. Drebin [f], Mithat Gönen [g], William R. Jarnagin [f], T.P. Kingham [f], Peter B. Vermeulen [h], Alice C. Wei [f], Dirk J. Grünhagen [a], Cornelis Verhoef [a], Micheal I. D'Angelica [f,1], Bas Groot Koerkamp [a,*,1]

[a] *Department of Surgery, Erasmus MC Cancer Institute, Erasmus University, Rotterdam, the Netherlands*
[b] *Department of Biomedical Data Sciences, Leiden University Medical Centre, Leiden, the Netherlands*
[c] *Department of Molecular Pathology, The Netherlands Cancer Institute, Amsterdam, the Netherlands*
[d] *Department Medical Oncology, Memorial Sloan Kettering Cancer Centre, New York, USA*
[e] *Department of Public Health, Erasmus MC, PO Box 20400, 3000 CA Rotterdam, the Netherlands*
[f] *Department of Surgery, Memorial Sloan Kettering Cancer Center, New York, USA*
[g] *Department of Epidemiology and Biostatistics, Memorial Sloan Kettering Cancer Center, New York, USA*
[h] *Translational Cancer Research Unit (GZA Hospitals and University of Antwerp), Antwerp, Belgium*

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KEYWORDS
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Abstract ***Background:*** The aim of this study was to develop a prediction model for 10-year overall survival (OS) after resection of colorectal liver metastasis (CRLM) based on patient, tumour and treatment characteristics.
Methods: Consecutive patients after complete resection of CRLM were included from two centres (1992–2019). A prediction model providing 10-year OS probabilities was developed using Cox regression analysis, including KRAS, BRAF and histopathological growth patterns. Discrimination and calibration were assessed using cross-validation. A web-based calculator was built to predict individual 10-year OS probabilities.
Results: A total of 4112 patients were included. The estimated 10-year OS was 30% (95% CI 29

* *Corresponding author*: Department of Surgery Erasmus MC Cancer Institute, r. Molewaterplein 40, 3015 GD Rotterdam, the Netherlands. Fax: +31 10 7032396.
E-mail address: b.grootkoerkamp@erasmusmc.nl (B.G. Koerkamp).
[1] Shared senior authors.

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–32). Fifteen patient, tumour and treatment characteristics were independent prognostic factors for 10-year OS; age, gender, location and nodal status of the primary tumour, disease-free interval, number and diameter of CRLM, preoperative CEA, resection margin, extrahepatic disease, KRAS and BRAF mutation status, histopathological growth patterns, perioperative systemic chemotherapy and hepatic arterial infusion pump chemotherapy. The discrimination at 10-years was 0.73 for both centres. A simplified risk score identified four risk groups with a 10-year OS of 57%, 38%, 24%, and 12%.

Conclusions: Ten-year OS after resection of CRLM is best predicted with a model including 15 patient, tumour, and treatment characteristics. The web-based calculator can be used to inform patients. This model serves as a benchmark to determine the prognostic value of novel biomarkers.

1. Introduction

Survival beyond 10-years after resection of colorectal liver metastases (CRLM) reflects cure in most (98%) patients [1,2]. While most recurrences occur within the first two years after resection, patients continue to be at risk for recurrence in subsequent years [1]. Five-year overall survival (OS) is typically reported in randomised controlled trials (RCTs) but does not reflect cure. Most studies reported a 5-year survival of roughly 50% and a 10-year survival of 25% after resection of CRLM. Ten-year estimates, however, vary across a wide range due to small sample size and limited follow-up of most studies [2–7].

Known unfavourable prognostic factors associated with 10-year survival include node-positive primary colorectal cancer (CRC), right-sided CRC, synchronous presentation, multiple metastases, CRLM large in size, high serum carcinoembryonic antigen (CEA) levels, presence of extrahepatic disease and positive resection margins. However, no single unfavourable factor precludes 10-year OS [1,2]. Biomarkers such as KRAS, BRAF and histological growth pattern (HGP) further improve prognostication after resection of CRLM. These biomarkers have been included in models to predict 5-year OS but sample size and length of follow-up were insufficient for 10-year OS [8–10].

Several RCTs have investigated perioperative systemic chemotherapy and hepatic arterial infusion pump (HAIP) chemotherapy [11–16]. Although long-term survival outcomes of these treatments have been published [17,18], these treatment factors have yet to be incorporated in prediction models.

The aim of this study was to develop a prediction model for 10-years OS for individual patients with resected CRLM based on patient, tumour and treatment characteristics.

2. Materials and methods

This study was performed according to the TRIPOD guidelines [19].

2.1. Patients

Consecutive patients who underwent resection and/or ablation of CRLM between January 1992 and January 2019 from Memorial Sloan Kettering Cancer Center (MSKCC; New York, USA) and between January 2000 and January 2019 from Erasmus MC Cancer Institute (Rotterdam, the Netherlands) were included.

2.2. Perioperative management

Preoperative systemic chemotherapy was administered in patients with borderline resectable or unresectable CRLM for downstaging in both centres. Neoadjuvant systemic chemotherapy (i.e. for resectable CRLM) and adjuvant systemic and/or HAIP chemotherapy were administered at MSKCC at the discretion of the treating physicians [20–22].

2.3. Definitions

Histopathological growth patterns (HGPs) were assessed on haematoxylin and eosin slides of resection specimens [23]. Two clinically relevant phenotypes are recognised; a desmoplastic and a non-desmoplastic type. CRLM displaying any replacement or pushing HGP were considered non-desmoplastic [9]. The definitions of all prognostic factors have been published previously [24].

2.4. Statistical analysis

The primary end-point in the analyses was OS, which was calculated from the time of resection to the time of death or the last follow-up. The median follow-up was calculated using the reversed Kaplan–Meier method. Continuous factors were compared using the Mann–Whitney U test and categorical factors using the Chi-square test. Missing data were multiply imputed by chained equations to avoid loss of information due to case-wise deletion [25]. Multivariable Cox proportional hazards regression analyses were performed, including predictors that were known to be associated with

OS [26]. Three-knot restricted cubic splines were used to assess linearity of continuous factors [27].

The model discrimination was evaluated by the time-dependent area under the receiver operating characteristic curve (AUC). The AUC was based on weighting by the inverse probability of censoring at 10-years [28]. Discrimination was evaluated with a leave-one-study-out cross-validation. That is, in each validation step, one centre is used to develop the model while the other is used as a validation set to provide the performance of the models in the two centres, although both centres were used to estimate the absolute risk [29]. The external validity was assessed according to the AUCs of both centres. Calibration was assessed visually by plotting the predicted probability against the actual observed frequency of predicted outcomes at 10 years [30]. The discriminative power of the model was compared with the clinical risk score (CRS) and the GAME score using the likelihood ratio test [8,31].

A separate multivariable model with dichotomised factors was used to develop a simplified risk score. Backward selection with the stepwise elimination of factors with a p-value >0.20 was performed. Points for the score were determined by multiplying each regression coefficient by 5 rounded to integers [32]. Next, four risk groups were proposed based on observed 10-year OS probabilities.

A p-value of <0.05 was considered as statistically significant. Analyses were performed in Rstudio (version 1.0.153, Boston, MA). The protocol of this study was approved by the Institutional Review Board of MSKCC (IRB number 16–533) and Erasmus MC (MEC-2020-0294).

3. Results

A total of 4539 patients underwent curative-intent surgery for CRLM at the two centres during the study period. Reasons for exclusion were incomplete liver resection (n = 251, 6%), residual extrahepatic disease (n = 124, 3%) and no colorectal resection (n = 52, 1%). The final group included 4112 patients; 3064 patients (75%) from MSKCC (period 1992–2019) and 1048 patients (25%) from Erasmus MC (period 2000–2019).

3.1. Patient characteristics

The median age was 61 years (Interquartile range (IQR) 52–69 years, Table 1). The majority of patients (n = 3366, 82%) had a resection since 2000. Extrahepatic disease was resected or ablated before or at the time of resection of CRLM in 468 patients (11%). KRAS mutational status was available in 1567 patients (38%) and mutated in 639 patients (41%). BRAF mutational status was available in 1358 patients (33%) and mutated in 55 patients (4%). HGP were assessed in 3136 patients (76%), and a desmoplastic HGP was found in 470 patients (22%). Perioperative systemic chemotherapy was administered in 3042 patients (74%); additional HAIP chemotherapy was administered in 1061 patients (26%). During follow-up, 2372 patients died. The median follow-up for survivors was 99 months (IQR 53–160 months).

3.2. 10-year OS for patient, tumour and treatment characteristics

Estimated median OS for the whole cohort was 59 months (95% CI 57–62 months) with an estimated 5-year OS of 49% (95% CI 48–51) and a 10-year OS of 30% (95% CI 29–32%). Poor prognostic factors associated with a 10-year OS probability below 20% were extrahepatic disease before or at the time of CRLM resection (14%, 95% CI 11–19%), 10 or more CRLM (14%, 95% CI 8–26%), a CEA level of more than 200 μg/L (19%, 95% CI 14–25%) and a positive resection margin (17%, 95% CI 13–21%, Table 1). Favourable prognostic factors associated with a 10-year OS rate above 40% were pT1 CRC (47%, 95% CI 36–61%) and desmoplastic HGP (41%, 95% CI 36–48%). Genomic alterations were associated with a 10-year OS of 27% (95% CI 30–39%) for KRAS mutants and 22% (95% CI 11–46%) for BRAF mutants (Table 1).

Perioperative oxaliplatin- or irinotecan-based systemic chemotherapy was associated with a 10-year OS probability of 34% (95% CI 32–36%), compared to 28% (95% CI 24–32%) for 5-FU only systemic chemotherapy and 26% (95% CI 22–30%) for no perioperative systemic chemotherapy ($p < 0.001$). Perioperative HAIP chemotherapy was associated with a 10-year OS probability of 40% (95% CI 36–43%) compared to 27% (95% CI 25–29%) without perioperative HAIP chemotherapy ($p < 0.001$).

3.3. Individual probability of 10-year OS

Fifteen independent prognostic factors for 10-year OS were included in the model; age, gender, location CRC, nodal status CRC, disease-free interval, number of CRLM, diameter of largest CRLM, preoperative CEA, resection margin, extrahepatic disease, KRAS mutation status, BRAF mutation status, histopathological growth pattern, perioperative systemic chemotherapy and perioperative HAIP chemotherapy (Table 2). The 10-year OS probability for individual patients can be estimated using the web-based calculator (www.oncocalculators.com) or using the equation in the Supplements. With the internal-external cross-validation, the AUC was 0.73 (95% CI: 0.68–0.78) for Erasmus MC and 0.73 (95% CI 0.70–0.75) for MSKCC.

Table 1
Patient characteristics and 10-year OS probabilities.

		Erasmus MC (%)	MSKCC (%)	Total (%)	Median OS			10-year OS	
					Months	95% CI	P-value	%	95% CI
Total number of patients		1048 (25)	3064 (75)	4112					
PATIENT CHARACTERISTICS									
Age	Median (IQR)	64 (58–71)	60 (50–68)	61 (52–69)			<0.001		
	=<60 years	349 (33)	1594 (52)	1943 (47)	65	60–69		35	33–38
	>60 years	699 (67)	1470 (48)	2169 (53)	56	53–59		26	24–29
Gender							0.19		
	Female	367 (35)	1323 (43)	1690 (41)	58	54–63		33	29–35
	Male	681 (65)	1741 (57)	2422 (59)	60	57–65		29	27–31
Year of surgery							<0.001		
	<2000	0	746 (24)	746 (18)	47	42–51		25	22–29
	≥2000	1048 (100)	2318 (76)	3366 (82)	63	60–67		32	30–34
DISEASE CHARACTERISTICS									
Location CRC							<0.001		
	Right-sided	192 (19)	836 (28)	1028 (26)	49	47–54		27	24–31
	Left-sided	454 (44)	1402 (47)	1856 (47)	65	61–70		33	30–35
	Rectum	379 (37)	725 (25)	1104 (28)	58	55–64		29	26–33
	Missing	23	101	124					
pT-stage							0.002		
	0[a]	26 (3)	13 (1)	39 (1)	94	63-NR		37	19–69
	1	14 (1)	85 (3)	99 (3)	105	59–155		47	36–61
	2	146 (14)	287 (10)	433 (11)	66	58–74		35	31–41
	3	731 (71)	1984 (72)	2715 (72)	58	56–63		30	28–32
	4	113 (11)	398 (14)	511 (13)	50	42–58		26	21–32
	Missing	18	297	315					
pT-stage							0.003		
	T 0-2	186 (18)	385 (14)	571 (15)	67	63–82		37	33–42
	T 3-4	844 (82)	2382 (86)	3226 (85)	57	55–61		30	28–32
	Missing	18	297	315					
Nodal status CRC							<0.001		
	N0	421 (41)	1126 (37)	1547 (39)	75	71–82		39	36–42
	N1	392 (38)	1168 (39)	1560 (38)	55	52–59		26	24–29
	N2	211 (21)	736 (24)	947 (23)	47	43–50		23	20–26
	Missing	22	43	65					
Nodal status CRC							<0.001		
	N0	420 (41)	1127 (37)	1547 (38)	75	71–82		39	36–42
	N+	609 (59)	1906 (63)	2515 (62)	52	50–55		25	23–27
	Missing	19	31	50					
Extrahepatic disease[b]							<0.001		
	No	940 (90)	2704 (88)	3644 (89)	63	60–67		32	31–34
	Yes	108 (10)	360 (12)	468 (11)	40	37–45		14	11–19
Disease-free interval							0.24		
	≤12 months	734 (70)	2085 (68)	2819 (69)	57	55–60		30	28–32
	>12 months	314 (30)	973 (32)	1287 (31)	64	59–70		31	28–34
	Missing	0	6	6					
Number CRLM							<0.001		
	1	452 (44)	1252 (41)	1704 (42)	71	66–76		35	32–38
	2	211 (20)	598 (20)	809 (20)	60	55–68		32	29–36
	3	118 (11)	391 (13)	509 (13)	55	49–58		29	24–34
	4	89 (9)	233 (8)	322 (8)	51	46–58		28	22–34
	5–9	139 (13)	451 (15)	590 (15)	47	42–52		23	19–28
	≥10	29 (3)	115 (4)	144 (4)	38	34–48		14	8–26
		10	24	34					
Size largest tumour							<0.001		
	≤5 cm	823 (83)	2285 (76)	3108 (78)	65	62–68		33	31–36
	>5 cm	163 (17)	729 (24)	892 (22)	43	39–48		22	19–26
	Missing	62	50	112					
Preoperative CEA							<0.001		
	≤200 μg/L	899 (92)	2497 (91)	3396 (92)	61	58–65		32	30–34
	>200 μg/L	80 (8)	234 (9)	314 (8)	48	41–51		19	14–25
	Missing	69	333	402					
Resection margin involved							<0.001		
	No	844 (85)	2686 (89)	3530 (88)	63	59–66		32	30–34

Table 1 (*continued*)

		Erasmus MC (%)	MSKCC (%)	Total (%)	Median OS			10-year OS	
					Months	95% CI	P-value	%	95% CI
	Yes	155 (15)	335 (11)	490 (12)	42	37–46		17	13–21
	Missing	49	43	92					
KRAS mutational status						72–86	<0.001		
	Wildtype	131 (61)	797 (59)	928 (59)	78	49–58		34	30–39
	Mutated	85 (39)	554 (41)	639 (41)	53			27	22–32
	Missing	832	1713	2545					
BRAF mutational status							<0.001		
	Wildtype	183 (97)	1120 (96)	1303 (96)	72	66–79		33	29–37
	Mutated	6 (3)	49 (4)	55 (4)	40	35–70		22	11–46
	Missing	859	1895	2754					
Histopathological growth pattern							<0.001		
	dHGP	216 (24)	254 (21)	470 (22)	86	75–104		41	36–48
	non-dHGP	696 (76)	970 (79)	1666 (78)	57	51–59		26	23–29
	Missing	136	1840	1976					
TREATMENT CHARACTERISTICS									
Perioperative systemic CTx							<0.001		
	No CTx	546 (53)	241 (9)	787 (21)	53	48–60		26	22–30
	5-FU only	25 (2)	549 (20)	574 (15)	53	50–59		28	24–32
	OXA- or IRINO	461 (45)	2007 (71)	2468 (64)	64	60–68		34	32–36
	Missing	16	267	283					
Perioperative HAIP CTx							<0.001		
	No	1037 (99)	2014 (66)	3051 (74)	55	53–58		27	25–29
	Yes	11 (1)	1050 (34)	1061 (26)	73	68–83		40	36–43

Abbreviations: CEA: carcinoembryonic antigen, CI: confidence interval, CRC: colorectal cancer, CRLM: colorectal liver metastases, CTx: chemotherapy, HAIP: hepatic arterial infusion pump chemotherapy, HGP: histopathological growth pattern. IRINO: irinotecan, IQR: interquartile range, OXA: oxaliplatin, NR: not reached, pT-stage: pathology tumour stage.

[a] Rectal cancer with complete response after neoadjuvant chemoradiotherapy.

[b] Resected prior or during CRLM resection.

Table 2
Multivariable Cox regression analysis.

Covariate	HR	95% CI	P-value
Age (10-year increase)	1.31	1.23–1.40	<0.001
Gender (male)	1.15	1.06–1.25	0.001
Location CRC			
Right-sided		REF	
Left-sided	0.90	0.81–0.99	0.04
Rectum	1.04	0.93–1.17	0.45
Node-positive CRC	1.45	1.33–1.59	<0.001
Disease-free interval	0.996	0.993–0.999	0.01
pT-stage (pT3-4)	1.03	0.91–1.15	0.65
Number CRLM	1.11	1.10–1.14	<0.001
Diameter CRLM (cm)	1.09	1.07–1.11	<0.001
Preoperative CEA level	1.003	1.001–1.005	0.004
Positive resection margin	1.40	1.24–1.58	<0.001
Extrahepatic disease	1.62	1.44–1.83	<0.001
Perioperative systemic CTx			
No CTx		REF	
5-FU only	0.83	0.73–0.95	0.005
Oxaliplatin or irinotecan	0.84	0.74–0.94	0.003
Perioperative HAIP CTx	0.73	0.65–0.81	<0.001
KRAS mutant	1.59	1.46–1.73	<0.001
BRAF mutant	1.69	1.42–2.01	<0.001
Non-dHGP	1.57	1.40–1.77	<0.001

Abbreviations: CEA: carcinoembryonic antigen, CI: confidence interval, CRC: colorectal cancer, CRLM: colorectal liver metastases, CTx: chemotherapy, HAIP: hepatic arterial infusion pump chemotherapy, HGP: histopathological growth pattern, pT-stage: pathology tumour stage.

Calibration showed slight overestimation of the model developed in Erasmus MC and validated in MSKCC. Calibration was good in the model developed in MSKCC and validated in Erasmus MC (Fig. 1). Interactions between centre and all candidate predictors were not statistically significant ($p > 0.05$).

This model outperformed the CRS by Fong (AUC 0.62, 95% CI 0.59–0.64, $p < 0.001$) and the GAME score by Margonis (AUC 0.66, 95% CI 0.64–0.69, $p < 0.001$).

3.4. Simplified risk score

A simplified risk score with 13 dichotomised prognostic factors is presented in Table 3. Disease-free interval and location of the primary CRC dropped out of the dichotomised model. The risk score is calculated by adding points for poor prognostic factors and subtracting points for treatment effects. The cumulative score ranges from −3 to 17. Four groups were identified; favourable (≤3 points), intermediate (4–5 points), unfavourable (6–8 points) and very unfavourable (≥9 points) with corresponding 10-year OS (95% CI) probabilities of 57% (51–60%; n = 692), 38% (34–42%, n = 993), 24% (23–29%, n = 1483) and 12% (10–15%, n = 944), respectively (Fig. 2).

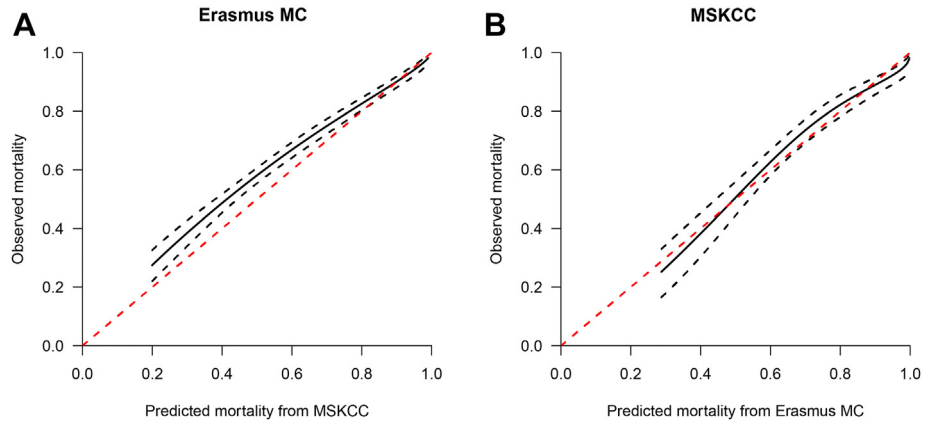

Fig. 1. **Calibration plots in the Erasmus and MSKCC cohort.** A) Full model developed in Erasmus MC and validated in MSKCC. B) Full model developed in MSKCC and validated in Erasmus MC. The black solid lines represent the predicted and observed mortality. The black dotted lines are the 95% prediction intervals. Perfect calibration would be present if the solid black line would overlap the red dotted line.

Table 3
Simplified risk scores for 10-year OS with dichotomised factors.

Prognostic factors	HR	95% CI	Points
Age > 60 years	1.31	1.20–1.42	**2**
Gender (male)	1.15	1.06–1.25	**1**
Node-positive CRC	1.47	1.35–1.60	**2**
More than one CRLM	1.37	1.26–1.50	**2**
Size CRLM > 5 cm	1.44	1.31–1.58	**2**
Preoperative CEA > 200 μg/L	1.13	0.99–1.30	**1**
Positive resection margin	1.48	1.32–1.66	**2**
Extrahepatic disease	1.57	1.39–1.77	**3**
KRAS mutant	1.58	1.45–1.72	**3**
BRAF mutant	1.74	1.46–2.07	**3**
Non-dHGP	1.63	1.45–1.83	**3**
Perioperative systemic CTx[a]	0.86	0.78–0.96	**−1**
Perioperative HAIP CTx	0.75	0.68–0.84	**−2**

Groups	**Sample size**	**10-year OS (%)**	**95% CI**	**Points**
Favourable	711	57	53–62	**≤ 3**
Intermediate	952	38	34–42	**4–5**
Unfavourable	1585	24	21–26	**6–8**
Very unfavourable	846	12	10–15	**≥ 9**

Abbreviations: CI: confidence interval, CRC: colorectal cancer, CRLM: colorectal liver metastases, CTx: chemotherapy, HAIP: hepatic arterial infusion pump chemotherapy, HR: hazard ratio, non-dHGP: non-desmoplastic histopathological growth pattern.

[a] Combining 5-FU-only and oxaliplatin- or irinotecan-based perioperative systemic chemotherapy.

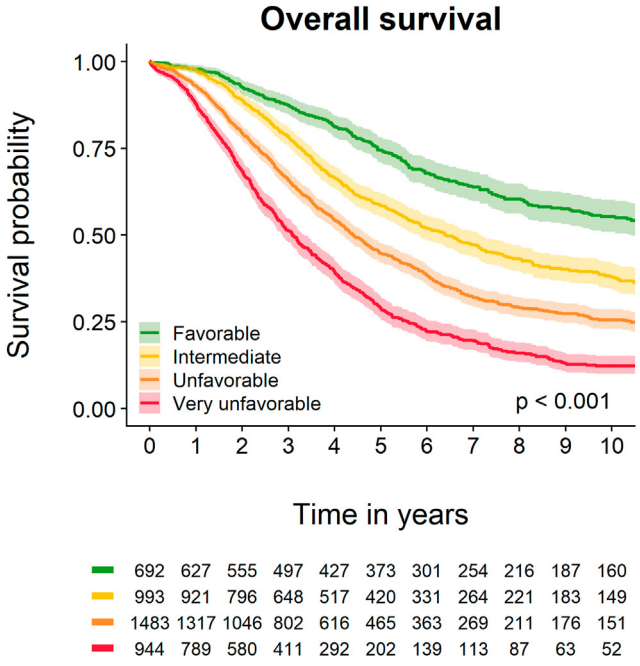

Fig. 2. Kaplan–Meier of 4 groups of the simplified risk score.

4. Discussion

We developed a web-based calculator to predict the individual patient's probability of 10-year OS after resection of CRLM using fifteen prognostic factors. The simplified risk scores distinguished four groups with a 10-year OS ranging from 12% to 57%. This is the first clinical prediction model for OS after resection of CRLM that incorporates BRAF and HGP. Moreover, systemic and HAIP chemotherapy were incorporated in addition to patient and tumour characteristics.

Several studies have reported a 10-year OS after resection of CRLM [2–7]. In a meta-analysis of eleven studies, together representing 2387 patients, the estimated 10-year OS ranged from 12% to 37% [3]. Two published prognostic models predicted 10-year OS, but considered only a small subset of all known prognostic factors [2,4]. Moreover, both models were developed using logistic regression analyses, which introduced bias by excluding patients lost to follow-up before 10-years.

Most published models predicted the recurrence of disease or short-term OS and had a small sample size below 1000 patients [8,31,33–38]. One of the first models was the CRS by Fong *et al.* [30]. The score is based on five prognostic factors; DFI, nodal status,

number of CRLM, size of CRLM and preoperative serum CEA level. The strength of the score is its simplicity with one point assigned to each factor. However, the score was developed to predict recurrence, included only 5 factors, and did not consider genomic alterations and treatment. These aspects may explain the poor performance of the CRS score in the external validations (range C-index 0.53–0.56) [39–41].

Several studies have demonstrated that KRAS mutation is an important prognostic factor for OS after resection of CRLM [8,42–45]. In the largest study with 2655 patients in the National Cancer Database, KRAS status was an independent prognostic factor for OS (adjusted HR 1.21 95% CI 1.04–1.39, p = 0.012) [45]. Two recent models have included KRAS mutation as a prognostic factor [8,37]. However, both the GAME model and the model of Goffredo *et al.* did not account for several known and readily available prognostic patient and tumour factors. The present study confirmed that KRAS is an independent poor prognostic factor for 10-year OS with an adjusted HR of 1.59 (95% CI 1.46–1.73). Moreover, the current model included BRAF mutation as prognostic factor with an adjusted HR of 1.69. The present model clearly outperforms both the CRS and GAME score in discriminative power.

A non-desmoplastic HGP was recently identified as a strong and independent poor prognostic factor [9]. Other studies demonstrated that a non-desmoplastic HGP is associated with positive resection margins and unsalvageable recurrences, both representing aggressive tumour biology [10,46,47]. The current study identified HGPs as an independent prognostic factor for 10-year OS with an adjusted HR of 1.6 for non-desmoplastic HGP.

The present model also contains systemic and HAIP chemotherapy. Two RCTs could not demonstrate superior OS of perioperative systemic chemotherapy for patients undergoing resection of CRLM [17,48]. These studies randomised about 300 patients and included mostly patients with a favourable risk profile (e.g. low number of CRLM). In the present study, perioperative oxaliplatin- or irinotecan-based systemic chemotherapy was an independent favourable factor for 10-year OS with an adjusted HR of 0.84. Perioperative HAIP chemotherapy was associated with a 10-year OS probability of 40%, which was similar to the 10-year OS of 41% in a RCT [18]. A 10-year OS of 61% (95% CI 51%–70%) was reported for patients treated with perioperative HAIP chemotherapy after 2003 in clinical trials [49]. Perioperative HAIP chemotherapy was also an independent prognostic factor for 10-year OS with an adjusted HR of 0.73 [15,18]. An ongoing phase III RCT investigates adjuvant HAIP chemotherapy in the current era [50].

A previous article investigating a 10-year OS after resection of CRLM concluded that none of the poor prognostic risk factors precluded cure [1,2]. In the present, much larger study, we identified additional independent poor prognostic factors for 10-year OS (i.e. KRAS and BRAF mutation and HGP). Again, none of these factors precluded 10-year OS, although several articles found a very poor prognosis in patients with BRAF mutation [51,52]. The probability of cure after resection of CRLM was 12% in the worst group of patients who had a combination of many poor prognostic factors (i.e. at least 9 points in the simplified risk score). This justifies curative-intent surgery for selected patients regardless of a combination of poor prognostic factors.

This study has several limitations. First, patient selection and treatment have changed during the long inclusion period required to estimate a 10-year OS. However, 82% of patients underwent a resection after 2000 and 15 prognostic factors including two treatment factors largely accounted for changes over time. Second, the two centres differed in perioperative treatment. In MSKCC, over 90% of patients received perioperative systemic chemotherapy. Dutch guidelines recommend systemic treatment for patients with (borderline) unresectable disease but not for resectable disease. Moreover, perioperative HAIP chemotherapy has been performed regularly at MSKCC, whereas at Erasmus MC only during the last year [20]. These differences between centres are in fact also strength since the dataset included patients with similar characteristics who did and did not receive perioperative systemic and/or HAIP chemotherapy. This allowed for assessment of treatment effects and improved generalisability (i.e. external validity) of the model, as reflected by good discrimination and calibration at cross-validation. Third, the model may appear applicable only in centres that offer HAIP chemotherapy. However, the model included more than 3000 patients who did not receive perioperative HAIP chemotherapy. The model and simplified score can be applied to patients who did and did not receive perioperative HAIP chemotherapy, as demonstrated by the good cross-validation of the MSK model in the Erasmus MC population. Lastly, genomic alterations in KRAS and BRAF, as well as HGP status were missing for many patients. Missing data were accounted for by multiple imputations, which may have led to bias but is methodologically superior to excluding patients with missing data [53].

In conclusion, this model with web-based calculator accurately predicts a 10-year OS after resection of CRLM based on 15 patient, tumour, genomic and treatment factors. This model may be used to inform patients and clinicians. Moreover, it serves as a benchmark for the evaluation of future prognostic biomarkers.

Author contributions

FEB, DJH, BG, PMHN, DJG, CV, MID, and BGK contributed to study design, data collection, data analysis, data interpretation, and writing of the report. DG, EWS, VPB, AC, JAD, MG, WRJ, TPK, PBV, and AW contributed to data collection, data analysis, data interpretation, and writing of the report.

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Conflict of interest statement

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: Dr Groot Koerkamp received pumps for intra-arterial chemotherapy for use in clinical trials from Tricumed.

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