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ORIGINAL ARTICLE

Comparison of outcomes of transplantation and resection in patients with early hepatocellular carcinoma: a meta-analysis

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Abstract

Objectives: Surgical decision making for patients with early hepatocellular carcinoma (HCC) and well-compensated cirrhosis remains controversial. The aim of the current study was to conduct a meta-analysis of published reports to compare survival outcomes after transplantation and resection, respectively, in patients with early HCC [i.e. HCC falling within the Milan Criteria (a solitary lesion measuring ≤5 cm or fewer than three lesions with a largest diameter of ≤3 cm, and absence of macroscopic vascular invasion or extrahepatic disease)] and well-compensated cirrhosis.

Methods: A total of 990 abstracts were identified through a PubMed-based search. Ten articles comparing transplantation and resection in patients with early HCC were included in the meta-analysis. Meta-analysis was performed using STATA 9.2 statistical software.

Results: Outcomes were analysed for a total of 1763 patients with early HCC. The 5-year overall survival (OS) for all patients was 58% (transplantation: 63%; resection: 53%). Meta-analysis of all 10 studies revealed a survival advantage for transplantation [odds ratio (OR) 0.581, 95% confidence interval (CI) 0.359–0.939; $P = 0.027$]. Analysis of only those reports that utilized an 'intention-to-treat' strategy failed to demonstrate a survival advantage for either treatment approach (OR 0.600, 95% CI 0.291–1.237; $P = 0.166$).

Conclusions: The current study demonstrates a favourable outcome in patients with early HCC treated by either transplantation or resection. Although transplantation was noted to have a survival advantage in some settings, resection continues to be a viable treatment approach.

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Introduction

Worldwide, hepatocellular carcinoma (HCC) is the fifth most common cancer, with an estimated 748 300 new cases diagnosed in 2008, and is also a leading cause of mortality, accounting for an estimated 695 900 cancer deaths in 2008.[1] Although HCC is much more frequent in eastern Asia, its incidence continues to rise in the United States (US) as a result of major risk factors such as hepatitis C virus (HCV)-induced cirrhosis and non-alcoholic steatohepatitis (NASH).[1–3] In 2011, an estimated 26 190 new cases and 19 590 deaths from liver and intrahepatic bile duct cancers were expected in the US.[4]

Several treatment options are available to patients with HCC and the ideal option is determined based on the burden of tumour and extent of underlying liver disease.[5,6] Transplantation and resection remain the major therapeutic options available to patients with HCC.[5–7] Patients with early-stage disease [i.e. HCC falling within the Milan Criteria (a solitary lesion measuring ≤5 cm or up to three lesions with a largest diameter of ≤3 cm, and absence of macroscopic vascular invasion or extrahepatic disease)] and advanced cirrhosis, including Child–Pugh class B/C disease and portal hypertension, are thought to be candidates for transplantation, whereas resection remains the treatment of choice in patients without underlying liver disease. However, significant controversy exists regarding the choice between transplantation and resection in the management of patients with well-compensated cirrhosis (i.e. patients with Child–Pugh class A disease and selected patients with class B disease) and early HCC.

Recently published studies from the Western hemisphere have added to the controversy by demonstrating the superiority of transplantation in one study and that of resection in the other.[8,9] Lastly, it is also known that the specialty of the surgeon and his or her expertise can influence the chosen treatment approach.[10]

Resection is available immediately, but is associated with recurrent disease, whereas outcomes after transplantation may be compromised by waiting times secondary to organ shortage. Because of this delay in organ availability, a subset of patients [approximately 10% (range: 0–30%) of patients at 6 months[11]] with early HCC, who are listed for transplantation, experience disease progression and ultimately succumb to the disease. Therefore, to determine true outcomes after transplantation, patients who demonstrate disease progression while on the waiting list (and become unsuitable for transplantation or die during waiting) should be included in the analysis. This type of analysis to determine overall outcomes after transplantation, which includes dropouts, is called an 'intention-to-treat' (ITT) analysis and was initially performed by Llovet *et al.*[12]

Most previous studies comparing outcomes after transplantation with those after resection have used a heterogeneous group of patients that included patients with different stages of underlying liver disease. These studies failed to limit the analysis to patients with early HCC and well-compensated cirrhosis and did not utilize an ITT strategy. Thus, because of the contradictory nature of the published evidence, the ideal treatment approach for patients with early HCC and well-compensated cirrhosis remains undetermined.

The aim of the current study was to perform a meta-analysis to compare overall survival (OS) following transplantation and resection, respectively, in patients with early HCC and well-compensated cirrhosis (Child–Pugh classes A and B in the absence of portal hypertension) using an ITT strategy.

Materials and methods

Search strategy and inclusion and exclusion criteria

The PubMed database was searched for articles published in English between January 1990 and March 2011 using the key words 'hepatocellular carcinoma' AND 'resection' AND 'transplantation'. A total of 990 articles were identified. The abstracts of the 990 articles were reviewed to identify relevant articles. An extensive backward search was performed using the bibliographies of relevant articles and review articles to ensure that the search was comprehensive. Figure 1 depicts the search strategy in detail.

The following articles were excluded from the analysis:

1 review articles and letters;
2 articles reporting outcomes in HCC after resection or transplantation alone;
3 articles comparing primary vs. salvage liver transplant;
4 articles comparing resection with non-resectional therapies;
5 articles primarily reporting the outcomes of non-resectional therapies;
6 articles including patients with non-cirrhotic HCCs, fibrolamellar HCCs and hepatocholangio carcinomas, and
7 articles that compared patients with no evidence of cirrhosis treated by resection with cirrhotic patients who underwent transplantation.

The following articles were included in the meta-analysis:

1 articles comparing OS in patients with HCC and cirrhosis undergoing transplantation vs. resection;
2 articles that reported 5-year OS percentages, and
3 articles that reported on samples of patients with tumours within the Milan Criteria (early HCC; solitary lesion measuring ≤5 cm or no more than three lesions with a largest diameter of ≤3 cm; absence of macroscopic vascular invasion and extrahepatic disease).

The full texts of 85 articles were reviewed. Of these, 24 articles were identified as comparing outcomes after transplantation and resection, respectively, in patients with HCC.[12–35] A recently published report by Koniaris *et al.* was excluded because its authors had included resection patients with no evidence of cirrhosis in their analysis.[9] Similarly, a comprehensive review by Kitisin *et al.* of over 1000 patients with HCC was excluded because its authors did not specify the size of HCC and included non-cirrhotic patients in their analysis.[8]

Data extraction and definitions

Estimates of the number of patients in the transplantation and resection subcategories, respectively, and 5-year OS were extracted from the studies (texts or tables). If a study reported 5-year OS for all patients (i.e. for patients with disease within and outside the Milan Criteria), only data on patients with disease within the Milan Criteria were extracted. Similarly, if a study reported 5-year OS data for both ITT and non-ITT analyses, only data from the ITT analysis were extracted. Meta-analysis was performed using the number of patients who were dead or alive, respectively, at 5 years in the transplantation and resection subgroups.

Statistical methods

Meta-analysis was performed using STATA Version 9.2 (StataCorp LP, College Station, TX, USA). Meta-analysis was performed in line with the Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) statement.[36] All data were treated as binary (dead vs. alive at 5 years; transplantation vs. resection). An estimate of the number of patients who survived 5 years was calculated by multiplying the total number of patients in the transplantation and resection subcategories included in the study by the corresponding 5-year OS estimate. Odds ratios (ORs) and 95% confidence intervals (CIs) computed from the binary data were used for the final meta-analysis. Because heterogeneity amongst the different studies was suspected, a random-effects

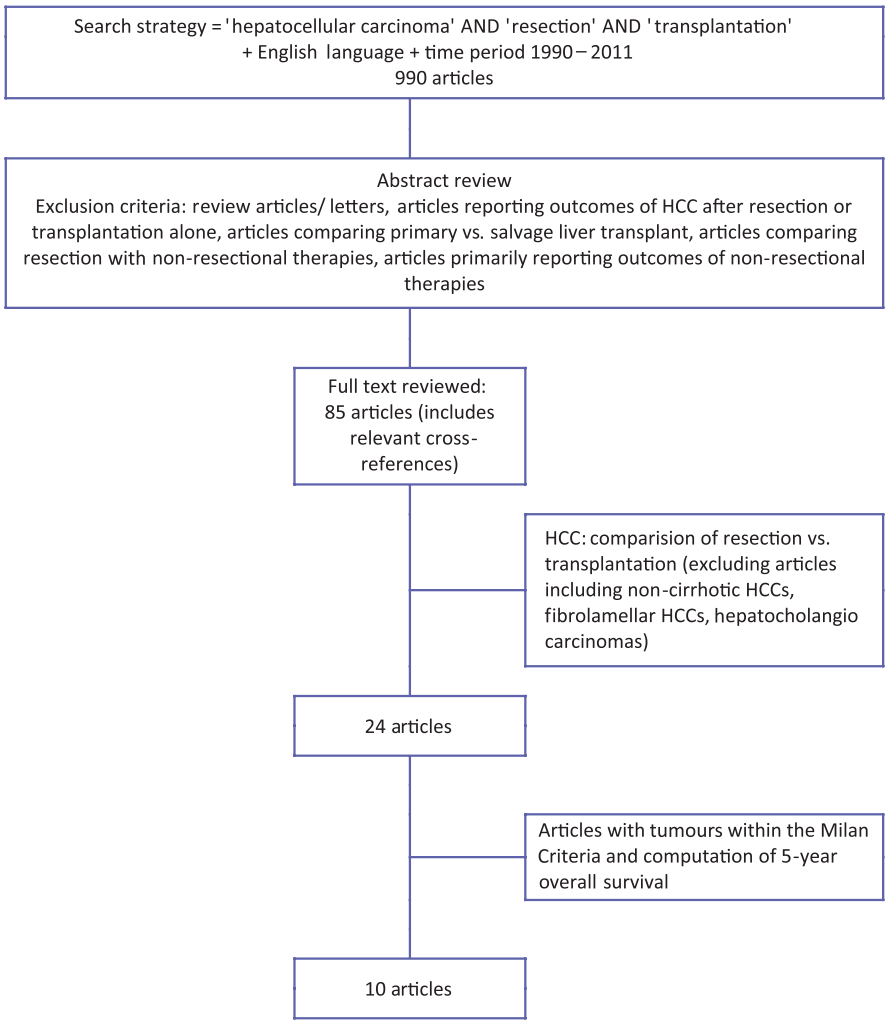

Figure 1 Flow diagram showing search strategy along with the selection and screening process for the eligible studies. HCC, hepatocellular carcinoma

model was used. Heterogeneity was explored using the chi-squared test with a significance level of $P = 0.10$. I^2 statistics were calculated to further quantify heterogeneity. A meta-regression analysis was also performed to explore the heterogeneity. Residual maximum likelihood was used to estimate the additive (between-study) component of variance for the meta-regression analysis. Bootstrap analyses were performed with the Monte Carlo permutation for meta-regression using 10 000 random permutations.[37] Publication bias was explored using funnel plots; the symmetry of funnel plots was analysed using objective tests such as Egger's and Begg's tests to rule out any bias from the studies with small patient samples.[38,39] In order to address the questions posed by the current meta-analysis and the issue of heterogeneity, subset analyses were also performed for studies that included patients with well-compensated cirrhosis, studies that utilized an ITT analysis, and both.

Results

Literature search and description of studies

After application of the exclusion and inclusion criteria, 24 studies that compared outcomes after transplantation and resection, respectively, in patients with HCC were identified.[12–35] Supporting

Table S1 (online) summarizes a few important characteristics of these 24 studies. Ten studies comparing outcomes of transplantation with those of resection in patients with early HCC, which reported 5-year OS, qualified for inclusion in meta-analysis.[12,14–16,21,25,26,28,30,33] Table 1 summarizes the important characteristics of these 10 studies. Although Facciuto *et al.* compared outcomes after transplantation and resection, respectively, in early HCC with well-compensated cirrhosis using an ITT analysis, the authors did not report 5-year survival rates and this study was therefore excluded.[22] All studies were retrospective in nature and six of the 10 studies had utilized an ITT strategy for analysis.[12,14,16,21,28,30] Additionally, six of the 10 relevant studies had either restricted their analysis to patients with well-compensated cirrhosis (i.e. patients with Child–Pugh class A disease and selected patients with Child–Pugh class B disease) or had reported results for patients with well-compensated cirrhosis separately.[12,15,16,25,26,30] Three of the 10 relevant studies met both these criteria in that they utilized an ITT analysis and included patients with well-compensated cirrhosis.[12,16,30]

A total of 1763 patients from the 10 relevant studies were included in the meta-analysis. The number of eligible patients per study in the 10 studies included in the meta-analysis ranged from 37 to 379. Most studies had a mean or median follow-up of approximately 2 years. Mean five-year OS in all patients with early HCC (treated with transplantation or resection) was 58% (median 57%, SE 0.108). Mean five-year OS was 63% (range: 44–78%, median 64%, SE 0.249)) in patients who underwent transplantation, and 53% (range: 27–70%, median 56%, SE 0.324)) in patients who underwent resection.

Meta-analysis of 10 studies comparing transplantation and resection in early HCC

Meta-analysis of the 10 studies[12,14–16,21,25,26,28,30,33] comparing the outcomes of transplantation and resection, respectively, in a total of 1763 patients with early HCC, revealed a statistically significant 5-year survival advantage for patients undergoing transplantation compared to resection (transplantation vs. resection, OR = 0.581, 95% CI 0.359–0.939; $P = 0.027$). A summary of the data and forest plot for the estimation of effect are shown in Fig. 2. Statistically significant between-study heterogeneity was identified (heterogeneity, $\chi^2 = 39.99$, $I^2 = 77.5\%$, $P < 0.001$). Assessment of the funnel plot (Fig. 3) ruled out any small study effects, which was confirmed by Egger's test (coefficient = −1.985, 95% CI −6.588 to 2.616; $P = 0.349$) and Begg's test (adj. Kendall's score = −9, $z = -0.80$, $P = 0.421$).

Because of the statistically significant heterogeneity amongst the studies, a meta-regression analysis was performed to identify factors that might account for the heterogeneity. None of the tested variables, including sample size ($P = 0.778$), year of publication ($P = 0.989$), use of ITT analysis ($P = 1.000$) and well-compensated cirrhosis ($P = 0.989$), were able to explain the heterogeneity. The standard error of the *P*-values using a Monte Carlo approach with 10 000 permutations was found to be 0.005.

Although the funnel plot was symmetrical overall, three studies were found to be outliers on visual inspection.[14,21,28] A subset analysis of the other seven studies revealed a similar statistically significant 5-year survival advantage for patients undergoing transplantation compared to resection (transplantation vs. resection, OR = 0.516, 95% CI 0.372–0.715; $P < 0.001$). No significant between-study heterogeneity was identified (heterogeneity, $\chi^2 = 8.16$, $I^2 = 26.5\%$, $P = 0.227$). Therefore, heterogeneity derives mainly from these three studies.[14,21,28]

Meta-analysis of six studies comparing transplantation and resection in early HCC with well-compensated cirrhosis

Meta-analysis of the six studies[12,15,16,25,26,30] comparing the outcomes of transplantation and resection, respectively, in a total of 994 patients with early HCC and well-compensated cirrhosis revealed a statistically significant improvement in 5-year OS in patients with early HCC and well-compensated cirrhosis undergoing transplantation versus resection (transplantation vs. resection, OR = 0.538, 95% CI 0.377–0.766; $P = 0.001$). A summary of the data and forest plot for the estimation of effect are shown in Fig. 4. There was no statistically significant between-study heterogeneity (heterogeneity, $\chi^2 = 7.36$, $I^2 = -32.1\%$, $P = 0.195$). Small study effects were estimated to be non-significant using Egger's test (coefficient = −0.256, 95% CI −4.461 to 3.948; $P = 0.874$) and Begg's test (adj. Kendall's score = 1, $z = 0.19$, $P = 0.851$).

Meta-analysis of six studies comparing transplantation and resection in early HCC using an ITT strategy

Meta-analysis of the six studies[12,14,16,21,28,30] comparing the outcomes of transplantation and resection, respectively, in a total of 1118 patients with early HCC, using an ITT strategy, failed to reveal a statistically significant difference in 5-year OS between transplantation and resection, although there was a trend towards better 5-year OS following transplantation rather than resection in this patient population (transplantation vs. resection, OR = 0.600, 95% CI 0.291–1.237; $P = 0.166$). Some of these studies included patients with Child–Pugh class A–C cirrhosis undergoing transplantation for early HCC.[14,21,28] A summary of the data and forest plot for estimation of effect are shown in Fig. 5. There was significant between-study heterogeneity (heterogeneity, $\chi^2 = 29.95$, $I^2 = 83.3\%$, $P < 0.001$). Again, underlying heterogeneity can be explained by three previously mentioned studies.[14,21,28] Small study effects were estimated to be non-significant using Egger's test (coefficient = −4.740, 95% CI −12.066 to 2.584; $P = 0.147$) and Begg's test (adj. Kendall's score = −7, $z = -1.32$, $P = 0.188$).

Meta-analysis of three studies comparing transplantation and resection in early HCC with well-compensated cirrhosis using an ITT analysis

Only three studies compared outcomes of transplantation and resection, respectively, in early HCC with well-compensated

Table 1 Characteristics of 10 studies comparing outcomes after transplantation and resection, respectively, in patients with early hepatocellular carcinoma

Authors, year	Country	Departments[a]	HR, *n*	LT, *n*	Tumour size	Child–Pugh class	ITT analysis	OS after LT at years:			OS after HR at years:			Length of follow-up
								1	3	5	1	3	5	
								%	%	%	%	%	%	
Lee *et al*. (2010)[25]	South Korea	Surgery	82	48	Within as well as outside the Milan Criteria[b]	A, B	No	85	78	78	88	75	58	Mean: LT 49.1 months; HR 66.5 months
Baccarani *et al*. (2008)[14]	Italy	Surgery and transplant	38	48	Milan Criteria	A, B, C	Yes	84	78	72	82	61	27	Median: LT 21 months (range: 1–85 months), HR 36 months (range: 10–84 months)
Bellavance *et al*. (2008)[15]	USA, Switzerland, Italy	Surgery, transplant, surgical oncology	245	134	Milan Criteria	A	No	91	79	66	93	71	46	Median: overall 2.5 years; LT 3.3 years; HR 2.3 years
Del Gaudio *et al*. (2008)[21]	Italy	Liver transplant	80	293	Milan Criteria	A, B, C	Yes			58			66	Mean: primary LT 36 months; salvage LT 26.2 months
Shah *et al*. (2007)[30]	Canada	Surgery	121	140	Milan Criteria	A, B	Yes	90	70	64	89	75	56	Median: 35 months
Poon *et al*. (2007)[28]	Hong Kong	Surgery	204	43	Milan Criteria	A, B, C	Yes			44			60	Median: LT 49 months (range: 8–123 months); HR 53 months (range: 8–124 months)
Margarit *et al*. (2005)[26]	Spain	Liver transplant	37	36	Milan Criteria	A	No	78		65	92		70	Median: LT 44 months; HR 50 months
Bigourdan *et al*. (2003)[16]	France	Visceral transplant	20	17	Milan Criteria	A	Yes		87	71		67	36	Median: 55 months
Llovet *et al*. (1999)[12]	Spain	Liver transplant	77	37	Milan Criteria	A	Yes	83	71	71	85	62	51	Median: LT 26 months; HR 32 months
Weimann *et al*. (1999)[33]	Germany	Transplant	32	31	Milan Criteria	Not mentioned	No	87	72	63	78	41	35	Not mentioned

[a]Countries of departmental affiliations indicated on the title page.
[b]Only data for patients with disease within the Milan Criteria were included in the meta-analysis.
LT, liver transplant; HR, hepatic resection; ITT, intention-to-treat; OS, overall survival.

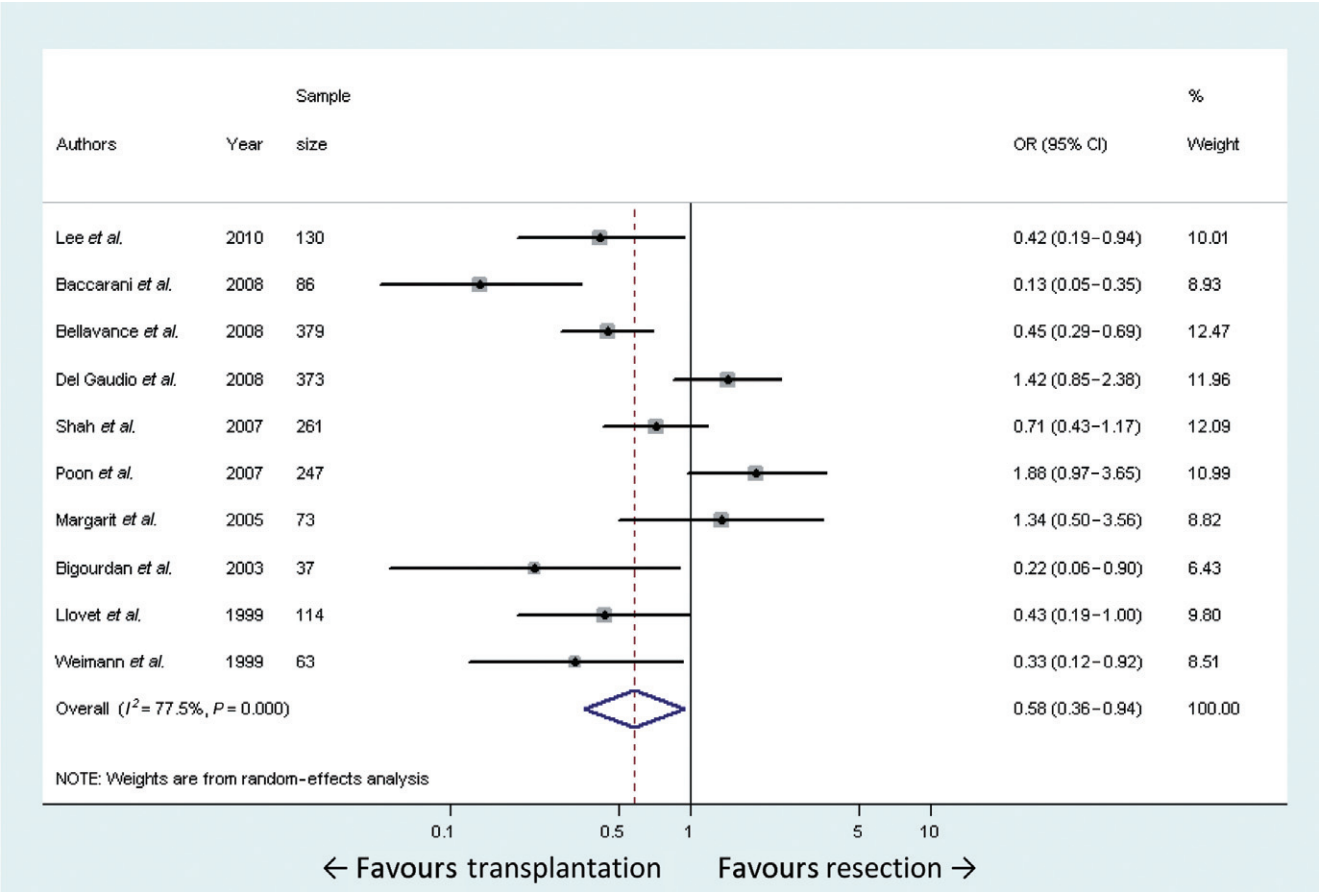

Figure 2 Meta-analysis of 5-year overall survival utilizing data from 10 studies comparing outcomes after transplantation and resection, respectively, in early hepatocellular carcinoma (i.e. within the Milan Criteria). Odds ratios (ORs) for overall survival in the transplantation and resection subgroups were calculated using the random-effects model. The diamond represents the overall effect; squares represent the effects for individual studies; bars indicate 95% confidence intervals (CIs)

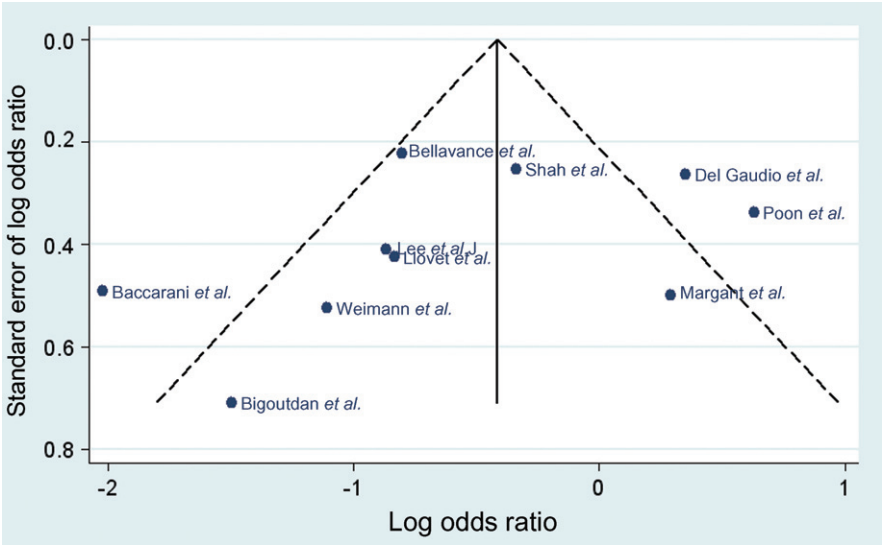

Figure 3 Funnel plot for the 10 studies comparing outcomes after transplantation and resection, respectively, in patients with early hepatocellular carcinoma

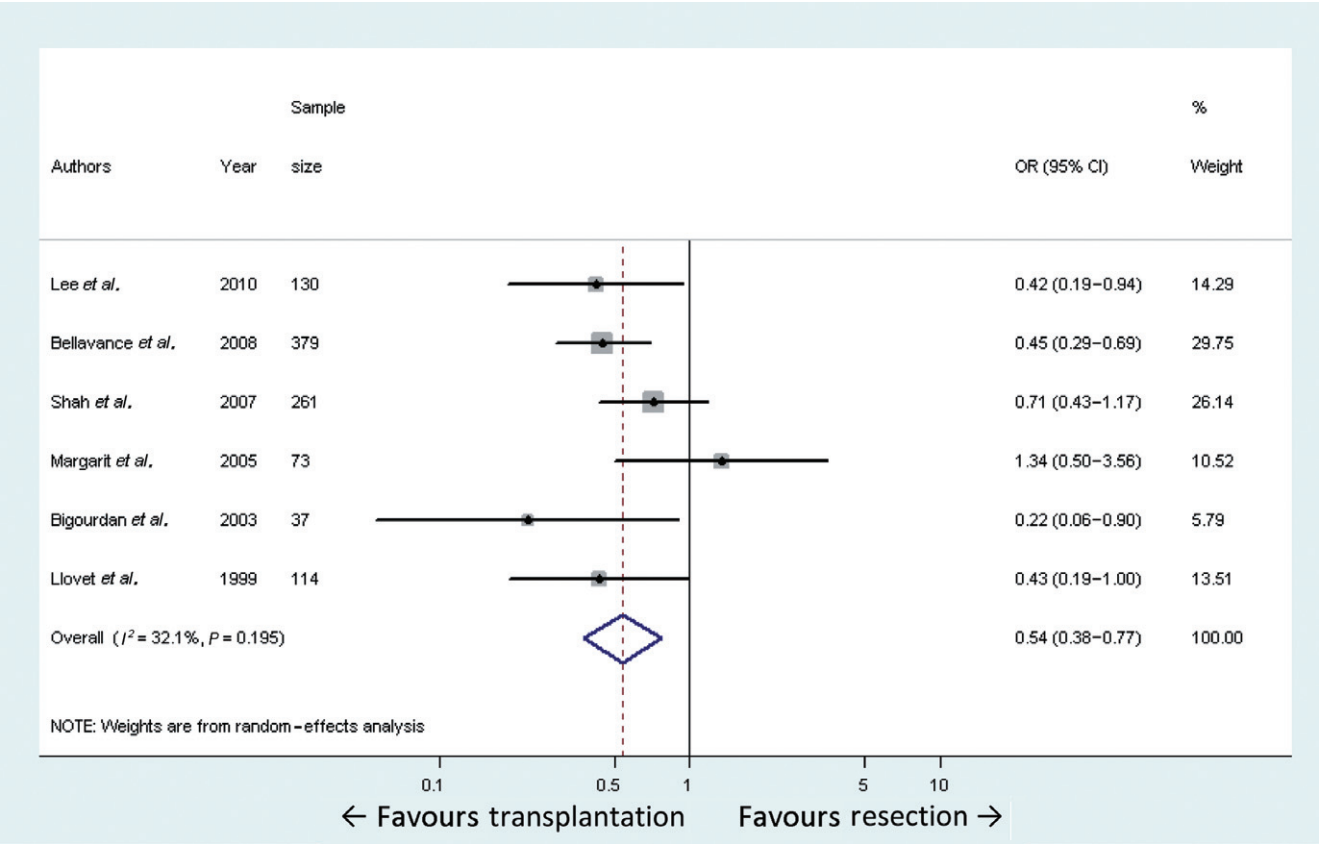

Figure 4 Meta-analysis of 5-year overall survival utilizing data from six studies comparing outcomes after transplantation and resection, respectively, in early hepatocellular carcinoma (i.e. within the Milan Criteria) in patients with well-compensated cirrhosis. Odds ratios (ORs) for 5-year overall survival in the transplantation and resection subgroups were calculated using the random-effects model. The diamond represents the overall effect; squares represent the effects for individual studies; bars indicate 95% confidence intervals (CIs)

cirrhosis, using an ITT strategy.[12,16,30] A meta-analysis of these three studies,[12,16,30] which included a total of 412 patients, was performed as the decision process is most controversial in this group of patients. Meta-analysis of these studies revealed a statistically significant 5-year survival advantage for patients with early HCC and well-compensated cirrhosis undergoing transplantation rather than resection (transplantation vs. resection, OR = 0.521, 95% CI 0.298–0.911; $P = 0.022$). A summary of the data and forest plot for estimation of effect are shown in Fig. 6. Between-study heterogeneity was not found to be statistically significant (heterogeneity, $\chi^2 = 2.91$, $I^2 = 31.3\%$, $P = 0.233$). Sensitivity analysis was not performed as only three studies qualified for meta-analysis.

Discussion

Transplantation and resection in various permutations with other modalities, such as ablation, remain the major treatment options available to patients with HCC. Both transplantation and resection have their own advantages and limitations.[5,6] Resection is available immediately and in carefully selected patients who are deemed eligible, is not limited by the Milan Criteria. However, underlying liver disease is known to preclude resection in many patients even if they have resectable disease.[5,40] Transplantation, by contrast, removes not only the tumour but also the pre-cancerous liver parenchyma. However, transplantation is limited by organ shortage and allocation, which causes patients to drop out from the waiting list. In patients with advanced liver disease, transplantation is considered preferable, whereas, in patients without underlying liver disease, resection is recommended. However, in patients with early HCC and minimal underlying liver disease, selection of the appropriate treatment remains controversial.

Several studies have tried to address this controversy by performing a comparative analysis of outcomes after transplantation and resection.[12–35] Some of these studies are hampered by the inclusion of patients with mismatched degrees of underlying liver disease and varying degrees of tumour burden. Studies that reported on resection have included patients with disease outside the Milan Criteria or tumours with vascular invasion, both of which inherently contribute to worse outcomes. However, the inclusion of patients who undergo resection in the absence of any

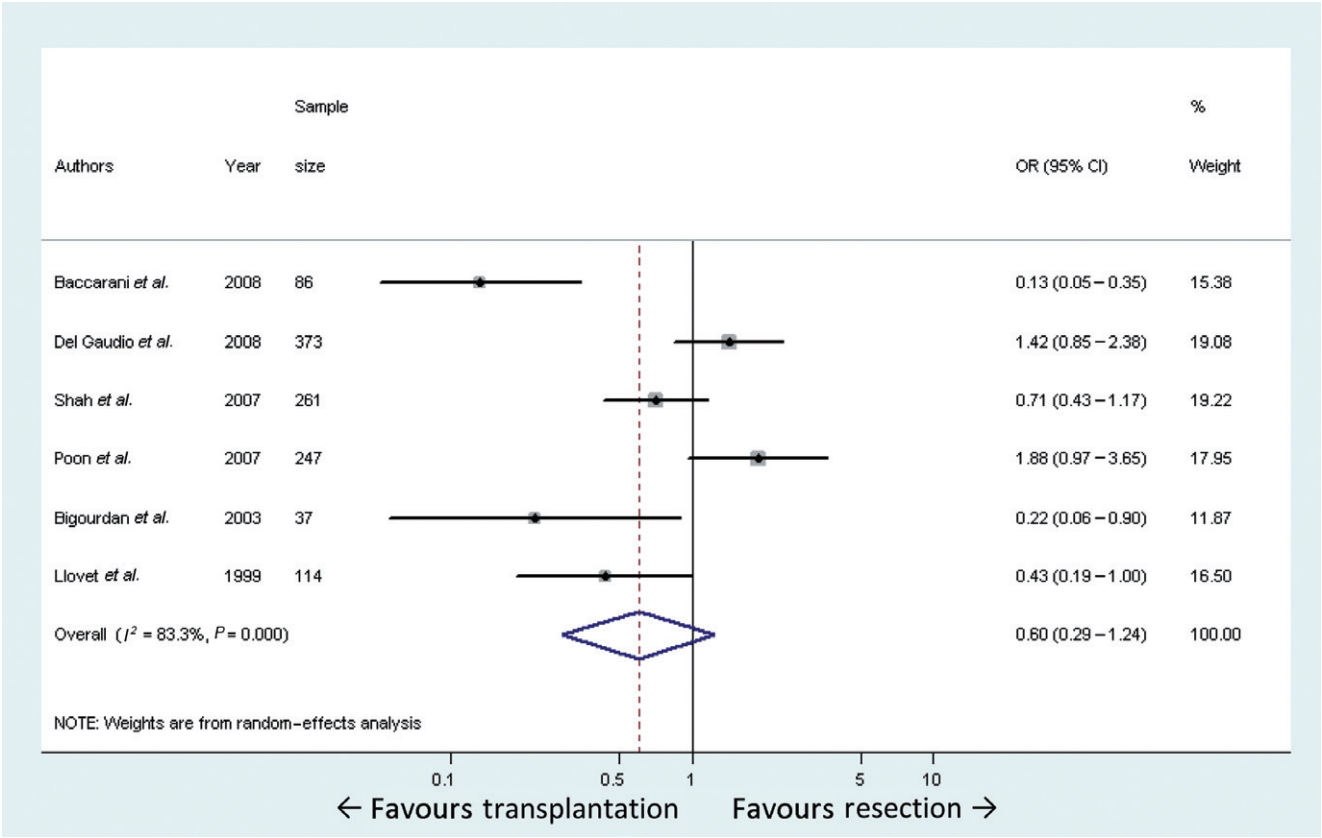

Figure 5 Meta-analysis of 5-year overall survival utilizing data from six studies comparing outcomes after transplantation and resection, respectively, in early hepatocellular carcinoma (i.e. within the Milan Criteria), utilizing an intention-to-treat analysis. Odds ratios (ORs) for 5-year overall survival in the transplantation and resection subgroups were calculated using the random-effects model. The diamond represents the overall effect; squares represent the effects for individual studies; bars indicate 95% confidence intervals (CIs)

underlying liver disease can influence the outcomes in favour of resection.[9] Similarly, studies that have included patients with advanced and decompensated liver disease and multiple comorbidities in analyses of outcomes of transplantation may have allowed the nature of their samples to adversely influence outcomes, whereas studies of outcomes after transplantation that have not performed an ITT analysis will have biased outcomes in favour of transplantation by excluding dropouts. Lastly, surgeon specialty is also known to influence surgical decision making as liver transplant (LT) and non-LT surgeons view various clinical factors differently.[10] Nathan *et al.* noted that non-LT surgeons are more likely than LT surgeons to choose liver resection (relative risk ratio = 2.67) for patients with early HCC.[10]

The aim of the current study was to address this controversy by performing a meta-analysis to compare the outcomes of transplantation and resection, respectively, in patients with early HCC and well-compensated liver disease. Stringent criteria were applied in the selection of studies for inclusion in the meta-analysis. To avoid the drawbacks associated with prior comparative studies, the final analysis in the present study was restricted to a select few studies that included only early HCC patients (with disease within the Milan Criteria) with well-compensated cirrhosis, and that performed an ITT analysis.

The present meta-analysis shows that in patients with early HCC, transplantation is associated with a statistically significant survival advantage over resection (transplantation vs. resection, OR = 0.581, 95% CI 0.359–0.939; P = 0.027). This advantage persisted in the subset of patients with well-compensated cirrhosis (transplantation vs. resection, OR = 0.538, 95% CI 0.377–0.766; P = 0.001). However, analysis of ITT studies only found no statistically significant difference amongst patients undergoing transplantation vs. resection (transplantation vs. resection, OR = 0.600, 95% CI 0.291–1.237; P = 0.166). Although studies that utilized an ITT analysis and included patients with well-compensated cirrhosis showed some survival benefit of transplantation compared to resection, the numbers of such studies and patients are small to draw any conclusions.

Any study that compares outcomes after transplantation and resection, respectively, should utilize an ITT strategy. The concept of ITT analysis with reference to transplantation outcomes was first introduced by Llovet *et al.*[12] Many patients experience disease progression while on the waiting list and become unsuitable for

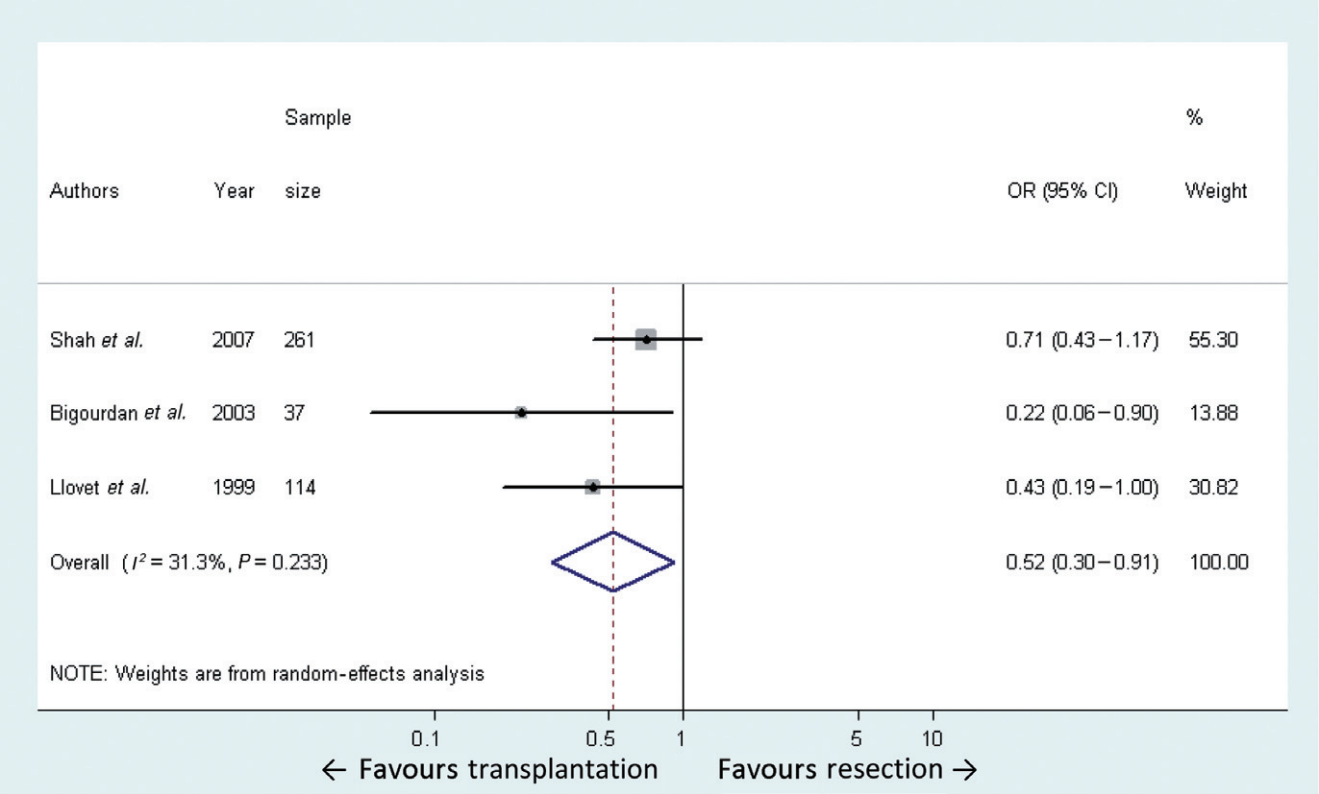

Figure 6 Meta-analysis of 5-year overall survival utilizing data from three studies comparing outcomes after transplantation and resection, respectively, in early hepatocellular carcinoma (i.e. within the Milan Criteria) in patients with well-compensated cirrhosis, using an intention-to-treat strategy. Odds ratios (ORs) for 5-year overall survival in the transplantation and resection subgroups were calculated using the random-effects model. The diamond represents the overall effect; squares represent the effects for individual studies; bars indicate 95% confidence intervals (CIs)

transplantation. The major predictors of dropout are: a solitary lesion measuring >3 cm in diameter; previous hepatic resection, and the presence of two or three tumour nodules at the time of initial diagnosis.[22,41] As Yao *et al.* report, dropout rates may be as high as 25% at 1 year, but excluding these patients diminishes the interpretive value of these studies by showing outcomes to favour transplantation.[41] Bellavance *et al.* conducted a multi-institution study that compared outcomes of transplantation and resection, respectively, in 379 patients.[15] Although transplantation was noted to be associated with better outcome (66% vs. 46%), the lack of an ITT analysis is a major limitation of this study.[15]

To address the issue of ITT analysis in patients with well-compensated cirrhosis [Model for End-stage Liver Disease (MELD) scores of <10], Koniaris *et al.* performed a large, single-institution analysis.[9] In a subset ITT analysis of patients with tumours within the Milan Criteria and MELD scores of <10, the authors showed that the rate of 5-year OS after resection was 63%, whereas that after transplantation was 41% ($P = 0.036$). Therefore, the authors concluded that resection is associated with superior OS and should be used as first-line therapy in these patients.[9] Although these authors used an ITT analysis, they included patients with no underlying cirrhosis in the resection group.[9] Because such patients rarely meet criteria for transplantation, these two groups are not ideal for comparison.

The current search strategy was extensive and identified only six studies that had utilized an ITT strategy to compare outcomes after transplantation and resection, respectively, in patients with early HCC and reported 5-year survival in both groups of patients.[12,14,16,21,28,30] Similarly, only six studies ensured that the two comparison groups included patients with the same extent of underlying liver disease.[12,15,16,25,26,30] Only three studies performed an ITT analysis and used cases matched for extent of underlying liver disease.[12,16,30] This emphasizes the lack of studies that compare outcomes after transplantation and resection, respectively, in equally matched groups of patients diagnosed with HCC, using an ITT analysis.

The present meta-analysis has several limitations. The limitations of meta-analysis in general and the current meta-analysis strategy using binary outcomes have been discussed previously.[42] Briefly, an ideal meta-analysis should be performed using individual patient data; however, individual patient data may not always be available or practical to use. Therefore, the majority of

meta-analyses, including that reported here, are performed using summary data, which is a well-accepted form of analysis. The next best option involves the performance of meta-analysis using hazard ratios. Because the studies reviewed here usually did not report hazard ratios, this method could not be utilized. The odds ratio method, although not as accurate as methods using individual patient data and hazard ratios, was found to be the most feasible approach and was therefore used in the current study. The calculation of odds ratios based on the Kaplan–Meier approach can be criticized with reference to the issue of censored data; this remains a weakness of the current study. Further, only one indexed database (PubMed) was searched for literature and not all studies may be indexed in one database. However, an extensive backward search using cross-references and review articles was performed to ensure the completeness of the literature search. Because of the stringent inclusion and exclusion criteria applied in this study, only a small number of studies were identified as suitable for inclusion in the meta-analysis. These stringent criteria were necessary because the topic is controversial in nature and the current meta-analysis sought to resolve specific questions. Most of the data from the reviewed studies were noted to be of insufficient quality and were derived from small, single-institution studies that were retrospective in nature. Similarly, most studies were carried out by transplantation groups and may show a bias towards transplantation, and most studies were not of US origin and their results may not be extrapolated to a US population. Several other confounding factors were not evaluated, such as the performance status, age, eligibility and willingness for transplantation of patients. The present meta-analysis does not address the issue of salvage liver transplantation, the role of ablative therapies, the role of downstaging, living donor liver transplantation, cost differences and quality of life after transplantation and resection, respectively. Neither did the current study address the issue of recurrence-free survival as its aim was to look at difference in OS. Similarly, even within studies that have performed an ITT analysis, regional variations in allocation times and organ availability may have some bearing. Meta-analysis involves a statistical examination of a set of scientific studies and is not actually scientific study in itself. The results of the meta-analysis are as good as the studies it examines. The aim of the present meta-analysis was to evaluate the published evidence for OS after transplantation and resection, respectively, in patients with early HCC and well-compensated cirrhosis. Despite these limitations, the current study represents a comprehensive analysis of comparisons of outcomes after transplantation and resection, respectively. Its major strengths refer to its inclusion of patients with matched extents of underlying liver disease, and its emphasis on the use of ITT analysis.

In summary, although transplantation was noted to be superior in some settings, this superiority was not maintained in the critical ITT analysis. The non-inferiority of either transplantation or resection in the ITT analysis demonstrates that both will remain viable treatment options for patients with early HCC and well-compensated cirrhosis. The comprehensive analysis also underscores the lack of well-conducted comparative studies that include patients who are matched equally for the extent of tumour and underlying liver disease. Further well-designed studies are crucial to address this controversial issue in order to establish optimal strategies for the care of this group of patients.

Conflicts of interest

None declared.

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Supporting information

Additional supporting information may be found in the online version of this article.

Table S1. Characteristics of all 24 studies comparing outcomes of transplantation and resection, respectively, in patients with hepatocellular carcinoma.

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