Available online at www.sciencedirect.com

ScienceDirect

EJSO 41 (2015) 484–492

EJSO the Journal of Cancer Surgery

www.ejso.com

The effect of a primary tumour resection on the progression of synchronous colorectal liver metastases: An exploratory study

A.A.P. Slesser [a,b], F. Khan [c], I. Chau [c], A.Z. Khan [d], S. Mudan [b,d], P.P. Tekkis [a,b], G. Brown [e,f,*], S. Rao [c]

[a] Department of Colorectal Surgery, The Royal Marsden Hospital, Fulham Road, London, UK
[b] Division of Surgery and Cancer, Chelsea and Westminster Campus, Imperial College London, UK
[c] Department of Oncology, The Royal Marsden Hospital, Fulham Road, London, UK
[d] Department of Hepato-Biliary Surgery, The Royal Marsden Hospital, Fulham Road, London, UK
[e] Department of Radiology, The Royal Marsden Hospital, Downs Road, Sutton, Surrey, SM2 5PT, UK
[f] Division of Medicine, Imperial College London, UK

Accepted 21 December 2014
Available online 17 January 2015

Abstract

Aim: The objective of this study was to determine the effect of an upfront primary tumour resection on the progression of synchronous colorectal liver metastases.
Materials and methods: Patients with synchronous colorectal liver metastases referred between 2005 and 2010 were identified. Patients were analysed according to the following two groups: 1) an upfront primary tumour resection and 2) neo-adjuvant chemotherapy. A univariate and multivariate analysis was performed to identify factors significantly contributing to progressive disease. Cox regression analysis was undertaken to determine the effect of management on overall survival (OS) and time to tumour progression (TTP).
Results: A total of 116 patients with synchronous colorectal liver metastases were identified of which 49 patients received an upfront primary tumour resection and 67 received neo-adjuvant chemotherapy. Liver resections were performed in 18 (36.7%) and 14 (20.9%) of the patients in the upfront and neo-adjuvant groups respectively (P 0.06). On multivariate analysis, an upfront primary tumour resection significantly affected progressive disease ($p < 0.001$, OR 5.67; 95% CI 2.71–11.79). An upfront tumour resection was not a significant predictor of overall survival ($P = 0.83$; HR 1.10; 95% CI 0.48–2.52).
Conclusion: Our findings suggest that an upfront primary tumour resection in patients with synchronous colorectal liver metastases results in progressive disease. These preliminary findings need to be validated in a future multi-centre independent study.

Keywords: Synchronous colorectal liver metastases; Hepatic metastases; Colorectal cancer

Introduction

Colorectal cancer is the fourth most common cause of cancer death worldwide.[1] Around fifteen per cent of patients with colorectal cancer will present with synchronous colorectal liver metastases.[2] Surgical intervention remains the only chance of long-term survival with the five year survival ranging between 35 and 58 per cent.[3] It is widely accepted that the progression of patients' hepatic metastases during treatment is a contra-indication to a liver resection.[4,5] It has become evident from the EORTC trial that the use of neo-adjuvant chemotherapy prior to a liver resection in patients with resectable colorectal liver metastases increases progression free survival.[6] The timing of the primary tumour resection in patients with synchronous

* Corresponding author. Department of Radiology, The Royal Marsden Hospital, Downs Road, Sutton, Surrey, SM2 5PT, UK. Tel.: +44 208 6613964.
E-mail address: Gina.Brown@rmh.nhs.uk (G. Brown).

http://dx.doi.org/10.1016/j.ejso.2014.12.009
0748-7983/

colorectal liver metastases is contentious. The traditional surgical treatment for patients with synchronous colorectal liver metastases has been a 'sequential' resection whereby the primary is resected first followed by a hepatectomy at a later stage.[7] However, there has been a shift in favour for 'simultaneous' resections in some centres.[8] Whilst some experts are now advocating the use of 'reverse' resections whereby the hepatectomy is performed first.[9,10] Despite this debate, there have been very few studies investigating the effect the timing of a primary tumour resection has on the progression of synchronous colorectal liver metastases. The aim of this exploratory study was to determine whether an upfront primary tumour resection affects the progression of synchronous colorectal liver metastases.

Materials and methods

The study proposal was evaluated by the Royal Marsden Clinical Audit Committee and it was deemed that an ethics application was not required for this study. Patients with colorectal liver metastases referred between 2005 and 2010 were retrospectively identified from a prospectively updated Hepatobiliary multi-disciplinary meeting database. A review of the patients' electronic patient records was undertaken to determine which patients met the inclusion criteria. Adult patients with synchronous colorectal metastases were included in the study if they met the following criteria: 1) patients with synchronous colorectal liver metastases referred for treatment; 2) patients had a (baseline) scan as well as three and six monthly scans and 3) scans had to be either consecutive computed tomography (CT) or magnetic resonance imaging (MRI). Patients were excluded from the study for the following reasons: 1) patients with metachronous colorectal liver metastases; 2) the presence of extra-hepatic metastases at the time of colorectal cancer diagnosis and 3) a lack of baseline imaging or three/six monthly scans.

Image analysis and data collection

High resolution magnetic resonance imaging (MRI) was the modality used to locally stage rectal primary tumours. In colonic primary tumours, computed tomography (CT) scans were used to stage the primary tumours. The extent of tumour infiltration, the presence of extra-mural venous invasion (EMVI) and length of the primary tumour were assessed. On MRI imaging the presence of EMVI was determined by any of the following features: signs of 'tortuous' vascular structures in the mesorectum/mesocolon, nodularity at the tumour margin which is associated with EMVI, the presence of tumour intensity in vessels close to the tumour and 'low-signal-intensity' vessels or an increase in vessel calibre.[11] On CT imaging, any of the following signs are considered to be consistent with the presence of EMVI: 'nodular spread into small vessels or definite enhancing tumour spread along a large vein'.[12] The T stage is staged according to the TNM classification. In particular, we sub-classify the T3 stage into four distinct sub-groups: T3a – the tumour extends <1 mm beyond the muscularis propria, T3b – the tumour extends 1–5 mm beyond the muscularis propria, T3c – the tumour extends >5–15 mm beyond the muscularis propria and T3d where the tumour extends > 15 mm beyond the muscularis propria.[13] On the baseline and consecutive scans, the following liver metastatic characteristics were reported: liver segmental sparing (≥three segments) and the number of metastases (solitary versus multiple). The cumulative metastatic sizes were compared between consecutive scans to assess for progressive disease. All the data collected was anonymised and entered into an electronic database (Microsoft Excel. Redmond, Washington: Microsoft, 2010. Computer Software). The following additional data items were collected: demographic data, site of primary tumour, date of primary and colorectal liver metastases diagnosis, dates of consecutive scans, pre-treatment Carcinoembryonic Antigen (CEA), use of chemotherapy, use of radiofrequency ablation, date and type of primary tumour resection, date and type of liver resection, primary tumour histology and survival status.

Endpoints

1) The primary endpoint of this study was to determine whether an upfront primary tumour resection was associated with the progression of synchronous liver metastases.
2) The secondary endpoint of this study was to assess the effect of the timing of a primary tumour resection on survival.

Definitions

The following definitions were used:

- There is, currently, no clear definition of what constitutes a 'synchronous presentation' in the literature with varied interpretations.[14] Synchronous disease in this study was defined as colorectal liver metastases present at the time of CRC diagnosis or diagnosed within one year of the primary colorectal cancer diagnosis.
- Upfront primary tumour resection: primary tumour resection without any neo-adjuvant treatment.
- Liver metastatic progressive disease was considered to be an increase in the size of liver metastases by twenty per cent or more as per the Response Evaluation Criteria In Solid Tumours 1.1 guidelines.[15] A six-month cut-off was used to assess the effect of a primary tumour resection on disease progression.
- Time to tumour progression (TTP): the time from the date of the liver metastases diagnosis to disease