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## Systematic review of randomized and nonrandomized trials of the clinical response and outcomes of neoadjuvant systemic chemotherapy for resectable colorectal liver metastases

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### CRD summary

This review concluded that available evidence suggested that objective response to neoadjuvant chemotherapy may be achieved, with improvement in disease-free survival, in patients with resectable colorectal liver metastases (secondary cancers). Given the possibility of language and publication bias, an evidence base of largely observational studies, and unknown study quality, these conclusions should be interpreted with caution.

### Authors' objectives

To investigate the response to neoadjuvant chemotherapy and survival outcomes of patients with resectable colorectal liver metastases.

### Searching

MEDLINE was searched (1966 to May 2009) for papers published in English after 1990 and search terms were reported. References of retrieved papers were manually searched.

### Study selection

Randomised controlled trials (RCTs), non-randomised controlled trials, well-designed cohort studies and observational studies (with at least 20 patients) where systemic chemotherapy was used in patients with resectable colorectal liver metastases before hepatectomy (neoadjuvant chemotherapy) were eligible for inclusion. The eligible systemic chemotherapy agents were: 5-fluorouracil, leucovorin, oxaliplatin, irinotecan, bevacizumab, cetuximab or other agents administered intravenously. Studies that used hybrid techniques (hepatectomy combined with ablation) as part of the aim of expanding the criteria for resection of colorectal liver metastases were also included. Studies that used ablative techniques after neoadjuvant chemotherapy were excluded.

The primary outcomes of interest were response to neoadjuvant chemotherapy (radiological or pathological), disease-free survival and overall survival. Secondary outcomes were surgical morbidity and mortality.

Most of the included patients had hepatic-only metastases. The median number of lesions ranged from two to seven; their median maximum size was 4cm (range 3 to 5cm). Approximately 80% of included patients had less than four lesions. The most common neoadjuvant therapy agents administered in included studies were 5-fluorouracil, leucovorin, oxaliplatin, and irinotecan either alone or in combination (FOLFOX or FOLFIRI). The median number of chemotherapy cycles was six (range two to 11), with median duration of four months (range three to eight months).

Two reviewers independently selected papers for inclusion and disagreements were resolved by discussion and consensus.

### Assessment of study quality

Methodological quality was not assessed. Studies were graded according to criteria of the US Preventative Services Task Force (RCTs rated as level I evidence; non-randomised controlled trials or well-designed cohort studies rated as level II; and observational studies rated as level III).

### Data extraction

Response to neoadjuvant chemotherapy (radiological/pathological), survival (disease-free survival and overall survival), hepatectomy, and perioperative outcomes were extracted. The Response Evaluation Criteria in Solid Tumor Group (RECIST) criteria were used to categorise response; complete response referred to total disappearance of all lesions and partial response referred to 30% decrease in the sum of the longest diameters of target lesions.

The authors did not state how many reviewers extracted the data.

### Methods of synthesis

The studies were pooled in a narrative synthesis. The authors reported that meta-analyses were not performed due to heterogeneity in methodology and treatment policy.

### Results of the review

Twenty-three studies were included in the review (n=3,278 patients; range 20 to 767); one RCT (level I evidence), three phase II studies (level II evidence) and 19 observational studies (level III evidence).

#### Neoadjuvant chemotherapy

**Radiological assessment (14 studies):** The overall (complete/partial) median rate of objective response to treatment was 64% (range 44 to 100%); complete response median rate was 4% (range 0-38%); and partial response median rate was 52% (range 10 to 90%). The median rate of stable disease was 26% (range 0 to 47%). A median rate of 15% of patients (range 0 to 37%) showed disease progression whilst on chemotherapy.

**Pathological assessment (five studies):** Pathological complete response was found in a median of 9% of patients (range 2 to 24%). A pathological partial response was seen in 36% of patients (range 20 to 60%).

**Survival:** Median disease-free survival (12 studies) was 21 months (range 11 to 40 months). Median overall survival (13 studies) was 46 months (range 20 to 67 months).

Further results were reported in the paper.

### Authors' conclusions

The available evidence suggested that objective response to neoadjuvant chemotherapy may be achieved with improvement in disease-free survival in patients with resectable colorectal liver metastases.

### CRD commentary

The review question was well defined. Searches were restricted to published studies in English, which increased the risk of publication and language bias. Study selection was performed by two reviewers, reducing the risk of error and bias. However, it was unclear whether similar steps had been taken for data extraction.

Study quality was not assessed, so the reliability of the primary studies was not known. However, most of the studies were observational studies (a less robust design). Narrative synthesis appeared to be appropriate considering the heterogeneity between studies.

Given the possibility of language and publication bias, an evidence base of largely observational studies, and unknown study quality, the authors' conclusions should be interpreted with caution.

### Implications of the review for practice and research

**Practice:** The authors stated that, for the approach of employing neoadjuvant chemotherapy prior to hepatectomy in patients with resectable colorectal liver metastases to become routinely practised, predictive factors that improve patient selection need to be identified through an individualised strategy and discussed within a multidisciplinary setting.

**Research:** The authors stated that a randomised clinical trial comparing neoadjuvant chemotherapy with adjuvant therapy after liver resection is required to determine the relative risk-benefit ratios of these approaches.

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### Bibliographic details

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**Other publications of related interest**

Chua TC, Liauw W, Saxena A, Chu F, Glenn D, Chai A, Morris DL. Systematic review of neoadjuvant transarterial chemoembolization for resectable hepatocellular carcinoma. *Liver International* 2010;30(2):166-174.

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