Hepatectomy and resection of concomitant extrahepatic disease for colorectal liver metastases – a systematic review

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CRD summary
This review concluded that surgical resection of colorectal liver metastases and concomitant extrahepatic disease, in carefully selected patients, could improve survival, compared with non-surgical treatment. Since there were no comparative groups, and the included studies had varying methods and were of low quality, the authors’ conclusions may not be reliable.

Authors’ objectives
To evaluate the efficacy and safety of hepatectomy, for colorectal liver metastases, and resection of concomitant extrahepatic disease.

Searching
MEDLINE was searched for publications in English, from January 2000 to January 2011; search terms were reported. The bibliographies of identified studies were searched manually.

Study selection
Randomised controlled trials (RCTs), non-RCTs, and cohort and observational studies, of hepatectomy for colorectal liver metastases, with resection of concomitant extrahepatic disease, were eligible for inclusion. Resection could be performed either at the time of hepatectomy or as a consecutive operation. To be eligible studies had to include 10 or more patients. Studies of resection of extrahepatic disease for recurrences after previous hepatectomy, and studies of metastasectomy of extrahepatic disease recurrence, following liver resection for colorectal liver metastases, were excluded. The primary outcomes were the site of extrahepatic disease, and disease-free and overall survival. The extrahepatic disease sites were: lymph node (porto-caval, coeliac or retroperitoneal); lung; peritoneal; or other (second primary, bone, brain, and other organs). Reviews and case reports were excluded.

Studies were conducted at worldwide sites. Where reported, neoadjuvant chemotherapy was used for a median of 53% of cases (range 26 to 100; 11 studies) and adjuvant chemotherapy in 63% cases (range 10 to 80; six studies). The surgical strategies were described. The resection of extrahepatic disease was mostly simultaneous with hepatectomy for lymph nodes and peritoneal metastases, and was simultaneous or delayed for pulmonary metastases.

The study selection was performed by two independent reviewers.

Assessment of study quality
Studies were assigned levels of evidence according to the US Preventive Services Task Force. Level one included RCTs; level two included non-RCTs and well-designed cohort studies; and level three included observational studies and less well-designed cohort studies.

The authors did not report how many reviewers assessed study quality.

Data extraction
The median length of survival, and percentage survival, at three and five years, were extracted. The authors did not report how many reviewers extracted the data.

Methods of synthesis
Median values were calculated across studies and reported with ranges. Survival was stratified according to extrahepatic disease site, where suitable data were available. A narrative review was reported.

Results of the review
Twenty-two studies, with level three evidence, were identified, with 1,142 patients (range 10 to 186). There were at
least 15 cohort studies, in which 12% of the 8,173 patients undergoing hepatectomy for colorectal liver metastases had extrahepatic disease.

Eleven studies reported a median of 42% (range zero to 66) of patients underwent hepatectomy and resection of colorectal liver metastases with extrahepatic disease, at the same time. The median number of hepatic tumours was two (range two to four; nine studies). The median maximum hepatic tumour size was 43mm (range 38 to 52; six studies). A median of 38% of patients (range 26 to 31; seven studies) had bilateral hepatic tumours. The sites of extrahepatic disease were reported in eight studies: lung metastases median was 33% (range three to 51); lymph node metastases median was 23% (range 15 to 68); and peritoneal metastases median was 15% (range 12 to 35).

**All sites:** Median disease-free survival was 12 months (range four to 22; six studies); median overall survival was 30 months (range 14 to 44; 17 studies); and median five-year survival was 19% (range zero to 42; 15 studies). The median five-year survival of patients with complete (R0) hepatectomy with resection of extrahepatic disease was 25% (range 19 to 36; four studies). The median postoperative mortality was 0.75% (range zero to four; 10 studies). The median postoperative complications were 28% (range 15 to 31; seven studies).

**By disease site:** For isolated lung metastases, the median survival was 41 months (range 32 to 46; eight studies), and median five-year survival was 27% (range zero to 33; seven studies). For isolated lymph node metastases, the median survival was 25 months (range 19 to 48; nine studies), and median five-year survival was 17% (range zero to 27; eight studies). For isolated peritoneal metastases, the median survival was 25 months (range 18 to 32; four studies), and the median five-year survival was 8% (range zero to 30; six studies). For extrahepatic disease at more than one site, the median survival was 17 months (range 13 to 25; five studies), and the median five-year survival was 7% (range zero to 28; six studies).

The results were reported for intraoperative blood transfusion, and median three-year survival.

**Authors’ conclusions**

Surgical resection of colorectal liver metastases and concomitant extrahepatic disease might improve survival, compared with non-surgical treatment, for selected patients who could achieve a complete hepatectomy and complete resection of extrahepatic disease.

**CRD commentary**

The review addressed a well-defined question for study design, participants and interventions, but the relevant outcomes were less clear. Only one database was searched, no efforts were made to identify unpublished studies, and only studies published in English were included, so some relevant studies may have been missed. The designs of the included studies were unclear. Study quality was only assessed for the overall level of evidence, with insufficient data to assess individual study quality.

Efforts were made to reduce error and bias in study selection, but they were not reported for data extraction and quality assessment. Some relevant study details were provided, but not the gender and age of patients. A narrative synthesis was provided due to the high variation between studies. The authors noted that most studies were retrospective and reported on patients who had successfully undergone hepatectomy and complete resection of extrahepatic disease, so there was likely to be selection bias.

Since there were no comparative groups, and the included studies had varying methods and were of low quality, the authors’ conclusions may not be reliable.

**Implications of the review for practice and research**

**Practice:** The authors noted that extrahepatic disease should not be a contraindication to hepatectomy. They recommended neoadjuvant chemotherapy for patients with combined pulmonary and hepatic metastases, followed by a staged hepatectomy and pulmonary metastasectomy, if the disease responded or remained stable, possibly with chemotherapy between surgeries. They recommended that patients with only one-site extrahepatic disease be selected for surgery, and only patients with limited peritoneal metastases should be operated on, with suitable chemotherapy at the time of surgery.

**Research:** The authors recommended trials to investigate the optimum perioperative chemotherapy regimen.
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Record Status
This is a critical abstract of a systematic review that meets the criteria for inclusion on DARE. Each critical abstract contains a brief summary of the review methods, results and conclusions followed by a detailed critical assessment on the reliability of the review and the conclusions drawn.