

Impact of primary cancer features on behaviour of colorectal liver metastases and survival after hepatectomy

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Background: Markers of tumour biology may be valuable prognostic indicators after hepatic resection of colorectal cancer liver metastases (CRLMs). Identification of the aggressiveness of these metastases might inform the appropriateness of hepatic surgery.

Methods: Patients undergoing liver resection for CRLMs between January 2001 and July 2013 in four tertiary hospitals were reviewed. A mathematical model to estimate CRLM doubling times was constructed for patients with metachronous metastases. Tumour doubling time was investigated in relation to the features of colorectal cancer, including *KRAS* status. The hazard rate for recurrence and death following hepatectomy was explored through the Kernel-smoothed estimator.

Results: Of 1063 patients undergoing liver resection for CRLMs, 361 with metachronous metastases undergoing single-stage hepatectomy were analysed. The mean doubling time in patients not receiving chemotherapy between surgery for colorectal cancer and CRLM was 71.4 days. Tumour doubling time was shorter in patients with more advanced primary tumour stages, with mutant *KRAS* and in those who did not receive chemotherapy. For fast-growing CRLMs (doubling time less than 48 days), the risk of recurrence was highest within the first postoperative year, and was about 7 per cent per month.

Conclusion: Primary features of colorectal cancer were linked to aggressiveness of CRLMs as measured by doubling time.

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Introduction

Colorectal cancer is one of the most common malignancies worldwide, accounting for at least one million new cancer cases each year¹. Spread to the liver occurs commonly, with roughly one-third of patients developing distant metastases^{2,3}. Although surgical therapy for patients with resectable colorectal liver metastases (CRLMs) offers a 20 per cent possibility of cure 6–7 years after resection, many will not achieve long-term benefit^{3,4}. As the indications for liver-directed therapies broaden, the ability to identify patients likely to benefit from intervention is important. Several morphological factors, such as number and size of metastases, carcinoembryonic antigen (CEA)

level and the interval between primary tumour and the recognition of hepatic metastases, have been shown to be useful in predicting outcome⁵.

The potential aggressiveness of colorectal cancer is readily evident when relapses occur early after resection of the primary tumour, when it recurs in the liver with large or bilobar metastases, and when there is little or no measurable response to chemotherapy. Indicators of tumour biology and how they might influence outcome are of increasing interest. Mutation of the *KRAS* gene may be an indicator of biological aggressiveness^{6–8}. The relationship between the growth rate of CRLMs and biological features of colorectal cancer may provide additional information related to outcome.

The aim of the present study was to estimate CRLM growth rate by assessing tumour doubling time in a consecutive series of patients with metachronous liver disease who had undergone liver resection. Although assessment of tumour growth rate requires at least two observations of volumes, it is difficult to justify this for every patient in a clinical setting. A mathematical approach was adopted to overcome this problem to validate and investigate the relationship of doubling time with clinical features and outcomes after liver resection.

Methods

The study was approved by the Institutional Review Boards and ethical committees of all participating centres.

Between January 2001 and July 2013, consecutive patients undergoing liver resection for CRLMs with no extrahepatic disease were identified from prospectively developed databases at four Italian tertiary referral hospitals for inclusion in the present analysis. Patients with incomplete data, who had undergone preoperative portal vein embolization, or in whom a two-stage hepatectomy had been adopted were excluded. Patients presenting with synchronous CRLMs were also excluded, retaining those with metachronous disease. In this group, those with no history of receiving chemotherapy in the interval between primary colorectal cancer surgery and CRLM resection were used for initial doubling time estimation.

Patients were deemed to have technically resectable disease when the metastases could be resected completely and the future remnant liver volume was considered adequate. Demographics, clinical data and CRLM features were collected for each patient. The resection margin was defined as ROPar when it was greater than 1 mm and as RIVasc when the CRLM was detached from a major vessel structure. Both were considered curative, as suggested recently^{9,10}. Otherwise, the resection margin was defined as R1Par. Primary tumour characteristics, time from resection of the primary tumour to liver resection and the adoption of chemotherapy (either adjuvant after primary colonic surgery or neoadjuvant before liver resection) were also detailed. When available, the mutational status of *KRAS*, determined on the primary colorectal cancer, was recorded. The chemotherapy strategy was prescribed by the oncologist in charge. Irinotecan, oxaliplatin, capecitabine and monoclonal antibodies were offered to patients after their approval by the Italian national healthcare system. Follow-up included clinical examination, estimation of serum CEA level, and CT or MRI at 3, 6 or every 12 months, as determined by the oncologist and clinical circumstances. Follow-up was carried out by assessing

the clinical records of the respective institutions or by telephone contact with the referring clinician or patient.

Growth evaluation

The solution proposed relied in the concept of the genesis of liver metastases from the deposition of undetected/microscopic colorectal cancer tumour spheroids that initiate CRLM macroscopic growth. On this basis, the following mathematical solution was adopted.

Patients with no history of chemotherapy in the interval between primary colorectal cancer surgery and CRLM resection were considered initially. The formula developed

Table 1 Characteristics of patients with metachronous colorectal liver metastases

	No. of patients (n = 361)
Age (years)*	68 (60–74)
Age ≥ 70 years	152 (42.1)
Sex ratio (M : F)	246 : 115
Primary tumour location	
Right colon	136 (37.7)
Left colon	137 (40.0)
Rectum	88 (24.4)
Primary tumour T category	
T1	12 (3.3)
T2	49 (13.6)
T3	253 (70.1)
T4	47 (13.0)
Primary tumour N category	
N0	156 (43.2)
N1	131 (36.3)
N2	74 (20.5)
AJCC tumour stage (7th edition)	
I	37 (10.2)
II	119 (33.0)
III	205 (56.8)
Primary tumour <i>KRAS</i> status	
Wild-type	63 (17.5)
Mutant	59 (16.3)
n.d.	239 (66.2)
Chemotherapy between surgery for CRC and CRLM	212 (58.7)
Disease-free interval ≥ 24 months	207 (57.3)
Largest CRLM size (cm)*	3.0 (2.0–4.5)
No. of CRLMs*	2 (1–3)
R0 resection†	309 (85.6)
Extension of hepatectomy	
Single or multiple wedges	160 (44.3)
Segmentectomy ± wedges	42 (11.6)
Bisegmentectomy ± wedges	58 (16.1)
Major hepatectomy ± wedges	101 (28.0)
Adjuvant chemotherapy after liver resection	226 of 329 (68.7)

Values in parentheses are percentages unless indicated otherwise; *values are median (i.q.r.). †Includes 17 patients with R1Vasc resection margin. n.d., Not determined; CRC, colorectal cancer; CRLM, colorectal liver metastasis.

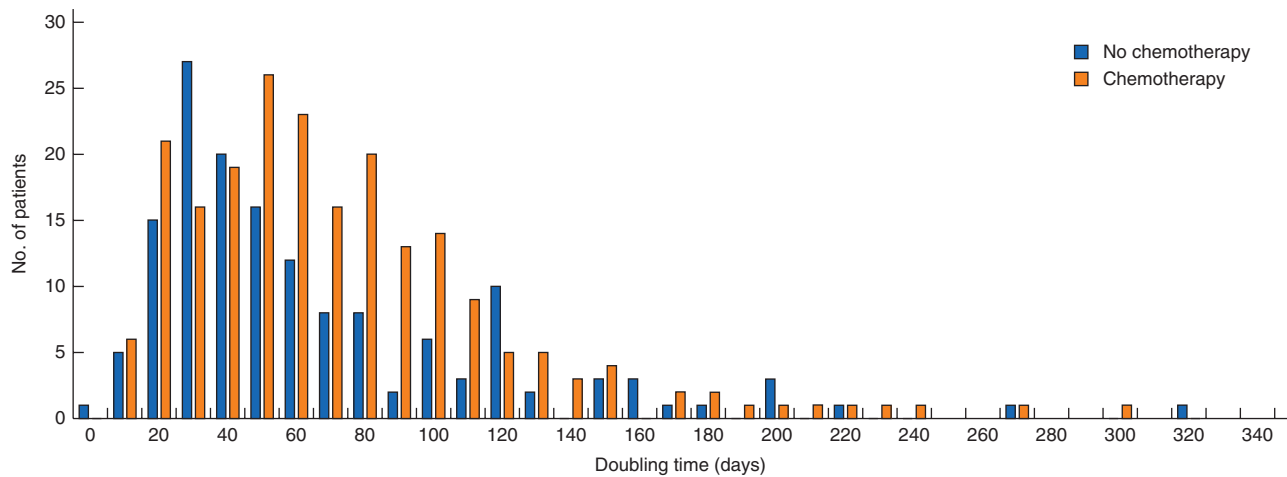


Fig. 1 Distribution of doubling time values estimated in patients without and with chemotherapy. The mean doubling time in patients with no chemotherapy between colorectal cancer surgery and metastasis resection was of 71.4 (95 per cent c.i. 62.8 to 79.9) days and that in patients receiving chemotherapy was 78.0 (71.4 to 84.8) days. Corresponding median values are reported in *Table 2*

Table 2 Univariable regression analysis of primary colorectal cancer features in relation to estimated doubling time

	Doubling time (days)*	Regression results	
		Coefficient†	P
Age (years)			
< 70	63.6 (44.3–95.4)	1.00 (reference)	
≥ 70	56.4 (31.1–93.3)	−0.09 (−0.22, 0.04)	0.184
Sex			
F	61.3 (37.6–94.1)	1.00 (reference)	
M	63.1 (41.3–94.7)	0.05 (−0.10, 0.19)	0.526
CRC location			
Right colon	57.0 (35.4–88.9)	1.00 (reference)	
Left colon	66.7 (39.8–93.4)	0.15 (0.00, 0.29)	0.044
Rectum	67.8 (40.4–97.1)	0.12 (−0.06, 0.30)	0.189
Primary CRC T category			
T1	125.9 (65.2–154.8)	1.00 (reference)	
T2	65.2 (45.6–103.6)	−0.54 (−0.85, −0.23)	0.001
T3	61.7 (38.3–94.0)	−0.61 (−0.89, −0.32)	0.001
T4	52.4 (31.9–72.0)	−0.79 (−1.11, −0.48)	0.001
Primary CRC nodal status			
N0	65.2 (44.2–103.3)	1.00 (reference)	
N1	64.3 (39.9–93.5)	−0.04 (−0.18, 0.10)	0.579
N2	52.8 (31.4–82.4)	−0.28 (−0.46, −0.09)	0.003
AJCC tumour stage (7th edition)			
I	72.5 (52.7–122.2)	1.00 (reference)	
II	61.3 (39.6–91.6)	−0.27 (−0.51, 0.04)	0.024
III	60.2 (37.2–95.6)	−0.34 (−0.54, −0.13)	0.001
KRAS primary CRC			
Wild-type	70.8 (40.2–122.7)	1.00 (reference)	
n.d.	63.0 (44.1–95.6)	−0.11 (−0.29, 0.08)	0.247
Mutant	49.5 (28.3–88.5)	−0.33 (−0.58, −0.14)	0.001
No. of CRLMs			
1	68.4 (44.2–103.6)	1.00 (reference)	
2–3	58.1 (39.2–91.8)	−0.05 (−0.19, 0.09)	0.448
> 3	52.4 (33.6–82.0)	−0.15 (−0.32, 0.02)	0.079
Chemotherapy between surgery for CRC and CRLM			
Yes	65.6 (45.0–100.9)	1.00 (reference)	
No	52.1 (35.9–94.7)	−0.14 (−0.25, −0.03)	0.013

Values in parentheses are 95 per cent confidence intervals unless indicated otherwise; *values are median (i.q.r.). †Coefficients relate to logistic transformation of doubling time. Time from primary colonic resection and colorectal liver metastasis (CRLM) size were not analysed as they are already included in the calculation of doubling time. n.d., Not determined; CRC, colorectal cancer.

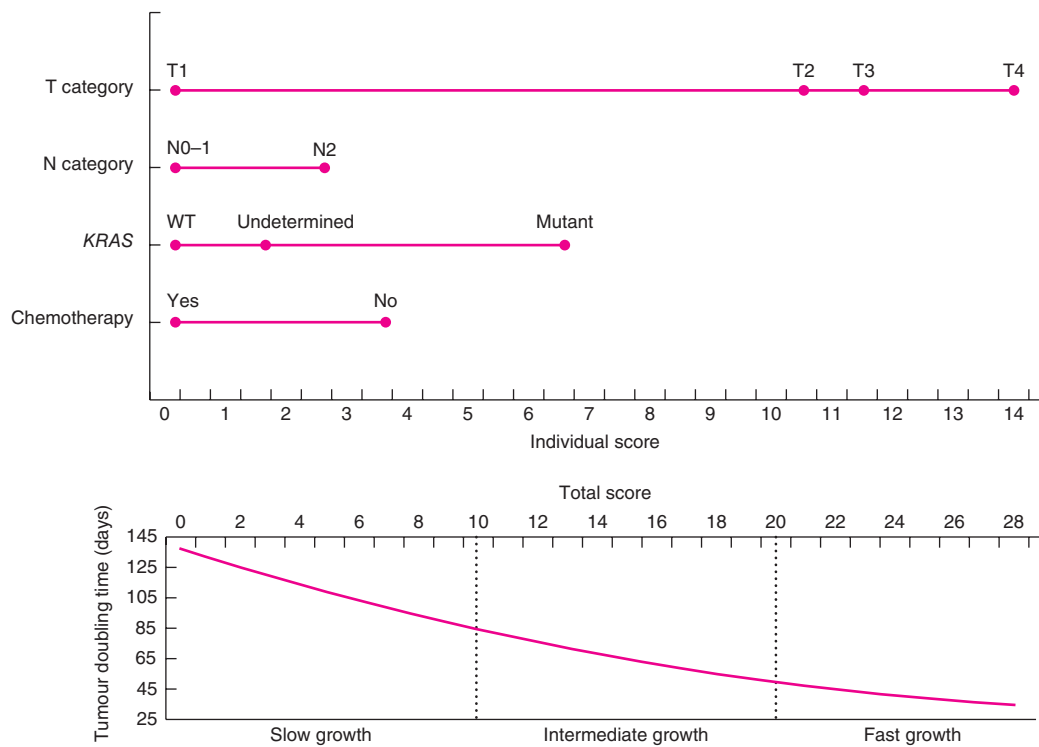


Fig. 2 Nomogram of the relationships between primary colorectal cancer features and estimated colorectal liver metastasis doubling times. Slow, intermediate and fast growth were based on the following tertiles for doubling time: fast, less than 48 days (120 patients); intermediate, 48–82 days (120 patients); slow, more than 82 days (121 patients). The score was obtained through the least common denominator of regression coefficients. Coefficients were as follows: T2, -0.53 (95 per cent c.i. -0.83 to -0.24 ; $P=0.001$); T3, -0.56 (-0.83 to -0.29 ; $P=0.001$); T4, -0.71 (-0.988 to -0.42 ; $P=0.001$); N2, -0.14 (-0.29 to -0.99 ; $P=0.042$); *KRAS* undetermined, -0.06 (-0.25 to 0.13 ; $P=0.519$); *KRAS* mutant, -0.32 (-0.57 to -0.07 ; $P=0.013$); no chemotherapy, -0.17 (-0.30 to -0.04 ; $P=0.010$). WT, wild-type

by Schwartz, doubling time $= t \times \ln 2 / (\ln(V_2) - \ln(V_1))$, was applied for estimation of doubling time, where t is the time interval between measurements, and V_2 and V_1 are the tumour volumes at the end and beginning of the time interval^{11,12}. V_2 was defined as the largest CRLM diameter in the resected specimen. V_1 was obtained by assuming that aggregates of colorectal cancer cells had already settled in the liver at the time of primary tumour surgery, but were as yet undetectable. A plausible range of CRLM sizes that would exist before macroscopic diagnosis at the time of colonic resection was assumed. Research suggested that V_1 could be calculated from a starting size of a tumour spheroid of 200 μm in radius, and a maximum diameter of 6 mm was taken on the basis that this represented the lower limit for CRLM identification by common imaging techniques^{13,14}.

Between the two V_1 extremes (from 200 μm to 6 mm), a triangular distribution of V_1 was assumed as the best approximation when the real distribution was unknown¹⁵. Ten different random V_1 values within the applied range

were simulated. The variable t was calculated as the time between primary colorectal cancer surgery, where undetectable tumour aggregates were assumed to be already present, and the time of liver resection, at which point the tumour size provided the V_2 estimate. Doubling time was calculated for each of the ten simulated values of V_1 , maintaining the value of t fixed as defined above. The average doubling time value over the ten simulations was used as the main outcome measure.

To provide plausibility and confirmation of the mathematical approach, obtained doubling time values were compared with available published data. A systematic search of PubMed and Institute for Scientific Information (ISI) Web of Knowledge databases was performed for articles published to 1 February 2018 relevant to the tumour doubling time assessment of CRLM. The PubMed database was searched using the following keywords: 'doubling time'[All Fields] OR 'growth rate'[All Fields] AND (colorectal[All Fields] AND ('liver'[MeSH Terms] AND/OR ('neoplasm metastasis'[MeSH Terms]

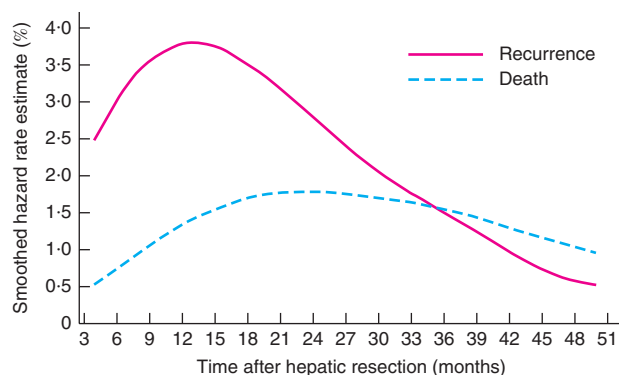
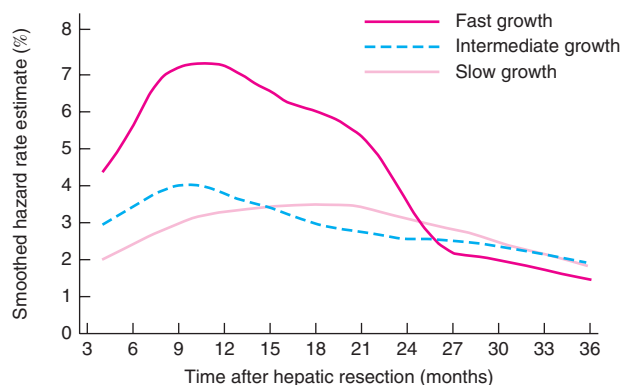


Fig. 3 Kernel-smoothed estimates of hazard rates over time for death and recurrence

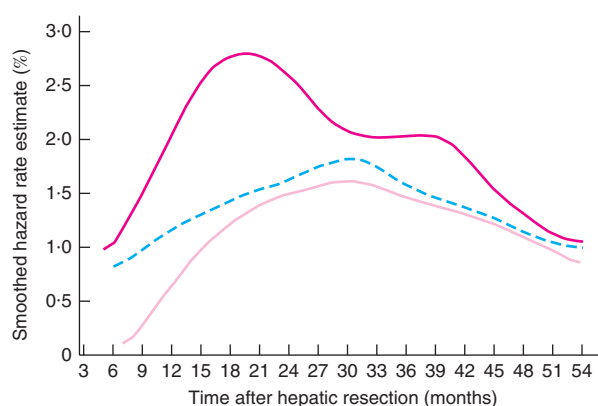
OR ('neoplasm'[All Fields] AND 'metastasis'[All Fields]) OR 'neoplasm metastasis'[All Fields] OR 'metastases'[All Fields])). ISI Web of Knowledge was searched using the following terms: ((TS='doubling time' OR TS='growth rate') AND (TS='colorectal' AND TS='metastases')) AND document types: (Article). The search was limited to human subjects and language limitations were imposed. The reference list of identified studies was also searched manually until no additional eligible trials could be identified. Additional articles were searched in Google Scholar without retrieving any additional available study.

Statistical analysis

The Mann–Whitney test was used to compare doubling time as the distribution was not normal. Natural logarithm conversion of doubling time was used in univariable and multivariable regression models. A nomogram to predict doubling time was generated using coefficients from the multivariable model through the least common denominator approach. Overall survival (OS) was calculated with the Kaplan–Meier method using the log rank test from the date of liver resection until the last follow-up visit (censored) or death. Recurrence-free survival (RFS) was calculated considering intrahepatic, extrahepatic or both types of metastasis as the event and censoring the last follow-up visit and deaths. The hazard rate (HR) of these survival measures was explored by applying the Kernel-smoothed estimator with Epanechnikov function^{16,17}. This analytical technique for lifetime data is flexible, model-free and data-driven, so that no shape assumption is imposed other than that of hazard function as a smooth function over time¹⁸. For OS and RFS over the entire study population, the Kernel-smoothed hazard estimator was initially unadjusted for possible confounding factors, whereas when analysing the relationship between doubling time and



a Recurrence



b Death

Fig. 4 Kernel-smoothed estimates of hazard rates for **a** recurrence and **b** death in relation to colorectal liver metastasis doubling time: fast growth, less than 48 days (120 patients); intermediate growth, 48–82 days (120 patients); slow growth, more than 82 days (121 patients)

RFS, the estimator was adjusted at the mean of other co-variables found able to modify prognosis¹⁷. Tumour doubling time data retrieved from literature were pooled using the random-effects model of DerSimonian and Laird. Statistical analyses were done using STATA[®] software (StataCorp, College Station, Texas, USA). $P < 0.050$ (two-tailed) was considered statistically significant.

Results

Of 1063 patients undergoing liver resection for CRLMs without extrahepatic disease who were identified originally, 97 were excluded because of incomplete data, preoperative portal vein embolization or a two-stage hepatectomy. A further 605 had synchronous CRLMs, leaving 361 patients who had undergone resection for metachronous disease including 149 with no history of chemotherapy in the

Table 3 Kernel-smoothed estimator of the monthly hazard rate of development of tumour recurrence after colorectal cancer liver metastasis resection in relation to characteristics at liver surgery and postoperative time interval

	Estimate of monthly hazard rate (%)*			
	0–6 months	7–12 months	13–24 months	25–36 months
CRLM doubling time				
Slow growth	2.1 (1.8–2.5)	3.0 (2.7–3.2)	3.3 (3.0–3.4)	2.2 (1.7–2.9)
Intermediate growth	3.1 (2.8–3.5)	3.8 (3.6–3.9)	2.8 (2.5–3.5)	2.2 (1.8–2.5)
Fast growth	4.9 (4.0–5.9)	7.0 (6.6–7.2)	5.4 (3.1–6.7)	1.9 (1.4–2.5)
No. of CRLMs				
1	3.3 (3.1–3.8)	4.5 (4.0–4.7)	3.5 (2.6–4.4)	2.3 (2.0–2.5)
2–3	3.2 (3.0–3.4)	3.9 (3.7–4.0)	3.2 (2.8–3.8)	1.8 (1.0–2.6)
>3	4.5 (4.3–4.7)	5.1 (4.8–5.3)	5.6 (5.0–5.9)	2.8 (0.8–4.7)
Resection margin				
R0Par/R1Vasc	3.2 (2.9–3.5)	4.1 (3.8–4.3)	3.4 (2.6–4.0)	1.8 (1.5–2.5)
R1Par	5.0 (4.6–5.4)	5.8 (5.6–6.0)	5.1 (4.5–5.9)	4.8 (4.2–5.3)
Chemotherapy after CRLM surgery				
Yes	2.8 (2.4–3.3)	4.3 (3.7–4.6)	3.7 (2.9–4.4)	1.9 (1.4–2.7)
No	5.8 (5.6–6.0)	5.4 (4.5–6.1)	3.4 (2.9–4.2)	2.4 (2.2–2.6)

*Values are mean (range). Each estimate was adjusted for the remaining variables. Slow, intermediate and fast growth of colorectal liver metastases (CRLMs) were based on the following identified tertiles for doubling time: fast, less than 48 days (120 patients); intermediate, 48–82 days (120 patients); slow, more than 82 days (121 patients). R0Par, resection margin greater than 1 mm; R1Vasc, CRLM detached from major vessel structure; R1Par, resection margin 1 mm or less.

interval between primary colorectal cancer surgery and CRLM resection. These patients were used for initial doubling time estimation, the remaining 212 patients being considered afterwards.

Baseline characteristics of the study population are shown in *Table 1*. The mean doubling time value in the 149 patients was 71.4 (95 per cent c.i. 62.8 to 79.9) days. Based on the literature search, 69 abstracts were screened. Of these, 61 abstracts were considered not pertinent and eight full texts were reviewed. Five studies^{19–23} were finally considered eligible for inclusion, reporting doubling time for 181 patients with CRLMs. The pooled mean doubling time was 73.7 (95 per cent c.i. 43.9 to 103.5) days. The distributions of doubling time values for patients without and with chemotherapy are depicted in *Fig. 1*.

The relationships between doubling time estimation and features of the primary tumour and CRLMs are reported in *Table 2*. In univariable analyses, doubling time was significantly shorter in patients with right-sided colorectal cancer, more advanced tumour stage, mutant *KRAS*, and in those who did not receive chemotherapy between primary colonic surgery and CRLM resection. Multivariable analysis confirmed stage, *KRAS* status and chemotherapy as independent predictors of doubling time (*Fig. 2*).

For the subsequent survival analyses, doubling times were divided into tertiles as follows: fast-growing CRLMs, doubling time less than 48 days (120 patients); intermediate-growing CRLMs, doubling time 48–82 days (120 patients); slow-growing CRLMs, doubling time more than 82 days (121 patients).

Survival analyses after resection of colorectal liver metastases

Within a median follow-up of 70.8 months after liver resection, 243 (67.3 per cent) of the 361 patients developed recurrence and 184 died (51.0 per cent). Of patients with recurrence, 151 had intrahepatic recurrences (97 confined to the liver, 54 both intrahepatic and extrahepatic). Median overall survival for the entire cohort was 49.1 months, and 1-, 3- and 5-year OS rates were 91.2, 58.8 and 45.0 per cent respectively. Median RFS was 17.2 months, and 1-, 3- and 5-year RFS rates were 62.8, 32.2 and 28.0 per cent respectively. RFS was significantly reduced by shorter doubling time ($P < 0.001$), higher number of CRLMs ($P = 0.002$), lack of posthepatectomy chemotherapy ($P = 0.002$) and positive resection margins ($P = 0.006$).

HRs over time for recurrence and death are plotted in *Fig. 3*. The HR for recurrence was greatest (approximately 3.8 per cent per month) between months 9 and 16 after surgery. The rate then started to decrease, becoming lower than the risk of death from the 36th month onwards. By contrast, the HR for death was greatest (about 1.8 per cent per month) between the 20th and 28th month after surgery, and subsequently decreased.

Adjusted results on HRs for recurrence by doubling time are depicted in *Fig. 4a*. Fast-growing tumours had the maximum risk of recurrence (approximately 7 per cent per month) between the ninth and 12th month after surgery. The risk of recurrence then slowly decreased until the 18th month, and then rapidly diminished. Intermediate-growing tumours showed a similar temporal

course, but with a monthly risk somewhat lower (about 4 per cent per month). In contrast, slow-growing tumours showed their maximum risk of recurrence (about 3.3 per cent per month) later in the postoperative period. After the second year from surgery onwards, the HR for recurrence was similar in these three groups.

The HR for death of fast-growing CRLMs was greatest (about 2.7 per cent per month) between the 16th and 22nd month after surgery, with another increase (around 2.0 per cent per month) between the 29th and 39th month. The HR for death then fell to the rates found for intermediate- and slow-growing tumours (*Fig. 4b*).

All adjusted HRs for recurrence in relation to features found during and after hepatectomy are reported in *Table 3*. The presence of more than three CRLMs resulted in a monthly HR greater than that of less advanced CRLMs in the first 2 years after surgery. Positive resection margins led to a consistently higher HR over time compared with the HR for negative resection margins. The positive impact of postoperative chemotherapy was confined to the first 6 months after operation.

Discussion

The development of CRLMs, recurrence after liver resection and life expectancy depend on the complex interaction between the primary colorectal cancer, treatments and patient response.

In this study a significant relationship between doubling time in the primary tumour and CRLM growth rate was observed. The fact that T status, N category and *KRAS* mutational status accounted for different CRLM doubling times relies on the 'seed and soil' concept in stochastic and deterministic ways^{24,25}. From a stochastic point of view, circulating tumour cells from the primary colorectal cancer are already present in the liver at the time of primary surgery, or might extravasate from the bloodstream at a second or different time point. In both cases they can either form macrometastases or remain dormant, often for a long period of time^{24,26–28}. The initial colorectal cancer stages may involve the dissemination of solitary and rare cell aggregates that cannot proceed to macroscopic tumour development, resulting in long doubling times (for example, T1 of 125.9 days). Conversely, more advanced colorectal cancer stages could determine the release of more tumour cell aggregates to seed the liver, with higher probabilities that one (or more) of them will grow into clinically detectable macrometastases, resulting in shorter doubling times (for example, T4 of 52.4 days).

The deterministic point of view is based on the fact that neoplasms contain genetically diverse tumour cell subpopulations (genetic heterogeneity), each with a different

metastatic potential. In the initial stages of colorectal cancer, genetic subpopulations with low metastatic potential may be less capable of progressing to macrometastases. On the other hand, advanced colorectal cancers may be more likely to give rise to macrometastases because further genetic changes have appeared. The present findings support this process. In fact, CRLMs from mutant *KRAS* tumours grew faster than those derived from wild-type colorectal cancers. The *KRAS* mutation has been associated with an increased rate of primary colorectal cancer vascular invasion and decreased expression of regulatory mechanisms, which result in faster proliferation, and an increased rate of haematogenous spread^{29–31}.

The complex interaction between tumour biology, treatments and patient responses after liver resection was evident in the variability of the monthly hazard of recurrence and death in different subgroups. Fast-growing tumours showed a peak in the HR for recurrence within the first year after surgery (up to 7.0 per cent). This suggests that aggressive colorectal cancers may have already seeded in the liver and other organs, and that their aggressiveness is maintained after hepatectomy³². This might account for high rates of early recurrence²⁵. This is supported by the observation that slow-growing CRLMs showed a peak HR late after surgery, usually at 1–2 years. Considering OS, the peak HR for death was advanced by about 1 year for fast-growing tumours with respect to the recurrence peak, and by about 2 years for more indolent tumours. After this time point, the recurrence HR for faster-growing tumours returned to a level similar (2.2 per cent) to that of less aggressive tumours (1.9 per cent), although the risk of death remained higher.

The ability to achieve an R0 resection clearly affected RFS. Almost all authors agree that R1 resection is associated with a higher local recurrence risk^{9,10,33,34}, but this cannot be the sole cause of intrahepatic recurrence. R1 resection may also indicate more diffuse intrahepatic disease, which in turn leads to a more demanding surgical procedure and a lower likelihood of obtaining an R0 resection³⁵. This latter contention is supported by the present results. If an R1 margin was simply due to surgical failure, the HR for recurrence should be high early after surgery and then decrease over time. Instead, it remained consistently above that for R0 margins, suggesting that an R1 margin reflects a more advanced tumour burden with higher metastatic potential over the entire postoperative time period.

The present study has limitations. First, only patients with metachronous disease were considered. Estimation of tumour doubling times in patients with synchronous metastases would provide a more comprehensive picture.

The second limitation relates to the reliability of the doubling time estimate. The literature measuring CRLM doubling time is more than 10 years old and, with modern treatments, comparability over such a long time interval may not be valid^{19–23}. Despite this, the present mathematical model has been built on a sound scientific rationale^{11–13}, and findings in the cohort not receiving chemotherapy after primary colorectal cancer resection were in keeping with observed doubling time values in earlier cohorts^{19–23}.

The present study has provided a comprehensive estimation of CRLM growth rates in patients with metachronous liver involvement. It would seem reasonable to explore this further in patients with synchronous metastases and to see how doubling time is affected by different chemotherapy regimens.

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