

Influence of the primary tumour location in patients undergoing surgery for colorectal liver metastases

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Abstract

Background: The prognosis of patients undergoing liver resection for colorectal liver metastases (CLM) seems to be altered when the primary tumour is right-sided. However, data are lacking and conflicting. We aimed to evaluate the influence of the primary tumour location on oncologic outcomes following such surgery.

Methods: We retrospectively analysed prospectively collected data from 376 consecutive patients who underwent liver surgery for CLM between June 2010 and August 2015. We compared the outcomes of patients with right colon tumours and those with left colorectal tumours. The splenic flexure was used as the cut-off point to determine the anatomic primary site.

Results: Among the 364 patients eligible, 74 (20.3%) had a right-sided primary tumour. These patients were older, had a poorer American Society of Anaesthesiologists status and had fewer node-positive primary tumours. The CLM characteristics were similar between both groups. Median PFS was not significantly different between the two groups at 9.9 months, as well as the pattern of recurrence. Median OS was shorter for patients with right-sided primary tumour (34.6 versus 45.3 months, $p = 0.035$). Similar results were observed when patients with rectal tumour were excluded from analysis (34.6 vs. 47.5 months, $p = 0.007$). Primary tumour site was an independent prognosis factor in multivariate analysis.

Conclusion: Right-sided location of the primary tumour is associated with worse OS after surgery for CLM, but seems to have no influence on PFS, and on the pattern of recurrence.

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Introduction

Liver surgery remains the only potentially curative treatment for colorectal liver metastases (CLM), with 10-year overall survival (OS) rates of up to 16% [1], but around 75% of patients will develop disease recurrence within 2 years [2]. Selecting patients for liver resection has always been a concern for liver surgeons, which explains the development of scoring systems over the last twenty years to stratify patients into different risk groups. Although some recent scoring systems use molecular data, such as RAS mutation

status [3], most of published scoring systems are based on clinical data only. These data consider the characteristics of the liver metastases, as well as the primary tumour, such as T and N status or grading [4]. The location of the primary tumour has never been taken into account in these scoring systems, but there is a growing interest about the prognostic significance of the anatomical site of the primary tumour. Right-sided and left-sided colorectal tumours have different embryonic origins (midgut for right-sided and hindgut for left-sided) [5], and they also have different molecular features. Right-sided colon tumours are often more advanced tumour (i.e. higher TNM stage), and are associated with a greater frequency of RAS, RAF and PI3KC gene mutations compared to left-sided tumours [6]. Hence, right-sided colon tumours are associated with a worse

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prognosis and may be less responsive to chemotherapy and targeted therapy [7]. There are few data concerning the outcomes of patients with a right-sided primary tumour who underwent a liver resection for CLM. Although right-sided primary tumours are associated with worse overall survival (OS), other results about oncologic outcomes, such as progression-free survival (PFS) or independence from RAS mutation status, are conflicting [8–10]. The aim of this study was to compare the pattern of recurrence, PFS and OS of patients who underwent liver surgery for CLM, based on whether they had a right- or a left-sided primary tumour in the era of modern chemotherapy regimens.

Patients and methods

Patient selection and follow-up

We analysed data of consecutive patients who underwent their first open liver surgery for CLM at a large tertiary hepatobiliary unit between June 2010 and August 2015. Liver surgery was performed only when R0/R1 resection could be achieved. All patients were discussed at a specialist hepato-biliary multidisciplinary team meeting attended by surgeons, oncologists and interventional radiologists. All patients had a triple phase CT chest, abdomen and pelvis, a diffusion-weighted liver MRI and a PET-CT scan, unless absolute contra-indications existed. Exclusion criteria were: multiple primary colorectal cancer; previous curative-intent percutaneous ablation for CLM; and two-stage hepatectomy.

Baseline characteristics, details about primary tumour, metastatic burden and peri-operative chemotherapy, and type of liver surgery were recorded. Postoperative 90-day morbidity and mortality were recorded, and postoperative complications were graded using the Dindo classification [11]. Follow-up included regular outpatient visits every three months for the first year, and every six months thereafter. All follow up visits included physical examination, carcinoembryonic antigen (CEA) measurements and contrast CT scans of chest abdomen and pelvis. The study had full ethical approval from the UK NHS Research Ethics Committee.

Procedure

All liver resection and intraoperative ablation were performed through a reverse L-shaped laparotomy or laparoscopically. Intraoperative ultrasound was routinely performed for staging and to guide surgical resection or ablation. A parenchymal preserving approach was performed whenever possible and use of intermittent Pringle manoeuvre was at the discretion of the operating surgeon. Liver parenchyma was transected with the Cavitron ultrasonic surgical aspirator (CUSA, Valleylab, Boulder, CO) or Kellyklasia. Intraoperative ablation technique used microwave ablation (MWA), with a standard energy delivery of 100 W for 90 s per lesion. Intra-operative MWA was considered as a parenchymal-sparing policy, for tumours

distant from major vessels and measuring less than 3 cm. All specimens were inked and positive margin (R1 resection) was defined as clearance less than one millimetre.

Patients were managed post-operatively within an enhanced recovery program [12].

Statistical analysis

The patients were divided into two groups: those who had right-sided colonic tumour and those who had a left colorectal tumour. Right-sided colonic tumour was defined as tumour located between the ileocaecal junction and the splenic flexure. Tumours at the splenic flexure were included in the left-sided primary tumour group. Baseline characteristics and peri-operative data were presented as the mean \pm standard deviation for continuous data, and as the number of patients and associated percentages for categorical variables. Comparisons of the patient's characteristics between groups were carried out using the Chi-squared test for categorical variables, and Student's *t*-test or the Mann-Whitney test when assumptions of the *t*-test were not met (normality studied using Kolmogorov–Smirnov test) for quantitative variables. OS was calculated from the date of liver surgery to the date of death from any cause or date of the last follow-up (censored observation). PFS was measured from the date of liver surgery to the time of disease progression or death, or was censored at the last follow-up. Survival estimates were calculated using the Kaplan–Meier method. Differences in survival between groups were assessed by log-rank test. Median follow-up was calculated using a reverse Kaplan–Meier estimate. All variables associated with PFS or OS on univariate analysis with *p* value < 0.10 were included in a multivariate cox proportional hazard model. A *p* value ≤ 0.05 was considered statistically significant. All analyses were performed with EZR software [13].

Results

Study population

Of 376 patients who underwent a liver surgery for CLM between June 2010 and August 2015, 364 were eligible for the study. Nine patients had a two-stage hepatectomy, one patient had a previous percutaneous ablation and two patients had multiple synchronous colorectal cancer. Seventy-four patients (20.3%) had a primary tumour located on the right side and 290 patients (79.7%) had a left-sided colorectal tumour, including 151 patients with a tumour located in the rectum. Patients with a right-sided primary tumour were older (68.8 ± 10.9 vs. 65.1 ± 10.6 , *p* = 0.003) and had a higher rate of American Society of Anaesthesiologists (ASA) status of 3–4 (34.7% vs. 20.4% of patients with, *p* = 0.013). When right-sided, primary tumours were less node-positive (40.5% vs. 65.5%, *p* = 0.0002), and more frequently T3–T4 (93.2% vs. 81%, *p* = 0.019). The characteristics of CLM were similar

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