Contour prognostic model for predicting survival after resection of colorectal liver metastases: development and multicentre validation study using largest diameter and number of metastases with RAS mutation status

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Abstract

Background: Most current models for predicting survival after resection of colorectal liver metastasis include largest diameter and number of colorectal liver metastases as dichotomous variables, resulting in underestimation of the extent of risk variation and substantial loss of statistical power. The aim of this study was to develop and validate a new prognostic model for patients undergoing liver resection including largest diameter and number of colorectal liver metastases as continuous variables.

Methods: A prognostic model was developed using data from patients who underwent liver resection for colorectal liver metastases at MD Anderson Cancer Center and had RAS mutational data. A Cox proportional hazards model analysis was used to develop a model based on largest colorectal liver metastasis diameter and number of metastases as continuous variables. The model results were shown using contour plots, and validated externally in an international multi-institutional cohort.

Results: A total of 810 patients met the inclusion criteria. Largest colorectal liver metastasis diameter (hazard ratio (HR) 1.11, 95 per cent confidence interval 1.06 to 1.16; $P < 0.001$), number of colorectal liver metastases (HR 1.06, 1.03 to 1.09; $P < 0.001$), and RAS mutation status (HR 1.76, 1.42 to 2.18; $P < 0.001$) were significantly associated with overall survival, together with age, primary lymph node metastasis, and prehepatectomy chemotherapy. The model performed well in the external validation cohort, with predicted overall survival values almost lying within 10 per cent of observed values. Wild-type RAS was associated with better overall survival than RAS mutation even when liver resection was performed for larger and/or multiple colorectal liver metastases.

Conclusion: The contour prognostic model, based on diameter and number of lesions considered as continuous variables along with RAS mutation, predicts overall survival after resection of colorectal liver metastasis.

Introduction

Liver resection remains the only potentially curative treatment option for patients with colorectal liver metastasis, and reported 5-year overall survival rates after resection are approximately 50 per cent[1,2]. To predict survival outcomes for patients with colorectal liver metastasis, various prognostic scoring systems based on clinicopathological factors have been proposed[3–8]. Most of these include largest diameter and number of colorectal liver metastases, factors that are used by clinicians (along with the location of colorectal liver metastasis) to determine oncological and technical resectability. Both parameters are often dichotomized around cut-off values. This approach is perceived to offer the advantage of simplifying statistical analysis, and the clinical

interpretation and presentation of results[9]. However, dichotomization also has disadvantages: underestimation of the extent of risk variation and substantial loss of statistical power compared with use of continuous variables[9,10].

Studies reported prognostic models for hepatocellular carcinoma, which were built on the largest diameter and number of tumors as continuous variables for paivertients undergoing l transplant[11,12] and undergoing liver resection, trans-arterial chemoembolization, and ablation[13]. The model for transplant was named the Metroticket model, because the 'cost' of travelling further on the contour plot (with larger and more lesions) was decreased post-transplant survival. The term Metroticket was used recently to describe a prognostic model developed for patients

undergoing resection of colorectal liver metastasis[14]. However, instead of predicting overall survival on the basis of largest diameter and number of colorectal liver metastases as independent continuous variables, largest diameter and number of colorectal liver metastases were combined into a Cartesian plane to produce a tumour burden score, representing the distance from the origin of the plane, which was then used to categorize patients into three groups. However, none of the existing prognostic models for patients undergoing resection of colorectal liver metastasis uses largest diameter and number as continuous independent variables. The diameter and number of colorectal liver metastases are always obtained by radiological cross-sectional imaging. When decision-making about the resectability of colorectal liver metastasis was based purely on radiological evidence, approximately 60 per cent of patients with colorectal liver metastasis deemed unresectable by non-specialists were considered to have potentially resectable disease by specialist liver surgeons[15]. A prognostic model that provides individualized survival probabilities after resection of colorectal liver metastasis based on diameter and number considered as continuous variables might narrow the gap between non-specialists and specialist liver surgeons in decision-making regarding the resectability of colorectal liver metastases.

To address these issues, the primary aim of this study was to develop and validate a new prognostic model predicting survival probability after resection of colorectal liver metastases, including largest diameter and number as continuous variables.

Methods

The study was conducted according to the principles outlined in the TRIPOD checklist[16] and the STROBE statement[17].

Study population

Patients who underwent initial liver resection of colorectal liver metastasis with curative intent at the University of Texas MD Anderson Cancer Center from January 1998 to March 2017 were identified from a prospectively compiled database. Patients with unknown *RAS* mutation status were excluded. Demographic and clinicopathological characteristics, and outcomes were collected. The study was approved by the institutional review board at MD Anderson Cancer Center.

Surgical management of colorectal liver metastasis

The institutional approach to surgical management of colorectal liver metastasis has been described previously[18]. Almost all patients have preoperative chemotherapy, followed by restaging. Colorectal liver metastases are deemed resectable when a hepatectomy can achieve a negative margin while preserving more than 30 per cent of the total estimated liver volume, sparing two contiguous hepatic segments, and maintaining vascular inflow, vascular outflow, and biliary drainage[19]. Second-line chemotherapy is considered for patients with disease progression or a suboptimal tumour response. For patients with synchronous colorectal liver metastasis and an intact primary tumour, the order of resection (primary tumour first, colorectal liver metastasis first, or simultaneous removal) is decided at a multidisciplinary conference. Patients with an anticipated insufficient future liver remnant are offered preoperative portal vein embolization and staged hepatectomy[20]. Postoperative chemotherapy is typically administered to complete 12 cycles, including the cycles of preoperative chemotherapy[21]. After resection, patients have a history

taken, physical examination, laboratory evaluation, and axial imaging every 3–4 months for the first 2 years, and every 4–6 months for the next 3 years[22].

Definitions

Largest diameter and number of colorectal liver metastases were assessed from radiological images taken just before surgery. Synchronous metastases were defined as metastases diagnosed within 12 months of the primary tumour diagnosis. A positive surgical margin was defined by the presence of tumour cells within 1 mm of the transection line. Tumour category was classified according to the American Joint Committee on Cancer Staging Manual, eighth edition[23]. Preoperative chemotherapy regimens were recorded and categorized according to whether they included an anti-vascular endothelial growth factor or anti-epidermal growth factor receptor (EGFR) agent.

Somatic gene mutation profiling

RAS status was determined from tumour tissue blocks or slides from the primary colorectal cancer or specimens of colorectal liver metastasis, as described previously[24], because the *RAS* mutation concordance rate between primary tumours and metastases is high (over 90 per cent)[25,26]. Routine PCR-based primer extension assay was performed to screen for mutations in *KRAS* codons 12 and 13 in all patients, and for mutations in *KRAS* codons 61 and 146 and *NRAS* codons 12, 13, and 61 in the majority of patients[27]. Single mutations in *KRAS* and *NRAS* were analysed together and reported as *RAS* mutations[28].

Prognostic model development

A Cox proportional hazards model analysis was used to derive a prognostic model for overall survival in patients undergoing resection of colorectal liver metastasis based on largest diameter and number of colorectal liver metastases as continuous variables. Cox model results were presented graphically as contour plots showing the joint effect of the model co-variables on survival probability.

External validation of the prognostic model

The prognostic model was validated in an external cohort of patients who underwent resection of colorectal liver metastasis at Catholic University of the Sacred Heart (Rome, Italy), University of Verona (Verona, Italy), or the University of Tokyo (Tokyo, Japan), and met the same inclusion criteria as patients in the development cohort.

Statistical analysis

Categorical variables are presented as numbers with percentages, and continuous variables as median (i.q.r.) unless indicated otherwise. Patients who were lost to follow-up or alive in March 2019 were censored at the date of last known follow-up. A Cox proportional hazards model initially included the following factors: age (continuous variable), sex, primary tumour location, tumour category, primary lymph node metastasis, prehepatectomy carcinoembryonic antigen level (continuous variable), timing of metastasis (synchronous *versus* metachronous), prehepatectomy chemotherapy, number of colorectal liver metastases (continuous variable), largest diameter of colorectal liver metastasis (continuous variable), surgical margin status (R1 *versus* R0), and *RAS* mutation status. A backward elimination process with a threshold P value of 0.050 was used to select variables for the final models. Hazard ratios and 95 per cent confidence intervals were

calculated for each factor. The proportional hazards assumption was tested by using Schoenfeld residuals[29].

To develop a prognostic model based on largest diameter and number of colorectal liver metastases as continuous variables, published methods were followed[12]. Largest diameter and number of colorectal liver metastases were modelled as continuous variables using three-knot restricted cubic splines[30], and diameter-by-number linear and non-linear interaction terms. Models were simplified by backward selection according to the Akaike information criterion[31]. Largest diameter of colorectal liver metastasis was plotted on the *x*-axis and number of colorectal liver metastases on the *y*-axis in a Cartesian plane[11,12]. The performance of the final fitted Cox model was assessed by calibration and discrimination. Calibration was performed by comparing the average overall survival probability predicted by the prognostic model with the average overall survival probability estimated by the Kaplan–Meier method after grouping predicted survival by quintile. Discrimination was evaluated using a Harrell's concordance statistic[32]. $P \leq 0.050$ was considered to indicate statistical significance. Statistical analysis was conducted with SAS® version 9.4 (SAS Institute, Cary, North Carolina, USA).

Results

Of 1131 patients who underwent resection of colorectal liver metastasis at MD Anderson Cancer Center during the study period and had known *RAS* mutation status, 810 met the inclusion criteria (*Fig. S1*). Demographic and clinicopathological characteristics are summarized in *Table 1*. The median largest diameter of colorectal liver metastasis was 2.3 (i.q.r. 1.5–3.7) cm. The median number of colorectal liver metastases was 2 (1–4). The rate of prehepatectomy chemotherapy was 88.4 per cent (716 patients). The median duration of follow-up was 5.5 (95 per cent c.i. 5.2 to 5.8) years based on the Kaplan–Meier method. During follow-up, 372 patients died (45.9 per cent) and 619 (76.4 per cent) experienced recurrence.

Predictors of overall survival after resection of colorectal liver metastasis

Multivariable Cox proportional hazards model analysis revealed that largest diameter of colorectal liver metastasis, number of colorectal liver metastases, *RAS* mutation status, age, primary lymph node metastasis, and prehepatectomy chemotherapy were significantly associated with overall survival (*Table 2*).

Prognostic model based on largest diameter and number of colorectal liver metastases, and *RAS* mutation status

On the basis of the results of the multivariable analysis, a prognostic model that incorporated largest diameter and number of colorectal liver metastases, and *RAS* mutation status as a prognostic factors was developed. Primary lymph node metastasis was not included because this information is not available when colorectal liver metastasis-first and simultaneous approaches are used in the treatment of synchronous colorectal liver metastasis. The use of prehepatectomy chemotherapy was also omitted from the model because this practice varies widely by institution.

A Cox regression model was evaluated for patients with mutant *RAS* and those with wild-type *RAS*. Results of models based on largest diameter and number of colorectal liver metastases are shown in *Fig. 1*. After application of a backward selection procedure, both models included a linear term for largest diameter,

Table 1 Demographic and clinicopathological characteristics of patients who underwent resection of colorectal liver metastais

	No. of patients* (*n* = 810)
Patient factors	
Age (years)[†]	55 (48–63)
Sex ratio (M : F)	477 : 333
ASA fitness grade $\geq$ III	680 (84.0)
Primary lesion factors	
Location	
Colon	594 (73.3)
Rectum	216 (26.7)
Tumour category $\geq$ T3[‡]	708 (87.4)
Lymph node metastasis[‡]	568 (71.9)
Liver metastasis factors	
Prehepatectomy CEA level (ng/ml)[†]	3.6 (1.8–11.9)
Synchronous metastasis	612 (75.6)
Prehepatectomy chemotherapy	716 (88.4)
> 6 cycles	239 (29.5)
Oxaliplatin-containing regimen	591 (73.0)
Irinotecan-containing regimen	166 (20.5)
With anti-VEGF agent	548 (67.7)
With anti-EGFR agent	75 (9.3)
Largest diameter of colorectal liver metastasis (cm)[†]	2.3 (1.5–3.7; 0.3–15.0)
No. of colorectal liver metastases[†]	2 (1–4; 1–30)
R1 surgical margin	138 (17.0)
Molecular biomarker	
RAS mutation	364 (44.9)

*With percentages in parentheses unless indicated otherwise; [†] values are median (i.q.r.; range). [‡] Data not available for tumour category in 14 patients and lymph node metastasis in 20 patients. CEA, carcinoembryonic antigen; VEGF, vascular endothelial growth factor; EGFR, epidermal growth factor receptor.

a cubic spline for number, and the linear-by-linear interaction diameter-by-number. *Fig. 1* shows 5-year overall survival estimates as a function of different values of largest diameter and number of colorectal liver metastases. The contour lines connect points of equal 5-year overall survival probability. The findings were also used to develop a tool based on Excel® (Microsoft, Redmond, Washington, USA) (called the 5-OS calculator for colorectal liver metastasis) in which one enters *RAS* mutation status, largest diameter of colorectal liver metastasis, and number of colorectal liver metastases, and the 5-year overall survival probability with its 95 per cent confidence interval is provided (*Appendix S1*). For example, if a patient has three colorectal liver metastases and the largest one measures 5 cm in diameter, the model estimates that the 5-year overall survival rate is 43.0 (95 per cent c.i. 34.1 to 51.6) per cent if the patient has mutant *RAS* disease, and 49.5 (40.7 to 57.6) per cent if the patient has wild-type *RAS* disease.

Fig. 2 shows the calibration of observed *versus* predicted survival probabilities. Observed survival lay within a 10 per cent margin of error around predicted survival in all instances. Harrell's concordance statistics was 0.629 (s.e. 0.021) in patients with *RAS* mutation and 0.625 (0.022) in those with wild-type *RAS*. On the other hand, Harrell's concordance statistics for the model including the other three risk factors (age, primary lymph node status, and prehepatectomy chemotherapy) was 0.644 (0.021) in patients with *RAS* mutation and 0.657 (0.021) in patients with wild-type *RAS*, which showed limited enhancement on model discrimination.

External validation of prognostic model

Of 1091 patients who underwent resection of colorectal liver metastasis at the three institutions during 2006–2018 and had

Table 2 Multivariable Cox proportional hazards model for overall survival after resection of colorectal liver metastasis in 790 patients

	No. of patients	No. of events	Multivariable analysis	
			Hazard ratio[*]	P
Largest diameter of colorectal liver metastasis (continuous variable)	–	–	1.11 (1.06, 1.16)	<0.001
No. of colorectal liver metastases (continuous variable)	–	–	1.06 (1.03, 1.09)	<0.001
RAS mutation status				
Mutant	354	179	1.76 (1.42, 2.18)	<0.001
Wild type	436	178	1.00 (reference)	
Age (per year, continuous variable)	–	–	1.02 (1.01, 1.03)	0.002
Primary lymph node metastasis				
Positive	568	268	1.58 (1.23, 2.03)	<0.001
Negative	222	89	1.00 (reference)	
Prehepatectomy chemotherapy				
Yes	697	318	1.47 (1.04, 2.08)	0.031
No	93	39	1.00 (reference)	

Values in parentheses are 95 per cent confidence intervals. Of 810 patients, 790 were included in the analysis because data were not available for lymph node metastasis in 20 patients. [*]Based on analysis of data from 787 patients with complete data on tumour category and primary lymph node metastasis, the six variables in the table were selected for the final model.
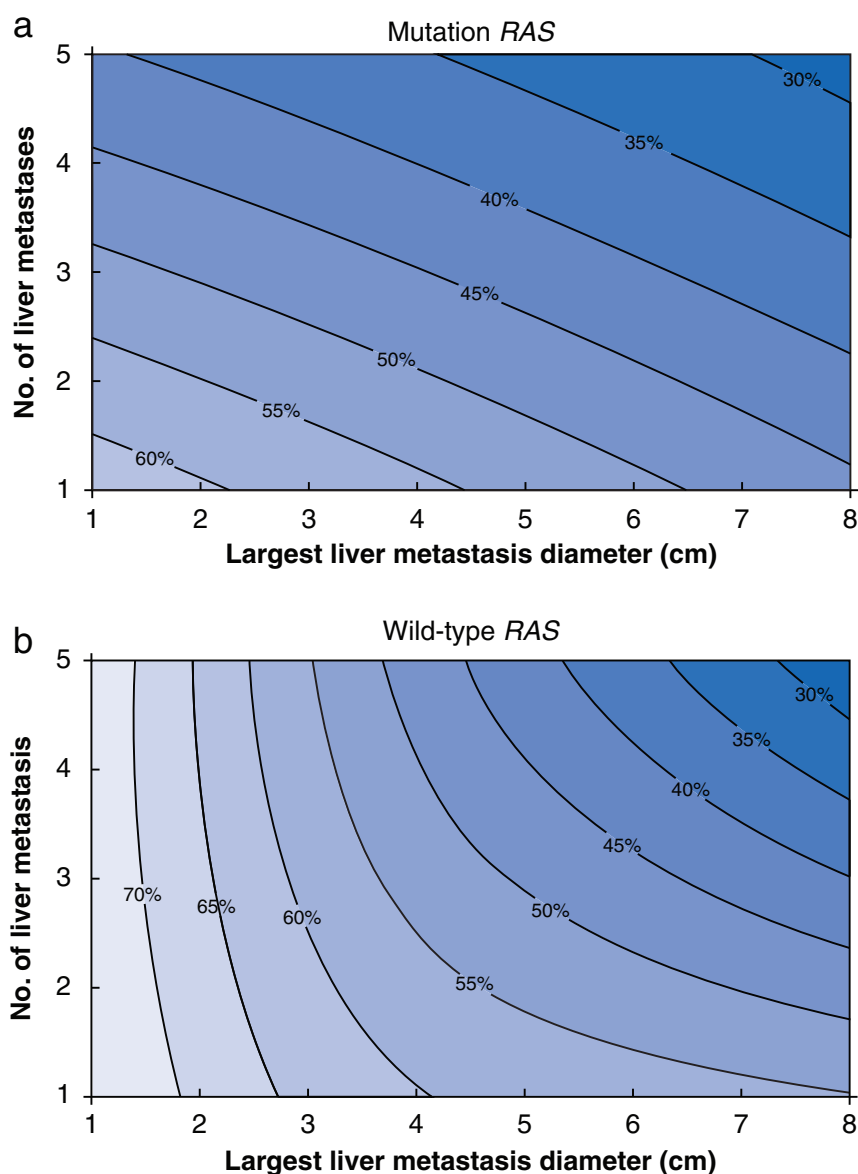

Fig. 1 Contour plot of 5-year overall survival probability according to largest diameter and number of colorectal liver metastases for patients with mutant RAS and wild-type RAS disease
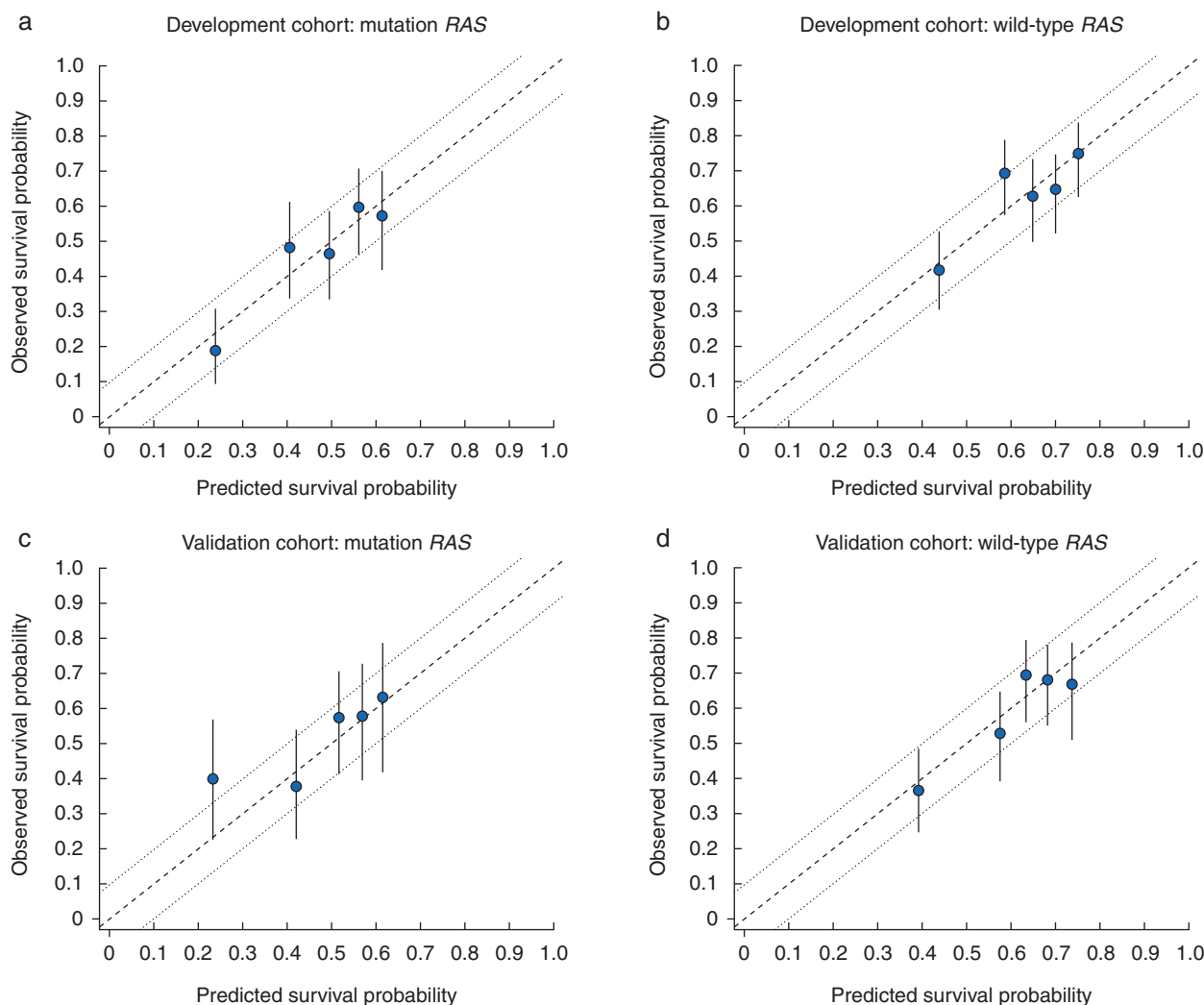
a Mutant RAS and **b** wild-type RAS.

Fig. 2 Calibration of prognostic model by mutant and wild-type RAS disease in development and external multi-international validation cohorts

Calibration plots for **a** mutant and **b** wild-type *RAS* disease in development cohort, and **c** mutant and **d** wild-type *RAS* disease in validation cohort. Observed overall survival probability was measured by Kaplan–Meier analysis; error bars represent 95 per cent c.i. The dashed line represents the ideal reference line where observed survival corresponds with predicted survival, and the dotted lines indicate the 10 per cent margin of error.

known *RAS* mutation status, 673 met the inclusion criteria (*Fig. S2*). Demographic and clinicopathological characteristics of these patients are summarized in *Table S1*. The rate of *RAS* mutation was 37.3 per cent (254 patients). The median largest diameter of colorectal liver metastasis was 2.6 (i.q.r. 1.6–4.1) cm. The median number of colorectal liver metastases was 2 (1–4). The rate of pre-hepatectomy chemotherapy was 63.3 per cent (422 patients) and differed widely by institution: 73.9 per cent (286 of 387) in Catholic University of the Sacred Heart, 66.4 per cent (79 of 119) in University of Verona, and 35.4 per cent (57 of 161) in the University of Tokyo. The characteristics of the external validation cohort were different from those of the development cohort, ensuring the efficacy of the validation. The median duration of follow-up was 4.7 (95 per cent c.i. 4.3 to 5.0) years based on the Kaplan–Meier method. During the follow-up period, 256 patients died (38.0 per cent) and 482 (71.6 per cent) experienced recurrence.

Similar to findings for the development cohort, a multivariable Cox proportional hazards model analysis showed that largest diameter of colorectal liver metastasis, number of colorectal liver metastases, RAS mutation status, age, primary lymph node metastasis, and prehepatectomy chemotherapy were significantly associated with overall survival in the validation cohort (*Table S2*).

Fig. 2 shows the calibration of observed *versus* predicted survival probabilities in the validation cohort. Observed survival almost lay within a 10 per cent margin of error around the predicted survival for both mutant *RAS* and wild-type *RAS* disease. Harrell's concordance statistic was 0.644 (s.e. 0.028) in patients with *RAS* mutation and 0.624 (0.026) in those with wild-type *RAS*.

Discussion

The present prognostic model was able to predict survival probabilities in patients undergoing resection of colorectal liver metastases based on largest diameter and number of colorectal liver metastases along with *RAS* mutation status. The model used diameter and number of colorectal liver metastases as continuous variables rather than dichotomous variables. *RAS* wild-type status was associated with better overall survival than mutant *RAS* status, even if liver resection was performed for larger and/or multiple colorectal liver metastases.

The most important finding of this study is that the impact of diameter and number of colorectal liver metastases on prognosis differed between patients with mutant *RAS* and those with wild-type *RAS* disease (Fig. 1). The performance of the model was good, as the observed survival corresponded closely with the predicted survival in the development cohort (Fig. 2), and mostly lay within a 10 per cent margin of error in an external validation cohort that had characteristics different from the development cohort (Fig. 2). The heterogeneity of prehepatectomy chemotherapy use in the external multi-international validation cohort (35.4–73.9 per cent) may confirm the appropriateness of the present model, irrespective of the effect of chemotherapy on diameter of colorectal liver metastases.

The present three-covariable model relies on variables that are widely and readily available, making it a useful tool that can be used by oncologists and surgeons in various clinical settings. An earlier study[15] showed that, when decision-making was based purely on radiological evidence, approximately 60 per cent of patients with colorectal liver metastasis deemed unresectable by non-specialists were considered to have potentially resectable disease by specialist liver surgeons. Individualized survival probabilities after resection of colorectal liver metastasis provided by the present model based on diameter and number of colorectal liver metastasis might narrow the gap between non-specialists and specialist liver surgeons in decision-making regarding resectability.

The Cox multivariable proportional hazards model suggested that age, primary lymph node metastasis, and prehepatectomy chemotherapy may improve prediction of survival compared with the three-co-variable model. However, barriers exist to the broad application of primary lymph node status and prehepatectomy chemotherapy. At MD Anderson Cancer Center, colorectal liver metastasis-first or simultaneous approaches were used in approximately half of patents with synchronous colorectal liver metastasis treated between 2005 and 2009[33]. For these patients, it is not known whether primary lymph node metastasis is present before resection of colorectal liver metastasis. With respect to prehepatectomy chemotherapy, it can be difficult to interpret the impact reliably because of the heterogeneity of the chemotherapy protocols employed and the lack of randomization. In addition, the improvement in discriminative ability for the six-co-variable model compared with the three-co-variable model is minimal. A model adding age alone (4-co-variable model) performs slightly better than the three-co-variable model in patients with *RAS* mutation (Harrell's concordance statistic 0.630, s.e. 0.021), but slightly worse than the three-co-variable model in patients with wild-type *RAS* (0.620, s.e. 0.022).

The present model performed better than Fong's model[4] (Harrell's concordance statistic 0.563), the tumour burden score model[13] (0.593), and the Genetic And Morphological Evaluation (GAME) model[34] (0.606).

A contour plot is a graphical depiction of a response variable as contours on a two-dimensional plane using two predictor variables plotted on the *x*- and *y*-axes. Contour plots are widely used in cartography, astronomy, meteorology, physics, and molecular biology[35,36]. An earlier study[11,12] originally reported the contour prognostic model used here, terming it the Metroticket system for predicting survival in patients undergoing liver transplant for hepatocellular carcinoma. A recently reported prognostic tool for patients undergoing resection of colorectal liver metastasis, referred to as a tumour burden score Metro-ticket model[1], is not a survival prediction model based on continuous variables of largest diameter and number of colorectal liver metastases, and is different from the previously reported model and also from the present model. The tumour burden score Metro-ticket model re-

categorized the combination of largest diameter and number of colorectal liver metastases into three categories (zone 1, zone 2, and zone 3) using the Pythagorean theorem. Patients in zone 2 of that model (the area represented by $3 \leq \sqrt{(\text{number of CLMs})^2 + (\text{largest CLM diameter})^2} < 9$, where CLM is colorectal liver metastasis) have wide-ranging 5-year overall survival probabilities based on the present contour prognostic model. Predicted 5-year overall survival rates for patients in zone 2 of the tumour burden score Metro-ticket model may range from 30 to 70 per cent for patients with wild-type *RAS* disease and from 30 to 50 per cent for those with mutant *RAS* disease. In contrast, the present contour prognostic model moves beyond previous systems for predicting prognosis after resection of colorectal liver metastasis, replacing the practice of categorizing patients into risk groups with an individualized risk prediction paradigm. The present contour prognostic model may help patients, oncologists, and surgeons make clinical decisions before and after resection of colorectal liver metastasis.

This study has several limitations. First, it was a retrospective analysis of patients undergoing resection of colorectal liver metastasis. Nonetheless, the performance of the contour prognostic model was validated externally in an international multi-institutional cohort, which differed in terms of demographic and clinical characteristics. Second, assessment of *RAS* mutation status may not be mandatory in some institutions. However, assessment of *RAS* mutation status for patients with colorectal cancer is strongly recommended when anti-EGFR therapy is being considered[37]. Moreover, as the impact of *RAS* mutation on both prognosis and treatment becomes clearer[27,38], it is likely that *RAS* testing will be performed more widely and routinely to guide medical therapy, especially for patients with metastases.

Supplementary material

Supplementary material is available at *BJS* online.

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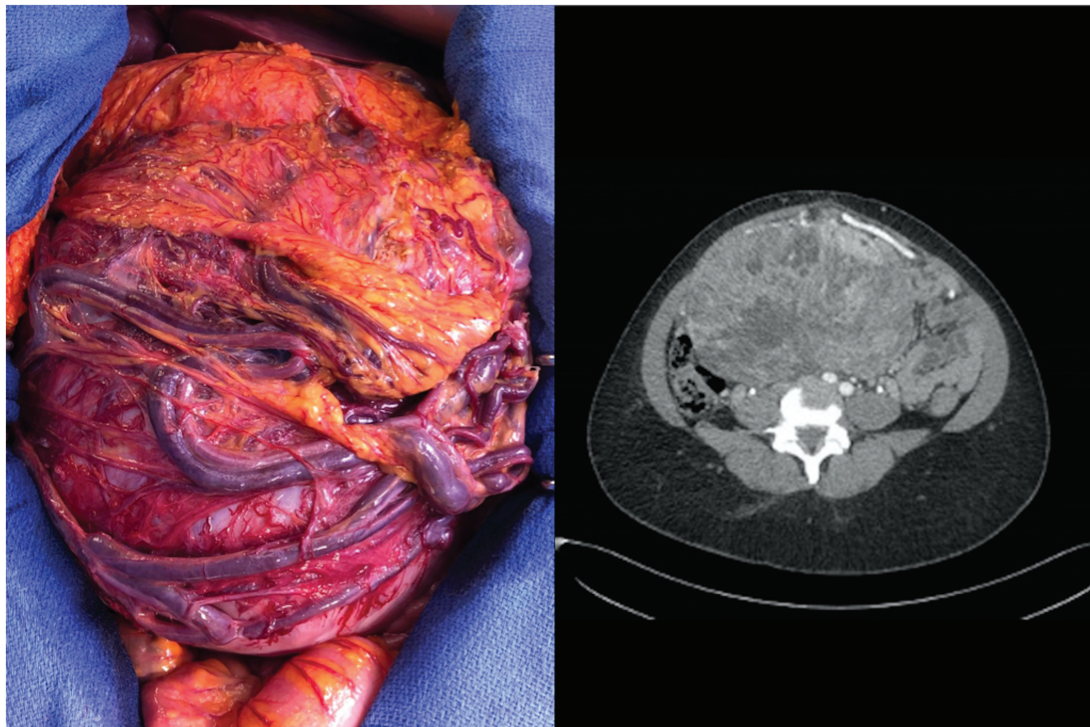
Snapshot Quiz

Question: A 34-year-old woman presented with a 20 cm intra-abdominal tumour with large draining veins and shunting surrounding the mass, detected by abdominal computed tomography (CT) scan. Six years before she underwent surgery for a pelvic tumour. What is the diagnosis?

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Answer: A solitary fibrous tumour (SFT) was suspected considering the large draining vessels, and the diagnosis was confirmed by preoperative core needle biopsy (CNB). Chest CT was negative. The multidisciplinary team decided to manage with preoperative chemotherapy (at first anthracycline, then pazopanib), resulting in stable disease. Intraoperative findings confirmed the CT images. The diameter of neovessels was up to 1.5 cm. The *en bloc* surgical resection was complete. SFT represents a mesenchymal fibroblastic tumour, potentially malignant, with typical CT findings (hypervascularized mass, prominent feeding vessels). However, in cases of intra-abdominal tumour (primary or after surgery), CNB is mandatory to confirm the diagnosis.