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# The pre-operative rate of growth of colorectal metastases in patients selected for liver resection does not influence post-operative disease-free survival

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## Abstract

*Aims*: To assess the potential association between the change in diameter of colorectal liver metastases between pre-operative imaging and liver resection and disease-free survival in patients who do not receive pre-operative liver-directed chemotherapy.

*Materials and methods*: Analysis of a prospectively maintained database of patients undergoing liver resection for colorectal liver metastases between 2005 and 2012 was undertaken. Change in tumour size was assessed by comparing the maximum tumour diameter at radiological diagnosis determined by imaging and the maximum tumour diameter measured at examination of the resected specimen in 157 patients.

*Results*: The median interval from first scan to surgery was 99 days and the median increase in tumour diameter in this interval was 38%, equivalent to a tumour doubling time (DT) of 47 days. Tumour DT prior to liver resection was longer in patients with T1 primary tumours (119 days) than T2-4 tumours (44 days) and shorter in patients undergoing repeat surgery for intra-hepatic recurrence (33 days) than before primary resection (49 days). The median disease-free survival of the whole cohort was 1.57 years (0.2–7.3) and multivariate analysis revealed no association between tumour DT prior to surgery and disease-free survival.

*Conclusions*: The rate of growth of colorectal liver metastases prior to surgery should not be used as a prognostic factor when considering the role of resection.



*Keywords:* Liver; Metastasis; Colorectal; Resection

## Introduction

Although the survival of patients with untreated metastatic colorectal cancer has been described[1] the rate of growth of untreated colorectal liver metastases (CRLM) has not been defined, as patients will either receive active treatment or be treated with palliative intent where assessment of tumour progression is rarely undertaken. CRLM may sustain a period of growth between diagnosis and treatment, and assessment of change in tumour size in this period allows an estimate of growth rate. Liver resection provides a potential cure for patients with CRLM with five-year survival rates ranging from 32 to 65%.[2,3] Factors shown to affect survival include CEA estimation,[4] tumour number,[4–6] tumour size,[4,6,7] resection margin involvement,[4,6,8] the presence of satellite lesions,[9] the ratio of

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neutrophils to lymphocytes in peripheral white blood cells[10] and the response to liver-directed chemotherapy.[11] Little information however is available regarding the influence of the pre-operative rate of growth of CRLM, often expressed as tumour doubling time (DT), on survival following liver resection.

The aim of this study was to assess the DT of CRLM in patients not receiving liver-directed chemotherapy between radiological diagnosis and liver resection and to explore potential associations with tumour recurrence and survival after resection.

## Materials and methods

Analysis of data retrieved from a prospectively maintained database of 319 patients undergoing liver resection for CRLM between May 2004 and December 2012 was performed. One hundred and fifty five patients receiving liver-directed chemotherapy were excluded. Imaging was performed with either computerised tomography (CT) or magnetic resonance imaging (MRI) and reviewed at the specialist HPB MDT. The diameter of the largest lesion was measured and recorded in the database for research purposes. Change in tumour size was assessed by comparing the maximum tumour diameter at radiological diagnosis and the maximum tumour diameter measured at examination of the resected specimen. Change in size was expressed as a function of time. Tumour DT was calculated using the equation:

$$DT = Ti \times Log2/(3 \times Log(Dp/Dr)$$

where Ti = time interval between radiological diagnosis and surgery, Dp = diameter at pathology and Dr = diameter at radiological diagnosis.[12]

Data relating to primary and secondary tumour pathology and other routine clinical information were retrieved. Liver resections were defined according to the Brisbane classification[13] and undertaken using standard techniques. Major resections were defined as resections of four or more segments.[14] Synchronous metastases were defined as those diagnosed prior to or within two months of primary surgery. Post-operative follow-up included surveillance CT scans at six-monthly intervals for three years and annually to five years after resection. The timing and site of tumour recurrence were recorded as well as dates of death. Follow-up was completed at March 2014.

Patients were excluded from survival analysis if they died without undergoing surveillance imaging or underwent palliative resections. Patients who developed tumour recurrence at the resection surface following a resection with a positive margin (R1) were excluded as these were deemed to have been due to technical failure rather than tumour recurrence.

Survival curves were constructed by the Kaplan–Meier method and differences in survival were assessed using the log rank method. Comparison between groups was performed using chi-square for categorical variables or Kruskal–Wallis test for continuous variables. Potential associations between pre- and intra-operative factors, as well as histological outcome and tumour recurrence were tested using univariate logistic regression for continuous variables or chi-square for discrete variables test at the level of $P < 0.25$.[15] Significant variables in the univariate analysis were included in the multivariate logistic regression model and were considered to be significant if $P < 0.05$. Univariate and multivariate analyses were carried out using the statistical package R 2.1.14.[16]

Ethical approval for the study was obtained from the South West Health Research Authority. Formal Research Ethics Committee review was not required because patient data were collected in the course of their normal hospital care and were anonymised for research purposes. No patient consent was required for this study.

## Results

During the study period 164 liver resections were performed for CRLM in 160 patients who did not receive pre-resection liver-directed chemotherapy. In seven cases no pre-operative imaging was available, leaving 157 resections for analysis, including 79 (50.3%) major and 78 (49.7%) minor resections. Details of patients undergoing surgery are displayed in Table 1. In sixty-six cases (42.0%), patients received adjuvant chemotherapy following primary colorectal surgery, of whom 19 (28.8%) were treated with 5-FU, 18 (27.3%) with capecitabine, 10 (15.2%) with capecitabine and oxaliplatin, two with capecitabine and bevacizumab and one with 5-FU and oxaliplatin. Details of the post-primary surgery adjuvant regime were not available in 16 patients (25%). The median number of cycles of adjuvant chemotherapy was six (1–8). The median interval between primary colorectal resection and the diagnosis of metachronous tumours was 15 months (3 months–7.9 years).

The median interval from diagnosis of CRLM to liver resection was 99 days (20–548 days). CRLM were diagnosed by MRI in one patient and by CT in 156 patients (99%). The median diameter of the largest tumour was 25 mm (5–110) at diagnosis and 35 mm (3–155) in the resection specimen ($P < 0.001$). The median change in diameter during this interval was +38% (−92% to +518%) and the median rate of increase in maximum tumour diameter was 2.92% per week (−7.0% to +37.7%) (Fig. 1). In 27 patients (17.2%) the maximum tumour diameter in the resection specimen was smaller than that determined by pre-operative imaging. The median calculated tumour DT was 47 days (−743 to 1081 days).