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REVIEW ARTICLE

Simultaneous versus delayed hepatectomy for synchronous colorectal liver metastases: a systematic review and meta-analysis

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Abstract

Objective: This was a systematic review and meta-analysis to compare outcomes between patients undergoing simultaneous or delayed hepatectomy for synchronous colorectal liver metastases.

Background: The optimal strategy for treating liver disease among patients with resectable synchronous colorectal liver metastases (CRLM) is unclear. Simultaneous resection of primary tumour and liver metastases may improve patient experience by reducing the number of interventions. However, there are concerns of increased morbidity compared to delayed resections.

Methods: A systematic literature search was performed using EMBASE, Medline, Cochrane library and Google scholar databases. Meta-analyses were performed using both random-effects and fixed-effect models. Publication and patient selection bias were assessed with funnel plots and sensitivity analysis.

Results: Thirty studies including 5300 patients were identified. There were no statistically significant differences in parameters relating to safety and efficacy between the simultaneous and delayed hepatectomy cohorts. Patients undergoing delayed surgery were more likely to have bilobar disease or undergo major hepatectomy. The average length of hospital stay was six days shorter with simultaneous approach [MD = –6.27 (95% CI: –8.20, –4.34), $p < 0.001$]. Long term survival was similar for the two approaches [HR = 0.97 (95%CI: 0.88, 1.08), $p = 0.601$].

Conclusion: In selected patients, simultaneous resection of liver metastases with colorectal resection is associated with shorter hospital stay compared to delayed resections, without adversely affecting perioperative morbidity or long-term survival.

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Introduction

At the time of diagnosis of colorectal carcinoma, approximately 25% of patients have synchronous liver metastases.[1] The optimal timing of resection of the primary and metastatic disease is contentious. The main arguments for a delayed approach, with the primary disease first, includes definitive control of the primary disease and source of metastases, reduction in the severity of complications that may be associated with simultaneous resection, and a 'test of time', as some patients may develop further metastatic disease in the interval between delayed resections.[2] This rationale is supported by authors who demonstrated that delayed interventions do not increase the risk of unresectability, but help for better selection of patients by discovering new hepatic and extrahepatic metastases.[3] On the contrary, supporters of a simultaneous approach consider that post-operative immunodeficiency may

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promote metastases with a delayed approach.[4,5] Furthermore, if simultaneous resection is safe, it could improve the patient experience, by reducing the time to definitive surgical control of all disease, reducing the total number of interventions and reducing the costs of hospital treatment. It may also reduce the time to adjuvant chemotherapy.[20,30,39]

However, the optimal strategy for the treatment of synchronous CRLM is unclear, as there are no randomised trials in this setting. Therefore, the aim of this study was to perform a systematic review and meta-analysis of available studies to address the question of whether synchronous or delayed resection of CRLM is the optimal strategy.

Methods

The PRISMA statements checklist for reporting systematic review and meta-analysis was followed.

Literature search

Using the search terms in both their free text and MESH terms (synchronous colorectal liver metastases; synchronous; simultaneous hepatectomy and liver resection; delayed hepatectomy and liver resection; staged hepatectomy and liver resection), a systematic search of the literature was performed using the EMBASE, Medline (Pubmed), Cochrane library and scholar Google databases from inception until December 2016. A grey literature search in the clinicaltrials.gov and the NEAR website was also performed. References of the retrieved articles were checked manually for further studies.

Study selection, inclusion and exclusion criteria

Only studies that compared simultaneous and delayed hepatectomy for synchronous CRLM were included in the study. Where two studies were reported from the same authors, the most recent was selected. Language or region restrictions were not applied to the systematic search.

Studies without comparative groups and/or clearly reported outcomes were excluded.

Data extraction and outcomes

Two reviewers (PG and KR) independently extracted the following summary data for the included studies: name of authors; study design and time period; number of patients included in simultaneous and delayed hepatectomy; age; gender; colonic primaries; patients treated with neoadjuvant and adjuvant therapy; major hepatectomies.

The primary outcome considered in the analysis was long-term overall survival. A range of secondary outcomes were also compared between the groups, namely: length of stay, operative time, blood losses, transfusion, Clavien-Dindo III-IV morbidity, perioperative mortality, wound infections, subphrenic/perihepatic abscesses, bile leak/biloma, transient hepatic insufficiency, abdominal/pelvic abscesses and anastomotic leak.

Statistical analysis

The methodological quality of all included studies was assessed with the validated Newcastle–Ottawa scale (NOS).[6] Studies scoring >7 were considered of high quality.

Review Manager 5.3 software (Cochrane collaboration, Oxford, England) was used for all statistical analyses. Heterogeneity was assessed with I^2 test and values of more than 30% were treated as being indicative of potentially important heterogeneity. Where this occurred, both fixed and random-effects models were produced, and the conclusions compared, with the latter used where there were discrepancies. In cases of I^2 values less than 30%, fixed effects models were used throughout.

Dichotomous variables were analysed based on odds ratios (OR) with 95% confidence intervals (CI). For the outcomes being considered, the reference categories were selected such that an OR < 1 favoured the simultaneous approach. The studies were then combined using the Mantel-Haenszel method in the first instance, with the Peto approach used for rare outcomes.[7] Continuous variables were combined based on both the mean difference (MD) and the standardised mean difference (SMD). For studies that did not report the means and variances for the two groups, these values were estimated from the median, range and the size of sample, where possible, using the technique described by Hozo SP *et al.*[8]

Analysis of long term survival was performed by combining the hazard ratios (HRs) and 95% CIs from the included studies. These were rarely reported, and so were estimated using the method described by Parmar MK *et al.*,[9] where this was possible. For studies that reported the numbers at risk, these were combined with either the quoted survival rates or values read from enlarged plots of the Kaplan–Meier curves to produce the estimates. Where numbers at risk were not quoted, constant censoring over the period of follow up was assumed in the estimation. The studies were weighted using an inverse variance approach and HRs < 1 favoured the simultaneous cohort.

In all analyses, the point estimate was considered significant at $p < 0.05$. Publication bias was explored for the primary outcomes by assessing visual asymmetry on a funnel plot.[10]

Sensitivity analysis of the included studies

A range of sensitivity analyses were performed, in order to ensure that the results of the analyses were robust. Analyses of both primary and secondary outcomes were calculated by using both random-effects and fixed-effect models, in order to assess the impact of heterogeneity on the conclusions. In addition, subgroup analyses were performed for those studies which scored more than seven stars of the modified NOS, studies with more than 50 patients in the simultaneous group, and studies published after 2010, to assess for consistency of data reporting.

Definitions

Major Hepatectomy was defined as a liver resection of ≥3 segments. Operating time was defined as the total time for

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