

REVIEW ARTICLE

A systematic review of two-stage hepatectomy in patients with initially unresectable colorectal liver metastases

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Abstract

Objectives: Selected patients with unresectable colorectal liver metastases (CLM) may be rendered resectable using the two-stage hepatectomy (TSH) approach. This review was conducted with the aim of collating and evaluating published evidence for TSH in patients with initially unresectable CLM.

Methods: Searches of the MEDLINE and EMBASE databases were undertaken to identify studies of TSH in patients with initially unresectable CLM. Studies were required to focus on the perioperative treatment regimen, operative strategy, morbidity, technical success and survival outcomes.

Results: Ten observational studies were reviewed. A total of 459 patients with initially unresectable CLM were selected for the first stage of TSH. Preoperative chemotherapy was used in 88% of patients and achieved partial and stable response rates of 59% and 39%, respectively. Postoperative morbidity and mortality after the first stage of TSH were 17% and 0.5%, respectively. Portal vein embolization (PVE) was used in 76% of patients. Ultimately, 352 of the initial 459 (77%) patients underwent the second stage of TSH. Major liver resection was undertaken in 84% of patients; the negative margin (R0) resection rate was 75%. Postoperative morbidity and mortality after the second stage of TSH were 40% and 3%, respectively. Median overall survival was 37 months (range: 24–44 months) in patients who completed both stages of TSH. In patients who did not complete both stages of TSH, median survival was 16 months (range: 10–29 months). The 3-year disease-free survival rate was 20% (range: 6–27%).

Conclusions: Two-stage hepatectomy is safe and effective in selected patients with initially unresectable CLM. Further studies are required to better define patient selection criteria for TSH and the exact roles of PVE and preoperative and interval chemotherapy.

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Introduction

Colorectal cancer is the third most common cancer worldwide.¹ Around 25% of patients have synchronous liver metastases at presentation and a further 25–50% subsequently develop metachronous liver disease.^{2,3} Surgical resection of colorectal liver metastases (CLM) is considered the only curative therapy and achieves 5-year overall survival (OS) rates of up to 58%.^{4–11} Nevertheless, fewer than 25% of patients with CLM are considered to have resectable disease.^{11–13} In the last decade, considerable efforts were directed towards developing strategies to increase the number of patients with CLM who could benefit from

surgical resection. In 2000, Adam *et al.* published the first series of two-stage hepatectomies (TSHs) in patients with unresectable bilobar CLM that were not amenable to resection in a single operation, even in combination with preoperative chemotherapy and portal vein embolization (PVE).¹⁴ Two-stage hepatectomy is conceived as a planned and potentially curative strategy and consists of the resection of CLM in one hemiliver during the first stage, followed by a second resection of CLM in the contralateral hemiliver during the second stage. This systematic review was undertaken to assess the published evidence for the safety and efficacy of TSH in patients with initially unresectable CLM.

Materials and methods

Literature search strategy

A search of the MEDLINE (1966 to June 2012) and EMBASE (January 1974 to June 2012) databases was undertaken. The search terms *colorectal cancer* or *colorectal neoplasm*, *liver metastases* or *hepatic metastases tumour*, *hepatectomy* or *liver resection* or *hepatic resection*, and *stage resection* or *two-stage hepatectomy* were used. These terms were mapped to MESH (*medical subject headings*) terms and were searched for as text items. Reference lists from relevant articles were searched and the authors' personal libraries were checked manually for other potentially relevant studies. No search was made of unpublished literature.

Study selection

The study evaluation was performed by two reviewers (VWTL and JML). Reviews, case reports, conference abstracts, non-human studies and case series in which TSH was completed in fewer than 10 patients were excluded. Abstracts of the remaining studies were retrieved and reviewed for relevance. The full texts of previously selected articles were thoroughly reviewed. Studies on which a decision could not be made based upon the abstract were also reviewed. Those studies which described the use of TSH with curative intent in patients with initially unresectable CLM were included for analysis. Studies that adopted hybrid approaches, combining liver resection with ablation techniques, or the resection of extrahepatic metastases with the aim of expanding the criteria for resection of CLM, were also included for review. Only studies reporting both short- and longterm outcomes of TSH were included. When multiple publications were identified from the same or overlapping patient series, only the most complete or recent publication was included. Study methodology quality was assessed according to the Newcastle–Ottawa scale.¹⁵ A score of ≥ 4 was required for inclusion.

Data extraction and critical appraisal

Two reviewers (VWTL and JML) independently appraised each article using predefined criteria. Data extracted included information on methodology, quality criteria, setting of the use of perioperative chemotherapy, response to chemotherapy, proportion of negative margin (R0) resections, disease-free survival (DFS) and OS, and morbidity and mortality in this multimodal approach. Discrepancies were resolved by consensus. Major hepatectomy was defined as the resection of three or more Couinaud segments. Because the reports included lacked control groups and the selected studies were heterogeneous, no meta-analysis could be carried out. A qualitative systematic review was performed without a comparator group by full tabulation of the results. The level of evidence of each article was scored according to the Hierarchy of Evidence table developed by the National Health and Medical Research Council of Australia.¹⁶ This systematic review was performed according to PRISMA (*preferred reporting items for systematic reviews and meta-analyses*) guidelines.¹⁷

Results

The literature search using the strategy described herein identified 226 studies. Duplicated studies, non-human studies, review articles, case reports and conference abstracts were excluded. The manuscripts of the 43 remaining articles were reviewed. Thirty-three articles that did not fulfil the inclusion criteria were excluded. The remaining 10 studies were individually reviewed (Fig. 1). No meta-analyses or randomized controlled trials (RCTs) were identified. Ten observational studies (Level IV evidence) were included for analysis.

This review pertains to 10 studies covering a combined total of 459 patients with unresectable CLM in whom the first stage of TSH was performed.^{18–27} One study, reporting TSH for initially unresectable liver metastases in 33 patients with colorectal cancer, three with neuroendocrine tumours, one with a gastrointestinal stromal tumour, one with ocular melanoma and one with salivary gland carcinoma, was included for analysis.²² Three studies with overlapping patient series^{28–30} were excluded, as was one study without longterm survival data.³¹ Three studies from the same institution reporting the use of ablation of CLM only at the first stage of TSH were excluded.^{32–34} Criteria used to define patients as initially unresectable were reported in eight studies (Table 1).^{18–22,24,25,27} Insufficient volume of the future liver remnant (FLR) was the most frequently documented reason for the designation of unresectability (six of eight studies).^{18–22,25} However, these studies did not uniformly identify an adequate FLR volume. Six studies reported patient selection criteria for TSH, but none of them used the same criteria (Table 1).^{18–20,23,26,27} Five studies included patients with extrahepatic disease in whom total metastasectomy was feasible and planned.^{20–22,24,27} Ten studies reported the number of patients with synchronous colorectal cancer and liver metastases; collectively, these patients represented 78% (range: 50–96%) of all patients (350 of 451 patients).^{18–27} Preoperative chemotherapy was administered to some patients in all 10 studies: 400 of 457 patients (88%; range: 64–100%) received chemotherapy.^{18–27} Five studies reported the rate of response to preoperative chemotherapy; partial response was achieved in 130 of 222 patients (59%; range: 43–73%) and stable response was achieved in 86 of 222 patients (39%; range: 19–57%).^{19,20,23,24,27}

The surgical characteristics and perioperative outcomes of the first stage of TSH are depicted in Table 2. Eight studies reported the proportion of patients undergoing concomitant colorectal resection to give a combined total of 126 of 355 patients (35%; range: 0–50%).^{20–27} Liver resection was performed in all 10 studies in a total of 443 of 453 patients (98%; range: 91–100%).^{18–27} Concomitant ablation of CLM was reported in all 10 studies in a total of 73 of 435 patients (17%; range: 0–67%). Concomitant portal vein ligation or PVE was reported in all 10 studies in a total of 87 of 435 patients (20%; range: 0–73%). Postoperative morbidity and mortality were reported in all studies and affected a total of 73 of 425 patients (17%; range: 0–26%) and two of 435 patients (0.5%),

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