REVIEW ARTICLE

Systematic review and meta-analysis of outcomes after liver resection in patients with hepatocellular carcinoma (HCC) with and without bile duct thrombus

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Abstract

Introduction: This meta-analysis aimed to compare perioperative and survival outcomes in patients who underwent hepatectomy with and without Bile Duct Tumour Thrombus (BDTT).

Methods: A comprehensive search of Cochrane Library, PubMed, MEDLINE and EMBASE was performed to identify relevant articles. The perioperative, postoperative and long term outcomes were compared.

Results: Eleven studies including 6051 patients met the inclusion criteria. The perioperative outcomes were comparable between the 2 groups. The BDTT group had higher proportion poorly differentiated tumours (OR = 1.87, X^2 = 10.00, df = 6, p = 0.002, I^2 = 40%), Lymphovascular invasion (LVI) (OR = 4.85, X^2 = 28.21, df = 9, p = <0.001, I^2 = 68%) and Macrovascular invasion (MVI) (OR = 5.41, X^2 = 8.73, df = 9, p = <0.001, I^2 = 0%). There was no difference in 1 and 3 year survival, however 5-yr survival was poorer in the BDTT group (OR = 0.37, X^2 = 37.04, df = 7, p = <0.001, I^2 = 81%). The mean difference (MD) in overall survival in the BDTT group was −20 months [−32.31, −7.06], p = 0.002, I^2 = 95%.

Conclusion: Patients with HCC with BDTT had more advanced stage HCC with adverse histological features including higher rates of MVI, LVI and poor differentiation. Hepatectomy in this group of patients offers similar survival at 3 years but inferior long-term survival and should be considered when feasible.

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Introduction

Bile duct tumour thrombus (BDTT) is an uncommon presentation in hepatocellular carcinoma (HCC) with a reported incidence between 1.2 and 12.9%.[1–4] The first description of BDTT was reported in 1947 and was termed as "icteric-type hepatoma"[5] due to the patients presentation with obstructive jaundice. Jaundice in patients with HCC can be secondary to a number of reasons including heamobilia, direct tumour infiltration into extra or intrahepatic biliary radicles, decompensated liver disease or portal lymphadenopathy. BDTT is considered a poor prognostic sign and prognostic staging systems such as the Liver Cancer Study Group of Japan (LCSGJ) staging system for HCC consider the presence of BDTT as an indicator of advanced stage, similar to macro vascular invasion.[6] Macrovascular invasion is known to be strongly associated with high rates of recurrence and diminished survival after liver resection or transplantation.[7,8] The pathological characteristics and prognostic implications of BDTT are however less well defined.

Although some retrospective studies assessing surgical outcomes in patients with BDTT have reported reasonable survival

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Abbreviations: BDTT, bile duct tumour thrombus; HCC, hepatocellular carcinoma; BCLC, Barcelona clinical liver cancer; RR, risk ratio; CI, confidence interval; NOS, Newcastle–Ottawa score.

following radical surgical resection[9–11] others have reported poor prognosis.[12,13] In addition, it is unclear as to what extent other adverse pathological prognostic variables, such as lymphovascular invasion, poor differentiation and macrovascular invasion are associated with BDTT. This meta-analysis aimed to assess these co-variables and compare the perioperative outcomes and survival in patients who underwent hepatectomy with and without a BDTT.

Methods

A systematic literature review of published articles comparing survival outcomes and clinico-pathological characteristics between patients undergoing resection with and without BDTT was conducted in accordance with the Preferred Reporting for Systematic Reviews and Meta-Analyses (PRISMA) guidelines, and as outlined in a predefined protocol.[14]

Data sources and search strategy

Although not strictly a "thrombus" HCC ingrowth into the biliary tree is now widely referred to as BDTT and hence this nomenclature has been maintained for the purposes of this study. To identify the relevant studies, the following databases were searched systematically: The Cochrane Cancer Group Controlled Trials Register, the Cochrane Central Register of Controlled Trials in the Cochrane Library, MEDLINE, Embase and Science Citation Index Expanded for articles published up to September 2015 using the medical subject headings (MeSH) terms 'bile duct thrombus' and 'liver resection'. Equivalent free-text search terms, such as 'bile duct thrombus' were used in combination with 'liver resection'. The references from the included studies were searched to identify additional studies comparing the two techniques. Inclusion criteria for searching were: prospective or retrospective clinical series reporting the outcome of patients undergoing liver resection for HCC with and without BDTT. Inclusion was irrespective of language, country of origin, hospital, sample size or publication status. The search strategy is illustrated in Fig. 1.

Data extraction and quality assessment

Studies were identified and data were extracted by two authors independently (i.e. T. Chang and S. Navadgi) the accuracy of the extracted data was further adjudicated by a third author (SP). The following items were extracted: title of study, year of publication, country of study and sample size. The baseline data extracted were aetiology of liver disease, UICC staging, Childs-Pugh scores, and extent of resection and classification of type of BDTT. The Newcastle–Ottawa score was assigned to each of these studies to assess the quality of the included publications. Relevant outcome variables included: overall survival, 1-, 3-, and 5-year survival, bile leak, positive margin, blood loss and tumour characteristics such as tumour size, poor differentiation, encapsulation, lymphovascular invasion and major vascular invasion.

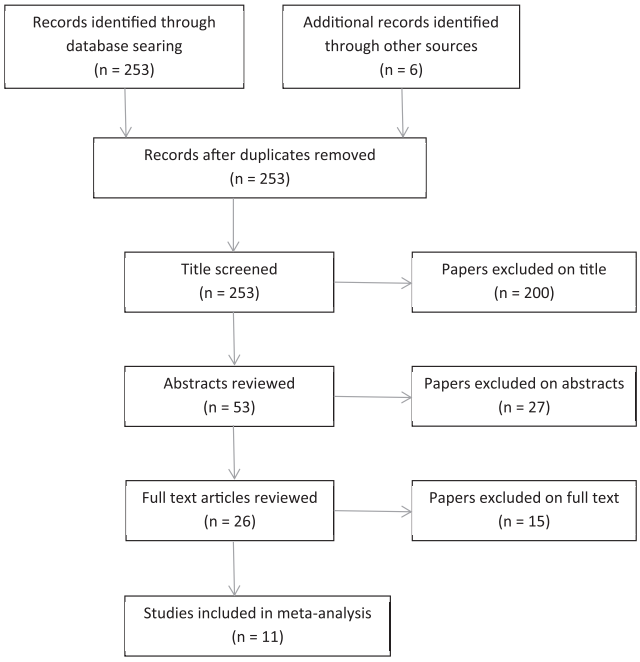

Figure 1 PRISMA flow diagram showing selection of studies for review

Statistical analysis

Review Manager Version 5.2 software (Cochrane Collaboration) was utilised for statistical analysis. The odds ratio (OR) with 95% confidence interval (CI) was calculated for categorical data, and the mean difference was 95% CI for continuous variable. Statistical analysis was made with data mean and variance for continuous data. If mean and variance were not available, they were calculated from median and data range by using the methods described by Hozo *et al.*[15] Random and fixed-effects models were used to calculate the combined outcomes of both binary and continuous data.[16] Only the results of the random-effects model were reported in case of heterogeneity. Heterogeneity was calculated using the Tau^2 test. Statistical significance was defined as p value less than 0.05. Low heterogeneity was defined as an I^2 value of 33% of less.[17] If the standard deviation was not available, it was calculated according to the guidelines of the Cochrane Collaboration.[18] This process involved assumptions that both groups had the same variance, which may not have been true, and variance was estimated either from the range. Results were displayed in Forest plots. The quality of included studies was assessed using the Newcastle–Ottawa score[19] for case-controlled studies.

Results

Baseline characteristics

A total of eleven studies[1,2,20–28] including, 6051 patients with HCC who underwent liver resection were chosen for this meta-analysis of which 281 (4.6%) patients were in BDTT group and 5770 (95.4%) patients in the NBDT group (Fig. 1). Fifteen