

Is Resection Equivalent to Transplantation for Early Cirrhotic Patients with Hepatocellular Carcinoma? A Meta-Analysis

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Abstract

Background Whether liver resection or liver transplantation is optimal therapy for patients with hepatocellular carcinoma (HCC) remains undefined. A meta-analysis was conducted to answer this question.

Study Design This study performed a systematic review of the published literature between January 2000 and April 2012.

Results Nine retrospective studies, totaling 2,279 patients (989 resected and 1,290 transplanted), met the selection criteria. Older patients with larger tumors and less severe cirrhosis were identified in the resection group. At 1 year, resection demonstrated significantly higher overall [odds ratio (OR)=1.54; 95 % confidence interval (CI), 1.19–1.98; $p=0.001$], but equivalent disease-free survival (OR=0.93; 95 % CI, 0.53–1.63; $p=0.80$). At 5 years, there was no difference in overall survival (OR=0.86; 95 % CI, 0.61–1.21; $p=0.38$), but a higher disease-free survival in transplanted patients was observed (OR=0.39; 95 % CI, 0.24–0.63; $p<0.001$). When limiting our analysis to studies conducted in an intent-to-treat fashion, there was no difference in 5 year overall survival (OR=1.18; 95 % CI, 0.92–1.51; $p=0.19$), but a significantly higher disease-free survival (OR=0.76; 95 % CI, 0.57–1.00; $p=0.05$) in transplanted patients. At 10 years, transplantation had higher overall and disease-free survival rates.

Conclusion Liver transplantation in patients with HCC results in increased late disease-free and overall survival when compared with liver resection. Nonetheless, the benefit of liver transplantation is offset by higher short-term mortality, donor organ availability, and long transplant wait times associated with more patient deaths. Understanding these differences in survival is helpful in guiding treatment. However, a properly controlled prospective trial is needed to define how best to treat HCC patients who are candidates for either therapy.

Keywords Outcomes · Cancer · Treatment · Hepatectomy ·
Liver transplantation · Liver resection

Introduction

Management strategy for patients with hepatocellular carcinoma (HCC) continues to evolve.^{1,2} Patients with large HCC tumors are generally not considered appropriate candidates for transplantation and are typically recommended to undergo surgical resection of the tumor if a complete resection can be achieved. It is also widely accepted that for patients with advanced cirrhosis, small HCC tumors, and multifocal disease within Milan criteria with no vascular invasion, transplantation is the optimal treatment choice. Patients undergoing resection in the setting of advanced cirrhosis are at increased risk for liver failure and/or tumor recurrence. Aside from these well-defined clinical scenarios, the optimal use of resection or transplantation for patients with HCC and early cirrhosis remains unclear.^{3–12} Some authors have advocated for hepatic resection, showing

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equivalent, if not superior, long-term outcomes relative to transplantation, while others have found transplantation to result in improved outcomes in this group of patients.^{9,12–23}

Transplantation has the theoretical advantage of treating HCC while preventing the development of a second primary by eliminating the diseased liver. Nonetheless, this approach may be associated with a number of short-term complications related to the technical demands of transplantation, and some long-term complications associated with immunosuppression. Furthermore, livers for transplantation are a scarce resource, and each patient listed for transplantation does not find an available recipient organ while on the wait list. Thus, a fraction of patients with HCC listed for transplantation have disease progression, leading to dropout or death prior to receiving an organ.^{13,18,23} Given these concerns, it is important to clearly define the clinical outcomes for surgical resection versus transplantation in cases of HCC.

Several single institutional studies have compared resection and transplantation for the treatment of HCC with no consensus.^{3–22} Therefore, to better clarify whether resection or transplantation might be superior for the treatment of HCC, we have conducted a meta-analysis of all available studies published in the last decade comparing these two treatment strategies.

Materials and Methods

A systematic review of the literature was conducted to identify studies comparing liver resection and transplantation in patients with HCC. Studies were identified by searching MEDLINE and PubMed databases from the year January 2000 to April 2012. The following keywords and phrases were used to search the database: “hepatocellular carcinoma,” “liver resection,” “hepatectomy,” and “liver transplantation.” The Cochrane Central Register of Controlled Trials was queried for the same time period utilizing similar keywords and phrases. Additional studies were identified using a manual search of the references from key articles. Select transplant surgeons and surgical oncologists were queried for relevant additional studies and unpublished data.

Selection Criteria

All studies that compared survival between liver resection and transplantation for patients with hepatocellular carcinoma were considered for inclusion. The main inclusion criteria included follow-up evaluation of at least 5 years for overall survival, with or without 5-year disease-free survival. Survival was calculated from the date of the initial procedure to the date of death or the date of last contact, or from the date of diagnosis/placement on transplantation waiting list to the date of death or the date of last contact.

Both prospective and retrospective studies were included in our selection criteria, in addition to studies limited to patients who underwent primary liver transplantation, and those with a sample size of at least 30 patients in each of the resection and transplantation groups.

Data Abstraction

Data from selected articles were abstracted using a pre-designed form. Overall and disease-free survival rates for both liver resection and transplantation were analyzed. Data on 1-, 5-, and 10-year overall and disease-free survival were evaluated for both resection and transplantation groups. Each of the selected studies was not required to include all survival time points but needed to report at least 5-year overall survival rates per group. Other compiled data included: year of publication, study period, study design, age of participants, tumor size, treatment methods (resection or transplantation), and selection criteria for both treatment strategies.

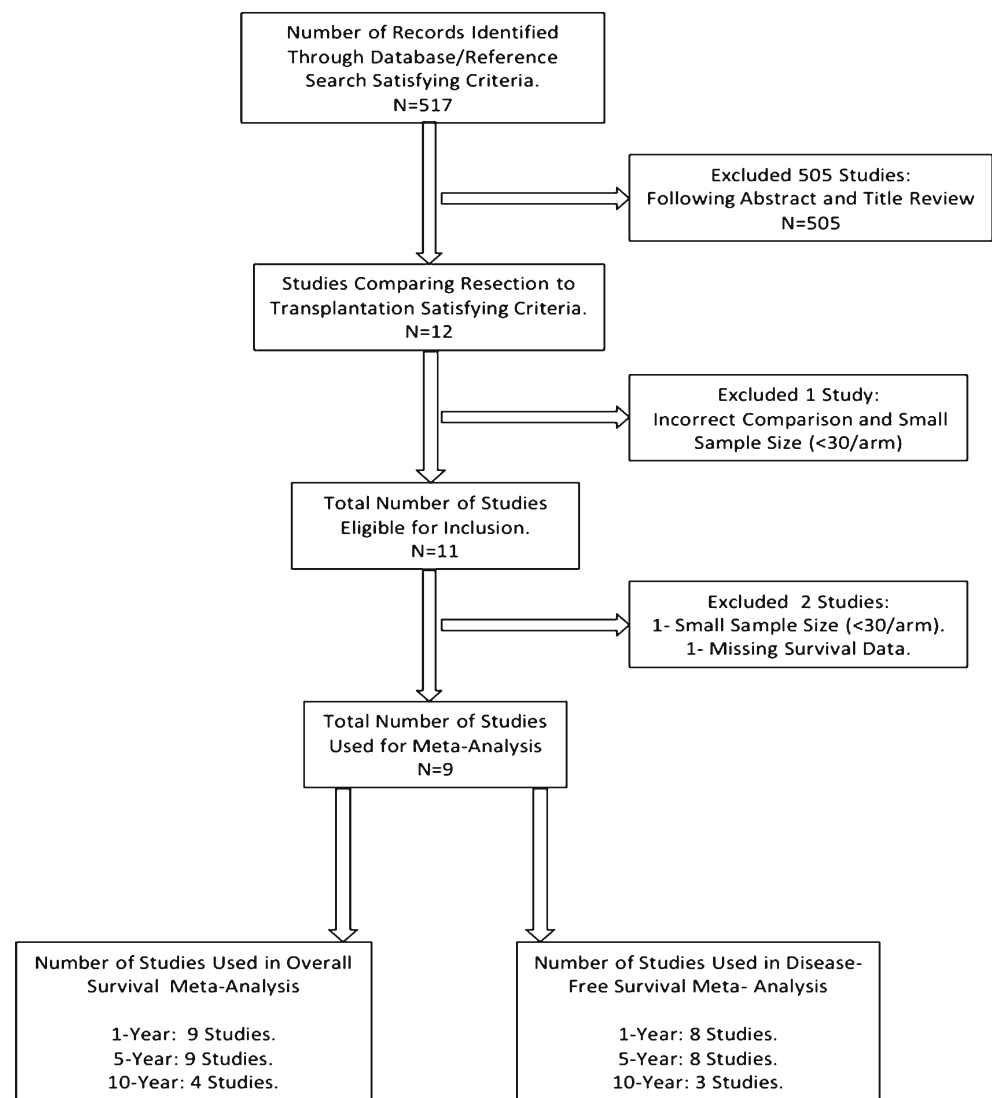
Studies were reviewed by two investigators (A.R. and F.P.) independently, and then compared for concordance. Overall, the concordance or inter-observer agreement was 98 % for all studies evaluated. Discrepancies were verified and resolved by consensus. For any unresolved discrepancies, another investigator (L.G.K.) reviewed the articles in question and acted as a third party to resolve disagreements. Overall, nine studies were identified that met the study criteria. A schematic depiction of study selection and abstraction is shown in Fig. 1.

Estimation of Treatment Effect

For all studies, survival rates with *p* values were obtained from the text, tables, or derived from Kaplan–Meier curves. One- and 5-year overall and disease-free survival rates for both liver resection and transplantation were reported in all nine studies used in the meta-analysis.^{8–10,15–18,24,25} Ten-year overall and disease-free survival rates were reported in only four studies.^{8,16,18,24} Disease-free survival rates were not available in one study.²⁴ The number of events for 1-, 5-, and 10-year survival rates for each study was calculated using survival rates and sample sizes in each arm.

Statistical Analysis

We used Comprehensive Meta-Analysis version 2 software (Comprehensive Meta-Analysis v2, 2005 Biostat Inc., Englewood, NJ) for all meta-analyses.²⁶ Odds ratios (ORs) with 95 % confidence intervals (CIs) were calculated for events in each study. Summary measures were obtained using both fixed and random effects models, and both models were then compared. If a considerable difference in effects between results of the two models, as well as significant heterogeneity, were

Fig. 1 Flow diagram for the selection of studies for meta-analysis

present, results of a random effect model were used. Heterogeneity of all studies was examined using Cochran's Q and I^2 tests. Publication bias was evaluated via funnel plots. Sensitivity analysis was performed in order to reexamine the effects of excluding outlier studies, as well as including studies that were initially excluded due to ineligibility for inclusion. The significance level for all statistical tests was set at $p \leq 0.05$.

Results

Flow of Manuscript Selection

Following a search of the MEDLINE, PubMed, and Cochrane databases; a manual review of references; and compilation of unpublished data from various transplant surgeons and surgical oncologists, a total of 517 studies were identified.¹⁴ One Italian study was identified by manual search of relevant

references, and translated to English. This study was found to meet all inclusion criteria and was included in our analysis.²⁴ A total of 12 potential studies based on abstract review satisfied inclusion criteria. Of the 12 studies, 1 study had a small sample size (less than 30, $N=18$ in one arm) with no direct comparison between primary liver transplantation and liver resection, and was excluded.²⁷ Two other studies were subsequently excluded from the meta-analyses for small sample size ($n=17$ in one arm)²⁸ and for an absence of sufficient follow-up for 5-year survival calculation. Therefore, a total of nine studies met our selection criteria and were included in our study (Fig. 1).

Characteristics of Included Studies

All studies were retrospective by design with a total of 2,279 patients (resection, $n=989$; transplantation, $n=1,290$), with 73 to 373 patients per study (Table 1). The mean age for this

Table 1 One, 5-, and 10-year overall and disease-free survival for all studies

Study, year publication	Study period	Study design	Total no. of pts.; non-ITT (ITT)	Group	Total no. of pts.; non-ITT (ITT)	Overall survival			Disease-free survival			
						1 year Non-ITT (ITT)	5 years Non-ITT (ITT)	10 years Non-ITT (ITT)	1 year Non-ITT (ITT)	5 years Non-ITT (ITT)	10 years Non-ITT (ITT)	
Koniaris et al. 2011 [25]	1999–2009	Retrospective	326 (363)	Resection Transplant	106 220 (257)	88 (88)	53 (53)	N/A	84	45	N/A	N/A
Lee et al. 2010 [9]	1997–2007	Retrospective	208	Resection Transplant	130 78	87 (81)	62 (52)	N/A	84	60	N/A	N/A
Del Gaudio et al. 2008 [15]	1996–2005	Retrospective	227 (373)	Resection Transplant	80 (80) 147 (293)	80	52	N/A	68	50	N/A	N/A
Shah et al. 2007 [18]	1995–2005	Retrospective	– (261)	Resection Transplant	121 – (140)	84	68	N/A	82	75	N/A	N/A
Poon et al. 2007 [17]	1995–2004	Retrospective	247 (313)	Resection Transplant	204 (228) 43 (85)	90 (90)	66 (66)	N/A	72 (72)	41 (41)	N/A	N/A
Margarit 2005 [16]	1988–2002	Retrospective	73	Resection Transplant	37 36	90 (80)	73 (58)	N/A	85 (76)	71 (54)	N/A	N/A
Adam et al. 2003 [8]	1984–2000	Retrospective	293	Resection Transplant	98 195	89	56	N/A	89	56	41	53
De Carlis 2001 [24]	1985–1999	Retrospective	275	Resection Transplant	154 121	90	64	N/A	76	60		
Figueras et al. 2000 [10]	1990–1999	Retrospective	120	Resection Transplant	35 85	68 (60)	81 (44)	N/A	69	42	N/A	N/A
						91 (88)	81 (44)	N/A	98	84	N/A	N/A
						92	70	50	84	39	18	56
						78	65	60	77	64	12	48
						90	50	28	90	18	33	71
						86	61	50	83	58	48	33
						85	40	30	86	38	71	N/A
						75	60	55	78	74	31	N/A
						83	51	N/A	70	31	N/A	N/A
						84	60	N/A	83	60	N/A	N/A

N/A not available, ITT intent-to-treat

cohort of patients ranged from 43 to 65 years of age (resection, mean=58, range=54.5 to 65 years; transplantation, mean=55, range=43 to 59.9 years), and the majority of patients were male (resection, 75 %; transplantation, 77 %). Overall, the mean tumor size ranged from 1.3 to 6.5 cm (resection, mean=4.4 cm, range=2.8–6.5 cm; transplantation, mean=3.0 cm, range=1.3–3.8 cm). The average number of nodules varied between 1 and 2.4 (resection, mean=1.2, range=1 to 1.4; transplantation, mean=1.9, range=1 to 2.4). Liver function was assessed using the Child–Turcotte–Pugh (CTP) classification in most studies. While most patients were categorized as CTP class A (CTP class A=82 %, B=17 %, and C=1 %) in the resection group, CTP class B was most commonly encountered in the transplantation group (CTP class A=28 %, B=48 % and C=24 %). Patient and tumor characteristics can be found in Table 2.

Meta-Analysis

A total of nine studies^{8–10,15–18,24,25} with 2,279 HCC patients treated either with liver resection ($n=989$) or transplantation ($n=1,290$) were included in our analysis. The majority of studies performed a non-intent-to-treat (non-ITT) analysis, omitting those patients who were placed on a transplantation waiting list but were unable to subsequently undergo transplantation. Several studies performed an intent-to-treat (ITT) analysis, in which patients who were listed but never transplanted due to tumor progression or death were included in the

data. Three studies reported results for both ITT and non-ITT analysis,^{15,17,25} one study performed an ITT analysis only,¹⁸ and the remaining five studies were limited to a non-ITT analysis alone.^{8–10,16,24} Hence, four and eight studies performed and reported an ITT or non-ITT analysis, respectively. Differences in overall and disease-free 1-, 5-, and 10-year survival rates between liver resection and transplantation were compared, and summary estimates were evaluated in three sets of meta-analyses: (1) a meta-analysis including only non-ITT analyses, (2) a meta-analysis including only ITT analyses, and (3) a meta-analysis including both non-ITT and ITT analyses.

Overall Survival

One-Year Overall Survival

When evaluating all studies, 1-year overall survival ranged from 80 to 92 % for patients treated with liver resection, and 75 to 98 % in patients treated with liver transplantation (Table 1). When restricting our meta-analysis to those studies that performed a non-ITT analysis ($n=8$), there was no significant difference in 1-year overall survival between resection and transplantation groups (87 and 85 % respectively, $p=0.21$), with an overall odds ratio of 1.21 (95 % CI, 0.90–1.64; $p=0.28$). No significant heterogeneity was found between studies ($Q=8.56$, $df=7$, $p=0.29$; $I^2=18.25$; Table 3, Fig. 2a). However, when performing a meta-analysis restricted to studies that performed an ITT analysis ($n=4$), 1-year overall survival rate was

Table 2 Patient demographics and tumor characteristics by study

Study, year publication	Treatment groups	Total pts	Mean age	Male gender (%)	Viral disease (%)	Childs A/B/C or average MELD	Mean max tumor size	No of nodules %S/M or mean	Time to transplant (days)
Koniaris et al. 2011 [25]	Resection	106	59.1	67.9	40.6	7.3	6.1	S 73 %; M 15 %	Median: 42
	Transplant	257	57.4	75.1	80.2	12.9	3.0	S 51 %, M 48 %	
Lee et al. 2010 [9]	Resection	130	54.5	79.2	86.9	113/17/0	4.5	1.2	N/A
	Transplant	78	51.1	84.6	85.9	35/43/0	3.8	2.1	
Del Gaudio et al. 2008 [15]	Resection	80	59	78.8	90.0	66/14/0	3.1	1.1	Mean: 154
	Transplant	293	54	83.6	90.8	23/139/131	1.3	1.7	
Shah et al. 2007 [18]	Resection	121	60	46	79.3	9	4	1.3	Median: 231
	Transplant	140	57	54	70.7	14	3.1	2.4	
Poon et al. 2007 [17]	Resection	204	56	80.9	93.6	195/9/0	<5	S 90 %, M 10 %	Median: 30
	Transplant	43	54	81.4	97.7	8/15/20	<5	S 72 %, M 28 %	
Margarit 2005 [16]	Resection	37	62	78.4	61	37/0/0	3.2	1	Mean: 95
	Transplant	36	59.9	61.1	83.3	36/0/0	3.0	1	
Adam et al. 2003 [8]	Resection	98	56.3	92.8	55.1	69/22/7	3.44	1.4	N/A
	Transplant	195	53.3	85.1	71.8	52/91/55	3.67	1.9	
De Carlis 2001 [24]	Resection	154	N/A	75.3	85.1	92/62 (B+C)	6.5	N/A	N/A
	Transplant	121		86.0	77.7	21/100 (B+C)	3.7		
Figueras et al. 2000 [10]	Resection	35	65	71.4	74.3	31/4/0	4.8	1.21	N/A
	Transplant	85	58	68.2	94.1	43/35/7	2.8	1.93	

N/A not available, S single, M multiple

significantly higher with resection as compared to transplantation (89 and 82 % respectively, $p=0.002$), with an overall odds ratio of 1.75 (95 % CI, 1.22, 2.49; $p=0.002$). Once again, no significant heterogeneity was observed between studies ($Q=3.58$, $df=3$, $p=0.31$; $I^2=16.21$; Table 3, Fig. 2b). Lastly, performing a meta-analysis inclusive of all nine studies (both non-ITT and ITT), the 1-year overall survival was significantly higher following resection when compared to transplantation (87 and 82 % respectively, $p<0.001$), with an overall odds ratio of 1.54 (95 % CI, 1.19, 1.98; $p<0.001$), and no significant heterogeneity between studies ($Q=10.22$, $df=8$, $p=0.25$; $I^2=21.71$; Table 3, Fig. 2c).

Five-Year Overall Survival

When evaluating all studies, 5-year overall survival ranged from 40 to 70 % for resection, and 52 to 81 % for transplanted patients (Table 1). When performing a meta-analysis inclusive of all studies that utilized a non-ITT analysis strategy, there was a significantly higher 5-year survival for transplanted patients when compared to the resection group (65 and 56 %, respectively; $p<0.001$), with an overall odds ratio of 0.62 (95 % CI, 0.50–0.76; $p<0.001$) and nonsignificant heterogeneity ($Q=5.52$, $df=7$, $p=0.60$; $I^2=0.00$) between studies (Table 3,

Fig. 3a). When performing a meta-analysis restricted to studies that conducted an ITT analysis, there was no significant difference in 5-year overall survival between resection and transplantation groups (59 and 56 %, respectively), with an overall odds ratio of 1.19 (95 % CI, 0.78, 1.80; $p=0.42$). However, there was significant heterogeneity between studies ($Q=8.61$, $df=3$, $p=0.04$; $I^2=65.17$) in this analysis (Table 3, Fig. 3b). Lastly, a meta-analysis on all studies (non-ITT and ITT) revealed no difference in 5-year overall survival in patients undergoing resection versus transplantation (54 and 58 %, respectively), with an overall odds ratio of 0.86 (95 % CI, 0.61, 1.21; $p=0.38$). Once again, significant heterogeneity ($Q=27.37$, $df=8$, $p=0.001$; $I^2=70.77$) was observed between studies (Table 3, Fig. 3c). However, when a sensitivity analysis was performed, excluding two outlier studies,^{17,24} the heterogeneity between studies became nonsignificant ($Q=10.00$, $df=6$, $p=0.13$; $I^2=39.97$), and the summary estimate for the differences between 5-year overall survival between resection and transplantation was also nonsignificant (OR=0.84; 95 % CI, 0.68, 1.04; $p=0.10$).

Ten-Year Overall Survival

Ten-year overall survival for all studies ranged from 28 to 50 % for resection and 50 to 60 % for transplantation

Table 3 Summary results of meta-analyses for the treatment of HCC patients with liver resection versus transplantation

	Type of analysis	Studies used	Percent survival		Odds ratio (OR) ^a	95 % CI	Significance <i>p</i> value	Measure of heterogeneity (<i>I</i> ²)
			Resection	Transplant				
Overall survival								
1 year	Non-ITT	8 [8–10,15–17,24,25]	87	85	1.21	0.90–1.64	0.21	18
	ITT	4 [15,17,18,25]	89	82	1.75	1.22–2.49	0.002	16
	Non-ITT+ITT	9 [8–10,15–18,24,25]	87	82	1.54	1.19–1.98	0.001	22
5 years	Non-ITT	8 [8–10,15–17,24,25]	56	65	0.62	0.50–0.76	<0.001	0
	ITT	4 [15,17,18,25]	59	56	1.19	0.78–1.80	0.42	65
	Non-ITT+ITT	9 [8–10,15–18,24,25]	54	58	0.86	0.61–1.21	0.38	71
10 years	Non-ITT	3 [8,16,24]	32	53	0.39	0.28–0.55	<0.001	0
	ITT	1 [18]	42	56	0.58	0.35–0.95	0.029	0
	Non-ITT+ITT	4 [8,16,18,24]	35	54	0.44	0.34–0.58	<0.001	9
Disease-free survival								
1 year	Non-ITT	7 [8–10,15–17,25]	75	84	0.67	0.38–1.18	0.17	68
	ITT	3 [15,18,25]	83	77	1.43	0.76–2.69	0.27	68
	Non-ITT+ITT	8 [8–10,15–18,25]	77	80	0.93	0.53–1.63	0.80	74
5 years	Non-ITT	7 [8–10,15–17,25]	40	64	0.29	0.20–0.42	<0.001	56
	ITT	3 [15,18,25]	49	54	0.76	0.57–1.00	0.05	0
	Non-ITT+ITT	8 [8–10,15–18,25]	42	58	0.39	0.24–0.63	<0.001	80
10 years	Non-ITT	2 [8,16]	14	49	0.16	0.09–0.28	<0.001	73
	ITT	1 [18]	41	53	0.63	0.38–1.03	0.06	0
	Non-ITT+ITT	3 [8,16,18]	27	51	0.27	0.10–0.76	0.014	85

ITT intent-to-treat

^a OR<1=favors transplant, OR>1=favors resection

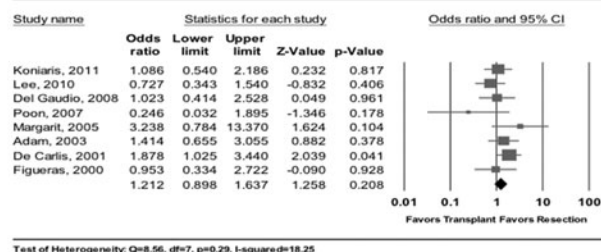
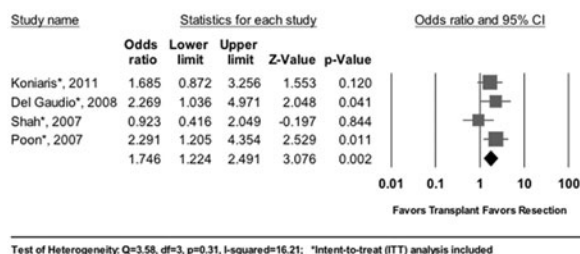
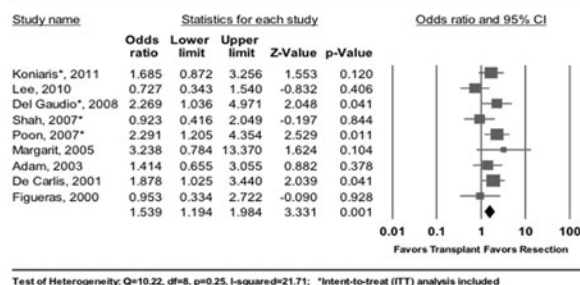
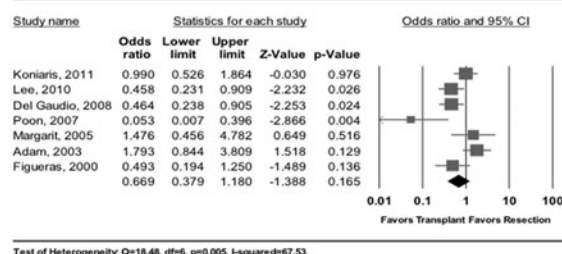
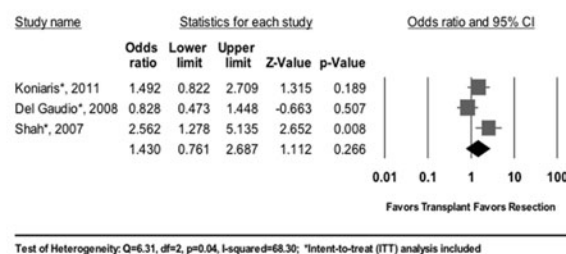
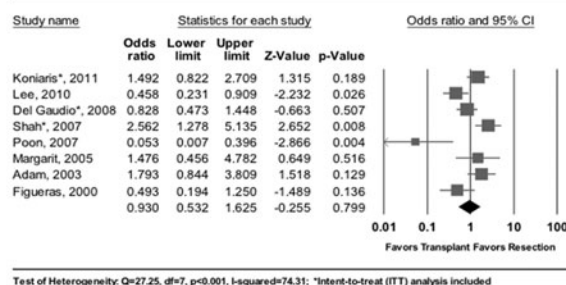
A) Non-ITT Studies.**1-Year Overall Survival in HCC Patients: Liver Resection vs. Transplant****B) ITT Studies.****1-Year Overall Survival in HCC Patients: Liver Resection vs. Transplant****C) Both Non-ITT and ITT Studies.****1-Year Overall Survival in HCC Patients: Liver Resection vs. Transplant****D) Non-ITT Studies.****1-Year Disease-free Survival in HCC Patients: Liver Resection vs. Transplant****E) ITT Studies.****1-Year Disease-free Survival in HCC Patients: Liver Resection vs. Transplant****F) Both Non-ITT and ITT Studies.****1-Year Disease-free Survival in HCC Patients: Liver Resection vs. Transplant**

Fig. 2 Overall (a–c) and disease-free (d–f) 1-year survival forest plots limited to a, d non-ITT studies; b, e ITT studies; and c, f both non-ITT and ITT studies with overall odds ratios in *black*

(Table 1). When performing a meta-analysis limited to studies that conducted a non-ITT analysis, there was a significantly higher 10-year overall survival for transplanted patients as compared to those undergoing resection (53 and 32 %, respectively), with an overall odds ratio of 0.39 (95 % CI, 0.28, 0.55; $p<0.001$). Heterogeneity between studies ($Q=1.58$, $df=2$, $p=0.45$; $I^2=0.00$) was nonsignificant (Table 3, Fig. 4a). Only one study performed an ITT analysis and reported a higher 10-year overall survival rate in transplanted patients as compared to resected patients (56 and 42 %, respectively), with an overall odds ratio of 0.58 (95 % CI, 0.35, 0.95; $p=0.03$; Table 3, Fig. 4c). When combining all studies that reported 10-year survival outcomes (non-ITT and ITT), there was an improved survival in transplanted versus resected patients (54 and 35 %, respectively), with an overall odds ratio of 0.44 (CI, 0.34, 0.58; $p<0.001$) and no significant heterogeneity ($Q=3.29$, $df=3$, $p=0.35$; $I^2=8.86$) between studies (Table 3, Fig. 4c).

Disease-Free Survival**One-Year Disease-Free Survival**

One-year disease-free survival rate for all studies ranged from 68 to 90 % for resected patients, and 76 to 98 % for transplanted patients (Table 1). For studies performing non-ITT analyses ($n=7$), there was no significant difference in 1-year disease-free survival between resected and transplanted patients (75 and 84 %, respectively, $p=0.17$). However, there was significant heterogeneity ($Q=18.48$, $df=6$, $p=0.005$; $I^2=67.53$) between the studies examined (Table 3, Fig. 2d). When limiting the data to studies that only performed an ITT analysis ($n=3$), there was no significant difference in survival between resection and transplantation groups (83 and 77 %, respectively; $p=0.27$), although there was a trend for higher survival for resected patients (overall odds ratio, 1.43; 95 % CI, 0.76, 2.69; $p=0.27$). However,

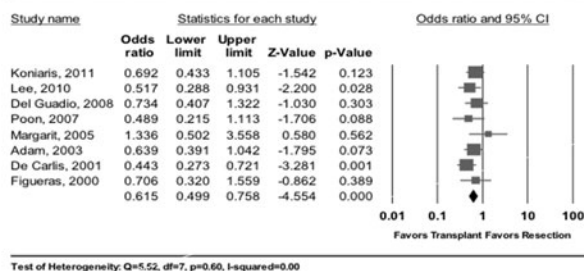
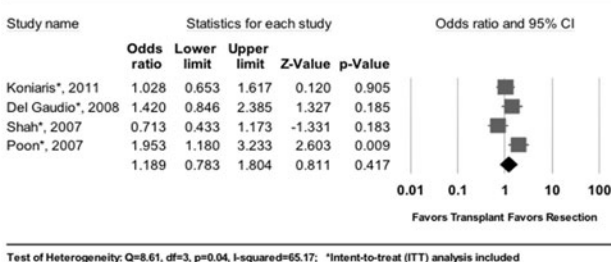
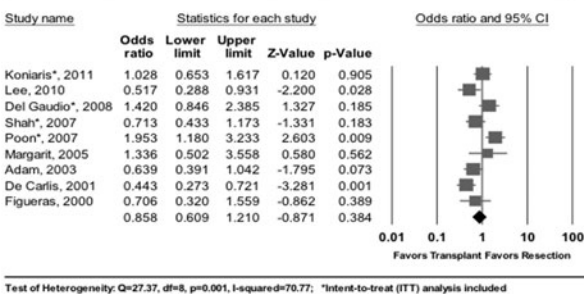
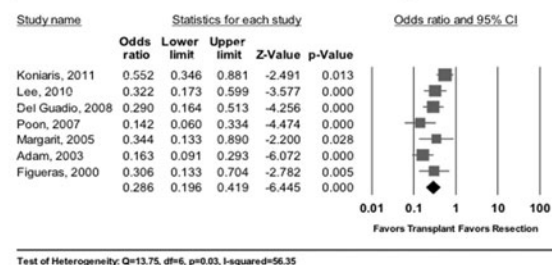
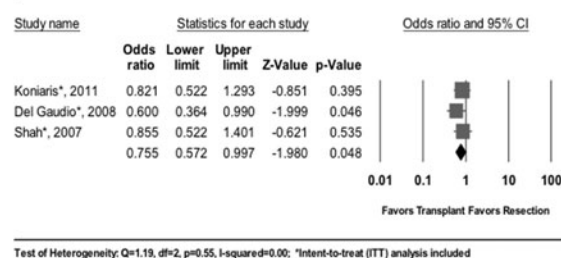
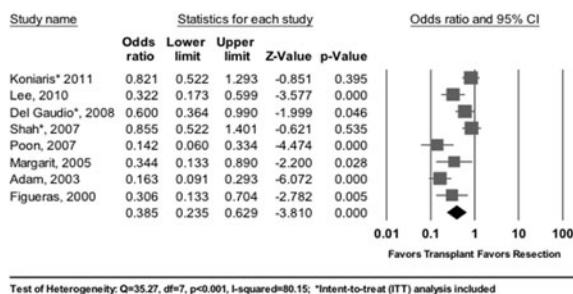
A) Non-ITT Studies.**5-Year Overall Survival in HCC Patients: Liver Resection vs. Transplant****B) ITT Studies.****5-Year Overall Survival in HCC Patients: Liver Resection vs. Transplant****C) Both Non-ITT and ITT Studies.****5-Year Overall Survival in HCC Patients: Liver Resection vs. Transplant****D) Non-ITT Studies.****5-Year Disease-free Survival in HCC Patients: Liver Resection vs. Transplant****E) ITT Studies.****5-Year Disease-free Survival in HCC Patients: Liver Resection vs. Transplant****F) Both Non-ITT and ITT Studies.****5-Year Disease-free Survival in HCC Patients: Liver Resection vs. Transplant**

Fig. 3 Overall (a–c) and disease-free (d–f) 5-year survival forest plots limited to a, d non-ITT studies; b, e ITT studies; and c, f both non-ITT and ITT studies with overall odds ratios in *black*

significant heterogeneity was found between studies ($Q=6.31$, $df=2$, $p=0.04$; $I^2=68.30$; Table 3, Fig. 2e). Lastly, when performing a meta-analysis on all studies (non-ITT and ITT), there was no significant difference between resected and transplanted patients (77 and 80 %, $p=0.80$), with an overall odds ratio of 0.93 (95 % CI, 0.53, 1.63; $p=0.80$). Again, significant heterogeneity ($Q=27.25$, $df=7$, $p<0.001$; $I^2=74.31$) was noted between studies (Table 3, Fig. 2f).

Five-Year Disease-Free survival

Five-year disease-free survival rate for all studies ranged from 18 to 56 % for resection, and 54 to 84 % for transplanted patients (Table 1). For those studies performing non-ITT analysis, 5-year disease-free survival was significantly higher in transplanted patients when compared to resected

patients (64 and 40 %, respectively; $p<0.001$), with an overall odds ratio of 0.29 (95 % CI, 0.20, 0.42; $p<0.001$). Significant heterogeneity ($Q=13.75$, $df=6$, $p=0.03$; $I^2=56.35$) was observed between studies, once again (Table 3, Fig. 3d). In studies that conducted ITT analysis, we found a marginally significant higher 5-year disease-free survival in transplanted patients when compared to resected patients (54 and 49 %, respectively; $p=0.05$), with an overall odds ratio of 0.76 (95 % CI, 0.57, 1.00; $p=0.05$), and no significant heterogeneity between studies ($Q=1.19$, $df=2$, $p=0.55$; $I^2=0.00$; Table 3, Fig. 3e). A meta-analysis that included both non-ITT and ITT data demonstrated a significantly higher 5-year disease-free survival for transplanted patients when compared to resected patients (58 and 42 %, respectively; $p<0.001$), with an overall odds ratio of 0.39 (95 % CI, 0.24, 0.63; $p<0.001$). Once again, significant

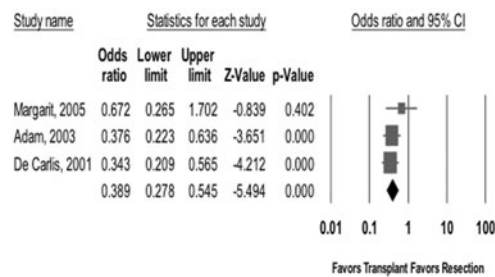
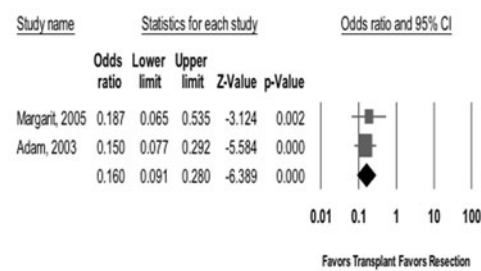
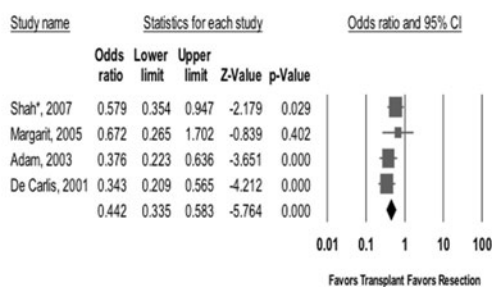
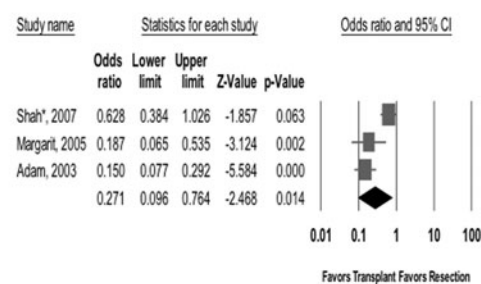
A) Non-ITT Studies.**10-Year Overall Survival in HCC Patients: Liver Resection vs. Transplant**Test of Heterogeneity: $Q=1.58$, $df=2$, $p=0.45$, $I^2=0.00$ **B) Non-ITT Studies.****10-Year Disease-free Survival in HCC Patients: Liver Resection vs. Transplant**Test of Heterogeneity: $Q=0.12$, $df=1$, $p=0.73$, $I^2=0.00$ **C) Both Non-ITT and ITT Studies.****10-Year Overall Survival in HCC Patients: Liver Resection vs. Transplant**Test of Heterogeneity: $Q=0.23$, $df=3$, $p=0.35$, $I^2=8.86$; *Intent-to-treat (ITT) analysis included**D) Both Non-ITT and ITT Studies.****10-Year Disease-free Survival in HCC Patients: Liver Resection vs. Transplant**Test of Heterogeneity: $Q=13.04$, $df=2$, $p=0.001$, $I^2=84.66$; *Intent-to-treat (ITT) analysis included

Fig. 4 Ten-year overall (a, c) and disease-free (b, d) survival forest plots limited to (a, b) non-ITT studies and (c, d) a combination of both non-ITT and ITT studies with overall odds ratios in *black*

heterogeneity ($Q=35.27$, $df=7$, $p<0.001$; $I^2=80.15$) was evident between studies (Table 3, Fig. 3f).

Ten-Year Disease-Free Survival

Three studies reported 10-year disease-free survival rates, which ranged from 12 to 41 % for resected patients, and 48 to 71 % for transplanted patients (Table 1). A meta-analysis limited to the two non-ITT studies found a significantly higher 10-year disease-free survival in transplanted patients compared to resected patients (49 and 14 %, respectively; $p<0.001$), with an overall odds ratio of 0.16 (95 % CI, 0.09, 0.28; $p<0.001$), and no significant heterogeneity between studies ($Q=0.12$, $df=1$, $p=0.73$; $I^2=0.00$; Table 3, Fig. 4b). When evaluating the single study that conducted an ITT analysis, there was no statistically significant difference in 10-year disease-free survival between resected and transplanted patients (41 and 53 %, respectively; $p=0.06$; Fig. 5). Lastly, a meta-analysis inclusive of all three studies that reported 10-year disease-free survival rates reported a significantly higher 10-year disease-free survival in transplanted patients compared to resected patients (51 and 27 %, respectively; $p=0.014$), with an overall odds ratio of 0.27

(95 % CI, 0.10, 0.76; $p=0.01$). Significant heterogeneity was found between studies ($Q=13.04$, $df=2$, $p=0.001$; $I^2=84.66$; Table 3, Fig. 4d).

Publication Bias and Sensitivity Analysis

Funnel plots were used to evaluate the possibility of a publication bias (Fig. 6a, b). A funnel plot analyzing all studies utilized in the 5-year overall survival analyses showed no asymmetry. When excluding the two outlier studies identified, the funnel plot did not demonstrate asymmetry, indicating minimal publication bias (Fig. 6b). A sensitivity analysis, excluding the two outlier studies, failed to show a change in overall effects (OR=0.84; 95 % CI, 0.68–1.04; $p=0.10$, vs. pooled OR=0.86; 95 % CI, 0.61–1.21; $p=0.38$), and there was no significant heterogeneity noted between studies ($Q=10.00$, $df=6$, $p=0.13$; $I^2=39.97$). A sensitivity analysis conducted on all studies (non-ITT and ITT, $n=11$) utilized in 1-year overall survival analyses, including all initially excluded studies, exhibited a pooled odds ratio of 1.43 (95 % CI, 1.13–1.83, $p=0.004$), which was similar to the pooled odds ratio found for 1-year overall

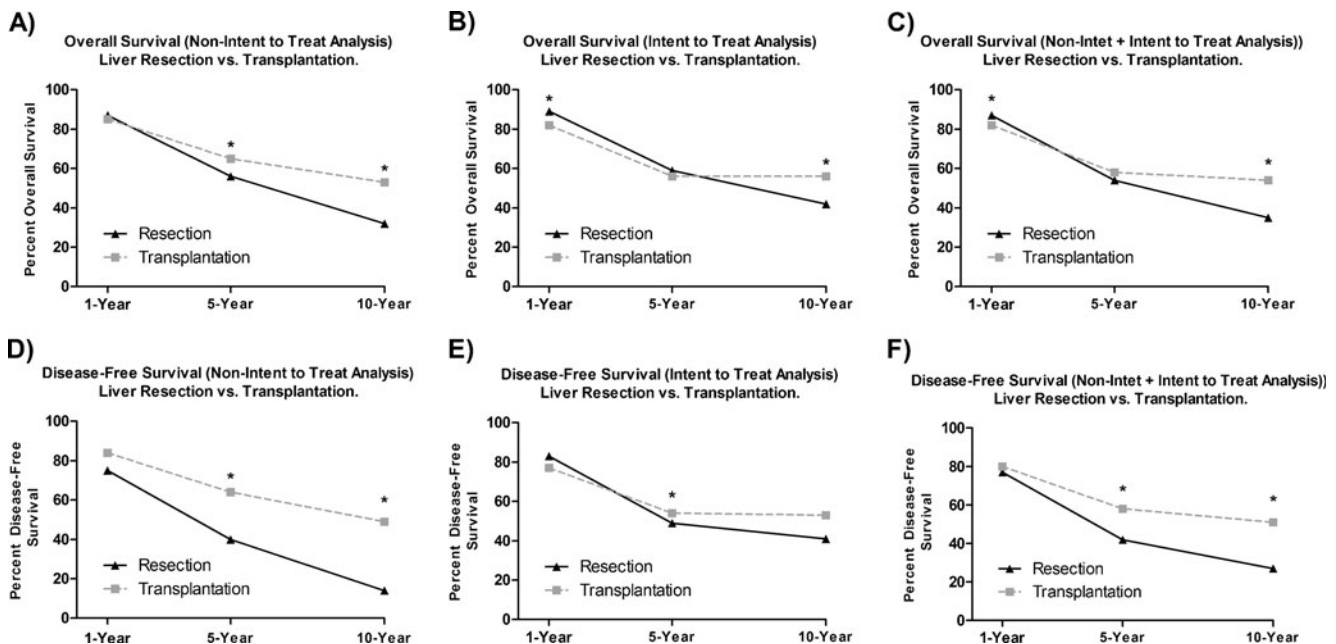


Fig. 5 Summary graphs of overall (a–c) and disease-free (d–f) survival at 1, 5, and 10 years by type of transplantation analysis: non-ITT (a, d), ITT (b, e), or both non-ITT and ITT (c, f). * $p \leq 0.05$, significant

survival in the current study (ITT and non-ITT, $n=9$; OR=1.54; 95 % CI, 1.19–1.98; $p=0.001$). Also, in a similar sensitivity analysis conducted on all studies ($n=11$) for 5-year overall survival rates, the pooled odds ratio was found to be 0.81 (95 % CI, 0.57–1.15; $p=0.23$), which was similar to the pooled odds ratio of 0.86 (95 % CI, 0.61–1.21; $p=0.38$) found in the meta-analysis that excluded the two studies not meeting primary selection criteria.

All Studies

In summary (Table 3, Fig. 5a–f), data compiled from all studies (non-ITT and ITT) and from those studies

performing ITT analysis alone demonstrated three key findings: 1-year overall survival was significantly higher for patients undergoing liver resection, 5-year overall survival was comparable for both groups, and 10-year overall survival was significantly higher in transplanted patients. Moreover, when examining data from non-ITT studies alone, no difference was observed in 1-year overall survival, but 5-year and 10-year overall survival rates were significantly higher for transplanted patients. No difference in 1-year disease-free survival was found between resected and transplanted patients, but significantly higher 5-year and 10-year disease-free survival rates were observed in transplanted patients.

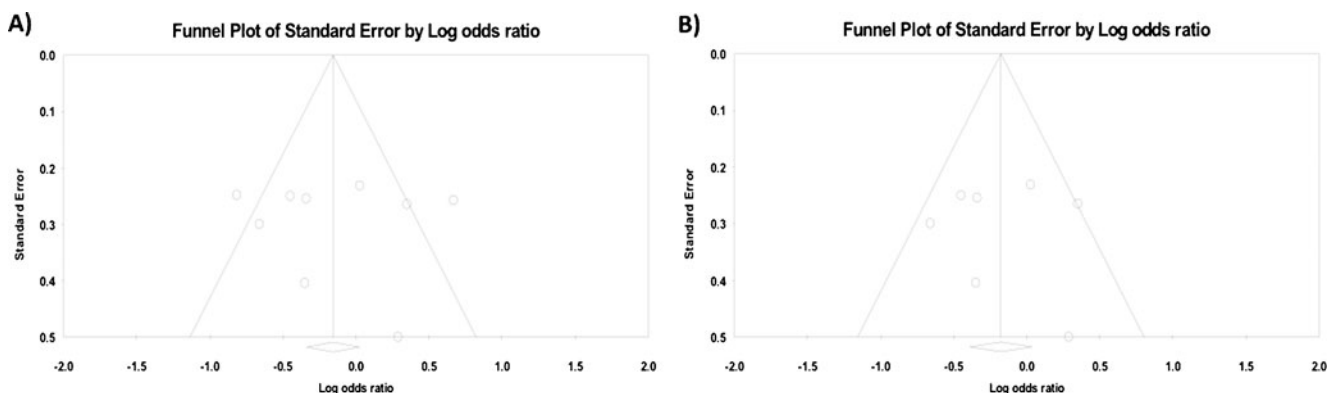


Fig. 6 Funnel plots evaluating publication bias including all studies (a) and excluding the two outlier studies (b)

Discussion

The aim of this meta-analysis was to objectively compare the role of liver resection to transplantation in the treatment of patients with HCC. To date, there remains no consensus regarding the best operative management for patients with HCC. Some authors have advocated for resection while others for transplantation. We performed three sets of meta-analysis, based on non-ITT and ITT studies, to evaluate the survival of patients following liver resection and transplantation.

The patient population undergoing liver resection was older and had larger tumors, but also demonstrated better hepatic function [lower Child–Turcotte–Pugh and Model for End-Stage Liver Disease (MELD) class]. As such, the resection group exhibited improved short-term outcomes, comparable at 5 years, when compared to the transplantation group. When evaluating disease-free survival, resection was comparable to transplantation at 1 year, but inferior to transplantation at 5 and 10 years. Furthermore, 1-year overall survival was found to be significantly higher in HCC patients who underwent resection versus transplantation when including both non-ITT and ITT analyses, with similar survival rates seen when examining ITT analyses alone. Exclusion of ITT studies demonstrated an equivalent 1-year overall survival between resected and transplanted patients (OR, 1.21; CI, 0.90–1.64; $p=0.21$), nonsignificantly favoring resection. The difference in 1-year disease-free survival was not significant between resected and transplanted patients, irrespective of transplant patient allocation (ITT and non-ITT). With higher or equivalent overall survival, and equivalent disease-free survival, the findings from our study favor resection to transplantation for 1-year survival. Several factors may explain these findings. First, preserved liver function and a reduced incidence of hepatitis as the etiology of cirrhosis may contribute to this observation. Second, these patients avoid a waiting list prioritization unlike those HCC patients undergoing transplantation. Third, higher posttransplantation complications observed in the first year, such as infection secondary to immunosuppression,^{29–31} renal failure,³² multi-organ failure,³¹ and acute graft rejection,³³ may also partially contribute to the superior outcome in resected patients at 1 year.

When evaluating 5-year outcomes, including both ITT and non-ITT studies, overall survival was similar between resection and transplantation groups (54 vs. 58 %, $p=0.38$). Similarly, there was no significant difference in survival found between the two groups when limited to ITT analysis alone. In contrast, when the analysis was conducted in non-ITT studies, transplantation appeared to be significantly superior. Furthermore, transplantation had a higher 5-year disease-free survival, irrespective of transplant patient allocations (ITT, non-ITT, or both). With respect to 5-year survival, resection was equivalent to transplantation when

analysis was conducted in an intent-to-treat basis, while transplantation was superior when analysis was conducted in non-ITT fashion. This finding may indicate that the higher recurrence of HCC and deaths in the resection group found during this 5-year period was counterbalanced by patient death secondary to disease progression, during the period when patients were listed for transplantation but were subsequently deemed ineligible to receive an organ. Overall, 5-year disease-free survival was improved in the transplantation group, in both ITT and non-ITT analyses, likely due to higher disease recurrence in the remnant liver of resected patients.

Transplantation was found to be superior to resection for both overall and disease-free 10-year survival, indicating that higher cirrhotic status (CTA class B and C) may be better managed with transplantation over resection. It also indicates that beyond 5 years, HCC recurs in many patients that were treated with resection. Nonetheless, only three studies had data available for 10-year survival, and among them, only one of these was conducted as an ITT analysis. In summary, when including all studies (both ITT and non-ITT), resection provided an improved and equivalent 1- and 5-year overall survival, respectively, while transplantation achieved the highest 10-year overall survival. Furthermore, the resection group was found to have inferior 5- and 10-year disease-free survival rates.

With an exhaustive demand for donor livers, transplantation may not be the most effective primary treatment strategy for patients with HCC who are candidates for either therapy. Our study suggests that the current literature identifies transplantation as superior for the treatment of patients with HCC who are candidates for both therapies, but only after periods of prolonged follow-up. At 1- and 5-year intervals posttreatment, resection is superior or equivalent to transplantation, particularly when also considering patients listed but never transplanted. The ability to offer transplantation as treatment for HCC depends upon local organ availability, as well as the list prioritization of tumor patients for transplantation. Organ distribution networks in many countries do not preferentially allocate livers to patients with HCC, heavily skewing the treatment of HCC toward resection or ablation. Dropout rates on the transplant list are associated with the duration of waiting time, with 6 months representing the point at which progression and dropout worsens without interval ablation.¹³ Certainly, centers with protracted waiting lists should consider this in discussing potential resection or transplantation with their patients. The use of transplantation as salvage therapy for patients with HCC who had undergone previous resection remains an area of study and has been supported in recent studies.^{34–36}

The current study has several limitations. First, this meta-analysis is based on retrospective studies, with no prospective randomized data available, which likely has led to a selection bias. Secondly, there is a possibility of publication bias. Funnel plots for each of the comparisons made, however, did not show a significant difference. Furthermore, when performing sensitivity analysis, excluding outlier studies, there was no significant change in pooled odds ratios. Hence, a publication bias, if present, should be minimal. Moreover, heterogeneity between studies was observed in several of our meta-analyses. Since the selected studies have diverse clinical and methodological backgrounds, some heterogeneity between studies, particularly when ITT analysis was combined with non-ITT analysis, is expected. Our meta-analyses utilized both fixed and random models with compared effects. When large differences in effect and significant heterogeneity were found, a random effects model was utilized. Also, sensitivity analysis was performed excluding study outliers and effects were compared, which did not show any significant difference.

Another variable was that the number of resected patients requiring re-resection or additional therapies (radiofrequency ablation or chemosembolization) was unknown. These adjunct therapies may have prolonged survival in the resected cohorts. Similarly, the number of transplanted patients, who underwent interventions while awaiting transplantation, also remained unknown.

It has been shown that dropout rates for HCC patients increases with time to transplantation, due to a progression of disease.^{13,18,23} Therefore, with some studies having longer waitlist times than others, survival for transplanted patients may be understated. In addition, some of the included studies were performed in countries without preference for transplantation in patients with HCC. As a result, waiting times may have been prolonged, resulting in increased dropout rates and worsened survival. Also, stratification for transplantation in the USA has changed in the last decade, with the advent of the Milan criteria and prioritization of patients with HCC. With many studies having overlapping periods, prior to and following the introduction of the Milan criteria, we may have included patients who may not have been previously considered candidates for transplantation. Most of tumors encountered in the studies, however, had mean tumor sizes that fell within the Milan criteria, thereby satisfying current organ allocation guidelines. Nonetheless, most resection series included patients with considerably larger tumors.

Beside specific tumor-related parameters and prolonged wait times, other factors such as age, medical comorbidities, clinical condition, and liver function may have affected prognosis, and thereby the selection process, for treatment

strategies. In our study, patients in the resection group were older and had larger tumors, while the transplantation group had more severe liver disease (Child's class B/C). The resection group had better liver function, with Child's class A cirrhosis being most common. A comparison of survival rates of cirrhotic and non-cirrhotic patients between the two groups was not possible, however, due to the lack of specific data on survival rates based on patients' cirrhotic status in these studies. Hence, this may represent a possible confounder in our study as transplanted patients had more severe cirrhotic disease and a worse overall survival (Table 2). However, when reviewing the one study which restricted their analysis to patients with only Child's class A disease for both treatment groups, there was a significant improvement in overall 1- and 5-year survival among resected patients.¹⁶

In conclusion, our study demonstrated better 1-year overall and disease-free survival in patients treated with liver resection. When dropout due to disease progression and death secondary to long wait list time for liver transplantation was taken into account, resection was found to be equivalent to transplantation at 5 years. For those patients expected to have longer survival, transplantation had improved 10-year overall and disease-free survival, and may be the preferred treatment in patients with more severe cirrhotic liver disease. Resection should be considered as first-line therapy for patients with reasonably preserved liver function in regions with long transplant wait times, reserving primary liver transplantation for patients who are not candidates for resection (Table 4). In regions where wait times are short, resection likely should be limited to those with MELD scores under 10 who meet Child's class A criteria.

When trying to navigate surgical options for HCC patients, there are several factors to consider. Our meta-analysis utilized the best available data to evaluate resection versus transplantation options in this patient population, and should serve as a guide when trying to best treat patients with HCC. However, a more comprehensive, randomized controlled trial would be optimal to further study this area.

Table 4 Factors favoring resection vs. transplantation

Favors resection	Favors transplant
Better liver function (CTP class A)	Poorer liver function (CTP class B/C)
Larger tumors (USCF criteria)	Smaller tumors (Milan criteria)
Less cirrhosis	More cirrhosis
Shorter life expectancy (<5 years)	Longer life expectancy (>5 years)
Long wait time for transplantation	Short wait time for transplantation

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