

# Pooled analysis of the surgical treatment for colorectal cancer liver metastases

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*Abbreviations:* CCO, Cancer Care Ontario; CRC, colorectal cancer; CT, chemotherapy; DFS, disease-free survival; EORTC, European Organisation for Research and Treatment of Cancer; FU, fluorouracil; GRADE, Grading of Recommendations Assessment, Development and Evaluation; HAI, hepatic artery infusion; HR, hazard ratio; IKNL, Integraal Kankercentrum Nederland; MDT, multidisciplinary team; NICE, National Institute for Health and Care Excellence, UK; OR, odds ratio; OS, overall survival; PFS, progression-free survival; PICO, Population-Intervention-Comparator-Outcome; QoL, quality of life; RFS, recurrence free survival; RCT, randomized controlled trial; RFA, radio-frequency ablation; SIGN, Scottish Intercollegiate Guidelines Network; SR, systematic review; WMD, weighted mean difference; yrs, years.

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## Abstract

Liver metastases in colorectal cancer patients decreases the expected 5 year survival rates by a factor close to nine. It is generally accepted that resection of liver metastases should be attempted whenever feasible. This manuscript addresses the optimal therapeutic plan regarding timing of resection of synchronous liver metastases and the use of chemotherapy in combination with resection of synchronous metachronous liver metastases. The aim is to pool all published results in order to attribute a level of evidence to outcomes and identify lacking evidence areas. A systematic search of guidelines, reviews, randomised controlled, observational studies and updating a meta-analysis was performed. Data were extracted and analysed. Data failed to demonstrate an effect of timing of surgery or use of chemotherapy on overall survival. Concomitant resection of liver metastases and the primary tumour may result in lower postoperative morbidity. Systemic peri-operative chemotherapy may improve progression free survival compared to surgery alone.

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**Keywords:** Colorectal cancer; Liver metastasis; Hepatic metastasis; Synchronous metastasis; Metachronous metastasis

## 1. Introduction

Colorectal cancer (CRC) is one of the most common cancers in the Western world. In the United States it is the second leading cause of cancer-related deaths and the third most common cancer in men and in women with an incidence of 46.4 per 100,000 in 2010 [1]. According to the Belgian Cancer Registry, CRC is the second and third most common cancer in women and men. Stage at diagnosis determines survival: the 5-years (yrs) relative survival rates range from 91.8% to 91.3% for stage I but only from 11.9% to 12.9% for stage IV in men and women respectively [2].

However, case series have shown that patients with liver metastases can achieve long-term survival when liver metastases are resected [3]. Based on these observations, recent guidelines recommend attempting curative resection of CRC liver metastases, sometimes in combination with other local treatment modalities such as radiofrequency ablation (RFA) despite lack of evidence from randomised controlled trials (RCT) [4–6]. A recent review reports that 15–30% of patients with liver metastases may be appropriate for curative resection. Five years survival then varies between 30% and 60% [7].

The criteria for resectability are discussed in the 2006 guideline of the Comprehensive Cancer Centre from the Netherlands (Integraal Kankercentrum Nederland) [8]. Important elements are the estimated residual liver volume, the number and location of lesions and the resection margins. Co-existing medical conditions need to be taken into account, but age per se is not a limiting factor. Portal vein embolization may optimise residual volume in the contra-lateral side. In a recent review [9] a 37.9% gain in liver volume occurred

2–4 weeks after embolisation in patients with preserved liver function and 6–8 weeks after embolisation in patients with cirrhosis or diabetes.

When patients are considered for resection of metastases, questions arise about the best timing for liver surgery (sequential or simultaneous with surgery of the primary tumour) and the timing of chemotherapy (CT). Current guidelines recommend multidisciplinary team (MDT) discussion [6] and staged surgery [8,10]. The importance of a centre's expertise is stressed [8]. Expert opinion was the sole basis to recommend peri-operative chemotherapy with a combination of oxaliplatin and 5-fluorouracil (FU)/leucovorin for a total period of 6 months [6] and similar modalities of neoadjuvant chemotherapy, whether or not combined with biological therapy both for synchronous and metachronous liver metastases [10]. We therefore undertook a systematic review (SR) to address the research question as to what is the best therapeutic sequence for CRC patients with resectable synchronous or metachronous liver metastases.

Table 1  
P.I.C.O.

What is the best therapeutic sequence for patients with resectable CRC metastases to the liver?

P (patient)	Patients with resectable colorectal liver metastases
I (intervention)	Simultaneous resection followed by systemic therapy (adjuvant chemotherapy)
C (comparison)	Simultaneous resection without systemic therapy or staged resection with or without chemotherapy
O (outcome)	PFS, OS, QoL

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