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REVIEW ARTICLE

Systematic review and meta-analysis of hepatic resection versus transarterial chemoembolization for solitary large hepatocellular carcinoma

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Abstract

Background: Surgical techniques and pre-operative patient evaluation have improved since the initial development of the Barcelona clinic liver cancer staging system. The optimal treatment for solitary hepatocellular carcinoma ≥5 cm remains unclear. The aim of this study was to review the long-term survival outcomes of hepatic resection versus transarterial chemoembolisation (TACE) for solitary large tumours.

Methods: EMBASE, MEDLINE, Pubmed and the Cochrane database were searched for studies comparing resection with TACE for solitary HCC ≥5 cm. The primary outcome was overall survival at 1, 3 and 5 years.

Results: The meta-analysis combined the results of four cohort studies including 861 patients where 452 underwent hepatic resection and 409 were treated with TACE to an absence of viable tumour. The pooled HR for 3 year OS rate calculated using the random effects model was 0.60 (95% CI 0.46–0.79, $p < 0.001$; $I^2 = 54\%$, $P = 0.087$). The pooled HR for 5 year OS rate calculated using the random effects model was 0.59 (95% CI 0.43–0.81, $p = 0.001$; $I^2 = 80\%$, $P = 0.002$).

Conclusion: Hepatic resection has been shown to result in greater survivability and time to disease progression than TACE for solitary HCC ≥5 cm. Where a patient is fit for surgery, has adequate liver function and a favourable tumour, resection should be considered.

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Background

Hepatocellular carcinoma (HCC) is the second most common cause of cancer-related death in the world.[1] Mortality rates and future incidence are predicted to increase significantly in the next decade, particularly in the Western world.[2,3] For optimal results in the management of HCC, treatment guidelines need to take into account patient's liver function, tumour stage and physical status.[4] The Barcelona Clinic Liver Cancer (BCLC) staging system links staging and treatment indications and was published as a practice guideline and updated in 2011. BCLC guidelines have been clinically validated[5] and are recommended by the American Association for the Study of Liver Diseases (AASLD)[6] and the European Association for the Study of the Liver (EASL).[7]

The EASL in their most recent guidelines for treatment of HCC,[7] clearly recommend that single tumours beyond 5 cm be considered for surgical resection as the first option. The justification for this is that solitary large tumours with no macrovascular involvement seen with modern MRI may reflect a more benign biological behaviour by the fact that these tumours have enlarged but remained single (without satellite nodules or metastases). The BCLC group have also recognised that HCC larger than 5 cm may show no vascular invasion or satellites, and state that a cut-off for surgical resection cannot be justified.[4]

Patients with large HCC are beyond the Milan criteria and therefore not considered for liver transplantation. Ablative therapies have low efficacy in achieving complete necrosis in tumours greater than 3 cm in diameter.[8–10] Transarterial chemoembolization (TACE) is currently recommended for 'unresectable' solitary HCC in patients with BCLC Stage B tumours and has been proven to be an excellent loco-regional therapy with a non-curative intent.[11] However, while there is a

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survival advantage in treating with TACE, the treatment is not considered to be curative. The only curative treatment available for patients with solitary large tumours is hepatic resection. The BCLC treatment strategy limits resection for large solitary tumours to those with Child-Pugh A cirrhosis, normal bilirubin and no portal hypertension.[6] In reality, tumours larger then 5 cm in patients with less than pristine liver function are being selectively resected worldwide with good results.[12,13]

There is currently no discussion in the literature that groups the available evidence for large solitary tumours which present the most straightforward first step in expanding the guidelines for hepatic resection. The aim of this study was to review the long-term survival outcomes of hepatic resection versus TACE for solitary large tumours.

Methods

The meta-analysis was performed using the Preferred Reporting Items for Systematic Reviews for Meta-analyses (PRISMA) guidelines.[14] A comprehensive search of the EMBASE, MEDLINE, Pubmed and the Cochrane databases was performed separately by a librarian and the authors to identify relevant studies to August 2016. The key words used were 'hepatocellular carcinoma' or 'carcinoma, hepatocellular' or 'hepatoma' or 'liver cell carcinoma' or 'heptocarcinoma' and 'liver resection' or 'hepatic resection' and 'TACE' or 'embolization' or 'chemoembolization' or 'Barcelona Clinic Liver Cancer.'

The following inclusion criteria were used to select included studies:

a. Population: patients diagnosed with a solitary HCC $\geq$5 cm
b. Intervention: hepatic resection alone
c. Comparison: TACE (multiple repeat procedures where necessary) without any alternative ablative techniques or radioembolisation, and
d. Outcomes: Overall survival, disease free survival and treatment related complications.

Two independent investigators (C. Stevens and A. Awad) performed the abstract and subsequent full text review. Discussion achieved consensus on included papers. To assess the quality of the non-randomised studies included in the meta-analysis the modified Newcastle–Ottowa Scale (NOS) was used.[15] The GRADE System was used to rate the quality of evidence and strength of the recommendations.[16]

Statistical analyses were performed using Review Manager Version 5.3 software (Cochrane Collaboration). The number of surviving patients at each time period (1, 3 and 5 years) was treated as a dichotomous variable with the number of survivors and total numbers of patients extracted from the included studies. The odds ratios with 95% CI were calculated and pooled estimated of the HRs and ORs were calculated using a random effects model to account for any heterogeneity in the data.

Results

The results of the literature search are shown in Fig. 1. Four retrospective cohort studies were included in the meta-analysis.[17–20]

A total of 861 patients made up the meta-analysis, 452 (52%) of these underwent resection and 409 (48%) were treated with TACE. Two of the studies were propensity score matched retrospective cohort analyses, however, the full dataset of each were used for this analysis.[19,20] The other two studies were unmatched retrospective cohort studies.[17,18]

All four studies included patients who underwent anatomical hepatectomy based upon the segmental division of the liver or nonanatomical resection with sufficient tumour margin where remnant liver volume was critical. TACE was administered using hepatic arterial angiography. An emulsion of lipiodol mixed with chemotherapy agents was infused and embolised with gelatin sponge particles. Chemotherapy agents varied between the four studies.

Characteristics and quality of included studies

Table 1 summarises the characteristics of the populations of each of the four included studies. All were published in 2014–15 and include patients treated as early as 1998. The range of 5-year survival for hepatic resection and TACE was 43–71% and 18–58% respectively.

Each of the studies were independently assessed using the NOS and overall the included studies were of high quality with scores ranging from 7 to 9. The GRADE Working Group grades of evidence were high for 3 and 5-year overall survival rates. The definition of survival time across all four studies was up to the most recent follow up date. Jianyong *et al.*[17] excluded patients lost to follow up.

Characteristics of the studied patients

The baseline characteristics of the patients enrolled in each of the studies is shown in Table 2. No study included patients with vascular invasion or distant metastases.

Portal hypertension was reported in three of the studies[17–19] and its presence was not significantly different in the cohorts of resection or TACE. Jianyong *et al.* reported on a larger group than specifically solitary tumours larger than 5 cm (they included multiple tumours) and did not separate the details of portal hypertension or Childs Pugh classification for the relevant tumour size. Therefore, these results could not be compared with the other studies in Table 2. However, across their complete studied population, 354/433 (82%) of the patients treated with hepatic resection and 420/490 (86%) of the patients treated with TACE had portal hypertension. This was defined as the presence of oesophageal varices or platelet count $<100 \times 10^9$ cells/L in association with splenomegaly. While not reported specifically for the solitary large tumours, Childs Pugh classification was similar across the two groups studied by Jianyong *et al.* with 105/433 (24%) of the resection group and 109/490 (22%) of the

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