World Journal of Gastroenterology

Online Submissions: http://www.wjgnet.com/1007-9327office
wjg@wjgnet.com
doi:10.3748/wjg.v18.i19.2415

World J Gastroenterol 2012 May 21; 18(19): 2415-2422
ISSN 1007-9327 (print) ISSN 2219-2840 (online)

BRIEF ARTICLE

Salvage liver transplantation in the treatment of hepatocellular carcinoma: A Meta-analysis

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Received: August 15, 2011 Revised: December 5, 2011
Accepted: March 10, 2012
Published online: May 21, 2012

Abstract

AIM: To evaluate survival and recurrence after salvage liver transplantation (SLT) for the treatment of hepatocellular carcinoma (HCC) compared with primary liver transplantation (PLT) using a meta-analysis.

METHODS: Literature on SLT versus PLT for the treatment of HCC published between 1966 and July 2011 was retrieved. A meta-analysis was conducted to estimate pooled survival and disease-free rates. A fixed or random-effect model was established to collect the data.

RESULTS: The differences in overall survival and disease-free survival rates at 1-year, 3-year and 5-year survival rates were not statistically significant between SLT group and PLT group ($P > 0.05$). After stratifying the various studies by donor source and Milan criteria, we found that: (1) Living donor liver transplantation recipients had significantly higher 1-year survival rate, lower 3-year and 5-year survival rates compared with deceased-donor liver transplantation (DDLT) recipients. And in DDLT recipients they had better 1-year and 5-year disease-free survival rate in SLT group; and (2) No difference was seen in 1-year, 3-year and 5-year survival rates between two groups who beyond Milan criteria at the time of liver transplantation.

CONCLUSION: SLT can be effectively performed for patients with recurrence or deterioration of liver function after hepatectomy for HCC. It does not increase the perioperative mortality and has a similar long-term survival rates compared to PLT.

Key words: Salvage liver transplantation; Primary liver transplantation; Hepatocellular carcinoma; Meta-analysis; Survival rate

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Li HY, Wei YG, Yan LN, Li B. Salvage liver transplantation in the treatment of hepatocellular carcinoma: A Meta-analysis. *World J Gastroenterol* 2012; 18(19): 2415-2422 Available from: URL: http://www.wjgnet.com/1007-9327/full/v18/i19/2415.htm DOI: http://dx.doi.org/10.3748/wjg.v18.i19.2415

INTRODUCTION

In a normal liver, liver resection for hepatocellular carcinoma (HCC) is the primary treatment of choice. But in cirrhotic livers, the presence of HCC and the limited liver capacity are the two intertwined issues rendering the HCC unresectable. Primary liver transplantation (PLT) is the most effective treatment for such HCC patients, especially for those who meet Milan criteria (solitary liver nodule not exceeding 5 cm in maximum diameter, or 2 or 3 tumors not exceeding 3 cm in diameter)[1]. It has been manifested to provide a considerable disease-free

survival and to be the first choice for these patients. Due to shortage of available donors, long waiting times may harm the benefit that might be acquired from PLT. Salvage liver transplantation (SLT) has been proposed and performed for those who undergo primary liver resection for HCC or HCC recurrence or deterioration of liver function[2]. SLT proposes liver resection as a bridge to prevent tumor progression in the waiting list. Although SLT might be an alternate choice for HCC patients as the preferred treatment, long-term results are difficult to ascertain. Moreover, few data are available on the overall and disease-free survival of patients. A few researches concern on the comparison between the result of SLT and PLT. In order to reduce research bias and difference, we did a meta-analysis to compare survival and recurrences for SLT strategy versus PLT in the treatment of HCC patients, in order to provide a reference for clinical practice.

MATERIALS AND METHODS

Literature search strategy

Search was applied to the following electronic databases: PubMed (1966 to July 2011), Embase (January 1996 to July 2011), CNKI (January 1996 to July 2011) and Cochrane database. The following key words were used: "liver resection" or "hepatectomy"; "liver transplantation" or "transplantation" or "salvage liver transplantation" or "salvage transplantation"; "hepatocellular carcinoma" or "HCC". The search was limited to the English language and humans. The relevant reference lists of reviews were also searched at the same time. Abstracts or unpublished studies were not considered. If more than 1 study was published by the same author using the same case series, only the most detailed study was included. And if necessary, authors were contacted to obtain more data on their study.

Definitions

SLT was defined as a liver transplantation performed for recurrent HCC or deterioration of liver function after primary liver resection.

Inclusion, exclusion criteria and quality of the studies

Inclusion criteria were as follows: (1) having definition of SLT; (2) follow-up 12 mo at least; (3) case-control or cohort design; and (4) sufficient data were obtained to calculate odds ratio (OR) with confidence interval (CI). Reasons for exclusion were: (1) no-control; (2) duplicate; and (3) no useable data reported. We also excluded articles published before 1996 because there was no definition for "SLT".

The scoring system was adapted from Stahl, the Cochrane Collaboration and others[3-5]. This system suits not only randomized control trial (RCT) but controlled trial or other studies well. Questions were placed on a 3 point scale: unclear/inadequate (0), adequate (1), good (2). Articles were considered for inclusion if their summary score exceeded 30.

Table 1 Details of studies included in the meta-analysis

Author	Year	Country	Study design	SLT (cases)	PLT (cases)	Score
Adam *et al*[6]	2003	France	Case-control	17	200	32
Belghiti *et al*[7]	2003	France	Case-control	18	70	33
Concejero *et al*[8]	2008	China	Case-control	7	28	31
Del Gaudio *et al*[9]	2008	Italy	Case-control	16	147	32
Facciuto *et al*[10]	2008	USA	Case-control	5	32	30
Hwang *et al*[11]	2007	Korea	Case-control	17	200	31
Kim *et al*[12]	2008	Korea	Case-control	15	31	30
Margarit *et al*[13]	2005	Spain	Case-control	5	36	31
Sapisochin *et al*[14]	2010	Spain	Case-control	17	34	33
Shao *et al*[15]	2008	China	Case-control	15	62	30
Vennarecci *et al*[16]	2007	Italy	Case-control	9	37	30

SLT: Salvage liver transplantation; PLT: Primary liver transplantation.

Data extraction

All data were extracted independently by 2 reviewers according to the selection criteria. We resolved disagreement through discussion. The following data were extracted: the last name of the first author, study design, publication year, definition of SLT, the type of population described [adults or children (< 18 years)], country of transplant center, number of SLT cases and control (PLT) studies, overall survival, overall recurrence and assessment of risk factors.

Statistical analysis

Meta-analysis was performed using fixed-effect or random-effect methods, depending on the absence or presence of significant heterogeneity. Statistical heterogeneity between trials was evaluated by the Cochran χ^2 test and was considered significant when $P < 0.10$. In the absence of statistically significant heterogeneity, the Mantel-Haenszel method in the fixed-effect model was used for the meta-analysis. Otherwise, the DerSimonian and Laird method in the random-effect model was selected.

The OR with 95% CI was used to assess treatment efficacy. The combined result was an average OR and 95% CI weighted according to the standard error of the OR of the trial. $P < 0.05$ was considered statistically significant. We used funnel plots to assess the publication bias, and tested for funnel plot asymmetry using Egger's test and Begg's test. All analyses were performed with Review Manager version 5.0.23 (RevMan, Cochrane Collaboration, Oxford, England).

RESULTS

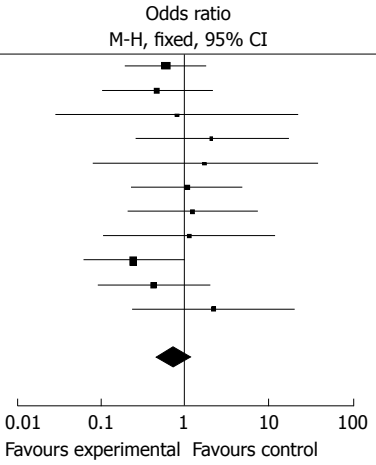
Studies included in the meta-analysis

There were 410 papers relevant to the search words. Via steps of screening the title, abstract reviewing and article reviewing, 11 studies which included 141 SLT cases and 872 PLT cases were identified to match our inclusion criteria[6-16]. Studies had been carried out in France, Italy, USA, China, Spain, Korea and Chinese Taiwan. Details of studies and the methodological quality of the studies assessed according to a score system described above are described in Table 1.

A Review: SLT *vs* PLT; Comparison: SLT *vs* PLT; Outcome: 1-year survival rates

Study or subgroup	SLT Events	SLT Total	PLT Events	PLT Total	Weight %	Odds ratio M-H, fixed, 95% CI
Adam *et al*[6]	12	17	156	195	20.9	0.60 (0.20, 1.80)
Belghiti *et al*[7]	15	18	64	70	12.4	0.47 (0.11, 2.09)
Concejero *et al*[8]	7	7	27	28	2.1	0.82 (0.03, 22.20)
Del Gaudio *et al*[9]	15	16	129	147	4.5	2.09 (0.26, 16.81)
Facciuto *et al*[10]	5	5	28	32	2.1	1.74 (0.08, 37.08)
Hwang *et al*[11]	15	17	175	200	9.2	1.07 (0.23, 4.97)
Kim *et al*[12]	13	15	26	31	6.4	1.25 (0.21, 7.34)
Margarit *et al*[13]	4	5	28	36	3.9	1.14 (0.11, 11.72)
Sapisochin *et al*[14]	10	17	29	34	22.6	0.25 (0.06, 0.95)
Shao *et al*[15]	12	15	56	62	12.4	0.43 (0.09, 1.96)
Vennarecci *et al*[16]	8	9	29	37	3.6	2.21 (0.24, 20.35)
Total (95% CI)		141		872	100.0	0.74 (0.46, 1.21)
Total events	116		747			

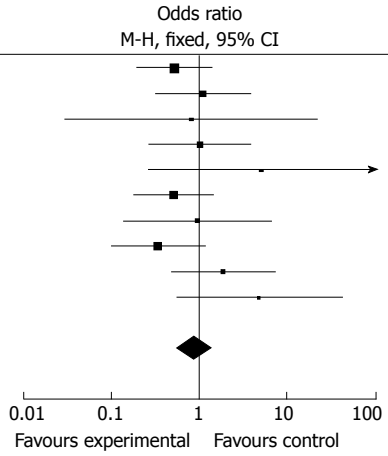
Heterogeneity: χ^2 = 6.42, df = 10 (P = 0.78), I^2 = 0%
Test for overall effect: Z = 1.20 (P = 0.23)



B Review: SLT *vs* PLT; Comparison: SLT *vs* PLT; Outcome: 3-year survival rates

Study or subgroup	SLT Events	SLT Total	PLT Events	PLT Total	Weight %	Odds ratio M-H, fixed, 95% CI
Adam *et al*[6]	9	17	133	195	22.9	0.52 (0.19, 1.42)
Belghiti *et al*[7]	14	18	53	70	11	1.12 (0.33, 3.87)
Concejero *et al*[8]	7	7	27	28	1.7	0.82 (0.03, 22.20)
Del Gaudio *et al*[9]	13	16	119	147	10	1.02 (0.27, 3.82)
Facciuto *et al*[10]	5	5	22	32	1.3	5.13 (0.26, 101.70)
Hwang *et al*[11]	11	17	156	200	19.7	0.52 (0.18, 1.48)
Margarit *et al*[13]	3	5	22	36	4.9	0.95 (0.14, 6.45)
Sapisochin *et al*[14]	9	17	26	34	18.6	0.35 (0.10, 1.19)
Shao *et al*[15]	12	15	42	62	7.5	1.90 (0.48, 7.52)
Vennarecci *et al*[16]	8	9	23	37	2.3	4.87 (0.55, 43.18)
Total (95% CI)		126		841	100.0	0.89 (0.58, 1.37)
Total events	91		623			

Heterogeneity: χ^2 = 9.37, df = 9 (P = 0.40), I^2 = 4%
Test for overall effect: Z = 0.51 (P = 0.61)



C Review: SLT *vs* PLT; Comparison: SLT *vs* PLT; Outcome: 5-year survival rates

Study or subgroup	SLT Events	SLT Total	PLT Events	PLT Total	Weight %	Odds ratio M-H, fixed, 95% CI
Adam *et al*[6]	7	17	119	195	23.8	0.45 (0.16, 1.22)
Belghiti *et al*[7]	10	18	37	70	14.3	1.11 (0.39, 3.16)
Concejero *et al*[8]	7	7	25	28	1.5	2.06 (0.10, 44.48)
Del Gaudio *et al*[9]	10	16	107	147	16.7	0.62 (0.21, 1.83)
Hwang *et al*[11]	9	17	144	200	22.5	0.44 (0.16, 1.19)
Margarit *et al*[13]	1	5	11	36	4.5	0.57 (0.06, 5.69)
Sapisochin *et al*[14]	9	17	22	34	14.6	0.61 (0.19, 2.00)
Vennarecci *et al*[16]	8	9	23	37	2.1	4.87 (0.55, 43.18)
Total (95% CI)		106		747	100.0	0.72 (0.46, 1.11)
Total events	61		488			

Heterogeneity: χ^2 = 6.05, df = 7 (P = 0.53), I^2 = 0%
Test for overall effect: Z = 1.50 (P = 0.13)

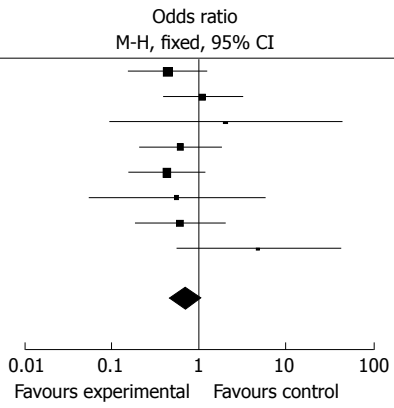


Figure 1 Fixed-effect model of odds ratio for 1-year survival rates (A), 3-year survival rates (B) and 5-year survival rates (C) after salvage liver transplantation and primary liver transplantation (Experimental: Salvage liver transplantation; Control: Primary liver transplantation). SLT: Salvage liver transplantation; PLT: Primary liver transplantation.

Meta-analysis

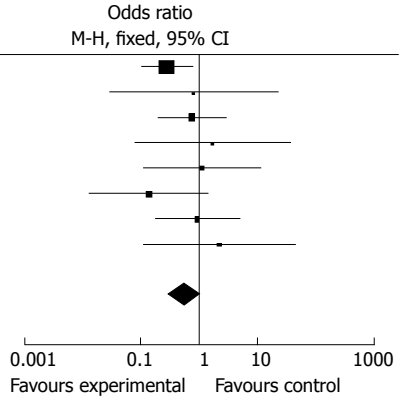
1-year survival after SLT and PLT: A total of 1013 patients were included in 11 articles. According to χ^2 test of heterogeneity (P = 0.78), a fixed-effect model was used. No difference between SLT group (82.3%) and PLT group (85.7%) were seen in the 1-year survival rate (OR: 0.74, 95% CI: 0.46-1.21, P = 0.23, Figure 1A).

3-year survival after SLT and PLT: A total of 967 patients were included in 10 articles. According to χ^2 test of heterogeneity (P = 0.40), a fixed-effect model was used. No difference between SLT group (72.2%) and PLT

A Review: SLT *vs* PLT; Comparison: SLT *vs* PLT; Outcome: 1-year disease-free survival rates

Study or subgroup	SLT Events	SLT Total	PLT Events	PLT Total	Weight %	Odds ratio M-H, fixed, 95% CI
Adam *et al*[6]	8	17	148	195	45.8	0.28 (0.10, 0.77)
Concejero *et al*[8]	7	7	27	28	2.7	0.82 (0.03, 22.20)
Del Gaudio *et al*[9]	13	16	125	147	16.8	0.76 (0.20, 2.90)
Facciuto *et al*[10]	5	5	28	32	2.7	1.74 (0.08, 37.08)
Margarit *et al*[13]	4	5	28	36	5	1.14 (0.11, 11.72)
Sapisochin *et al*[14]	14	17	33	34	14.2	0.14 (0.01, 1.48)
Shao *et al*[15]	13	15	54	62	10.2	0.96 (0.18, 5.08)
Vennarecci *et al*[16]	8	8	33	37	2.6	2.28 (0.11, 46.66)
Total (95% CI)		90		571	100.0	0.56 (0.31, 1.00)
Total events	72		476			

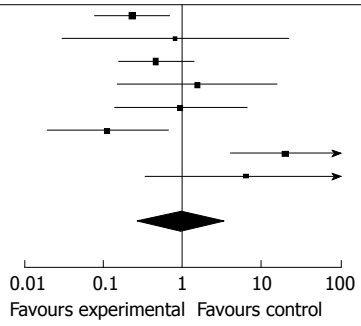
Heterogeneity: χ^2 = 5.48, df = 7 (P = 0.60), I^2 = 0%
Test for overall effect: Z = 1.95 (P = 0.05)



B Review: SLT *vs* PLT; Comparison: SLT *vs* PLT; Outcome: 3-year disease-free survival rates

Study or subgroup	SLT Events	SLT Total	PLT Events	PLT Total	Weight %	Odds ratio M-H, random, 95% CI
Adam *et al*[6]	5	17	125	195	15.8	0.23 (0.08, 0.69)
Concejero *et al*[8]	7	7	27	28	8.1	0.82 (0.03, 22.20)
Del Gaudio *et al*[9]	10	16	115	147	15.8	0.46 (0.16, 1.37)
Facciuto *et al*[10]	4	5	23	32	11.2	1.57 (0.15, 15.97)
Margarit *et al*[13]	3	5	22	36	12.7	0.95 (0.14, 6.45)
Sapisochin *et al*[14]	11	17	32	34	13.4	0.11 (0.02, 0.65)
Shao *et al*[15]	13	15	15	62	13.9	20.37 (4.12, 100.69)
Vennarecci *et al*[16]	8	8	27	37	9.1	6.49 (0.34, 122.71)
Total (95% CI)		90		571	100.0	0.98 (0.27, 3.47)
Total events	61		386			

Heterogeneity: Tau^2 = 2.34; χ^2 = 29.43, df = 7 (P = 0.0001), I^2 = 76%
Test for overall effect: Z = 0.04 (P = 0.97)



C Review: SLT *vs* PLT; Comparison: SLT *vs* PLT; Outcome: 5-year disease-free survival rates

Study or subgroup	SLT Events	SLT Total	PLT Events	PLT Total	Weight %	Odds ratio M-H, random, 95% CI
Adam *et al*[6]	12	17	113	195	25.5	1.74 (0.59, 5.14)
Concejero *et al*[8]	7	7	25	28	7.7	2.06 (0.10, 44.48)
Del Gaudio *et al*[9]	8	16	104	147	26.1	0.41 (0.15, 1.17)
Margarit *et al*[13]	1	5	11	36	11.9	0.57 (0.06, 5.69)
Sapisochin *et al*[14]	10	17	30	34	20.6	0.19 (0.05, 0.79)
Vennarecci *et al*[16]	8	8	27	37	8.3	6.49 (0.34, 122.71)
Total(95% CI)		70		477	100.0	0.75 (0.29, 1.96)
Total events	46		310			

Heterogeneity: Tau^2 = 0.63; χ^2 = 9.81, df = 5 (P = 0.08), I^2 = 49%
Test for overall effect: Z = 0.59 (P = 0.56)

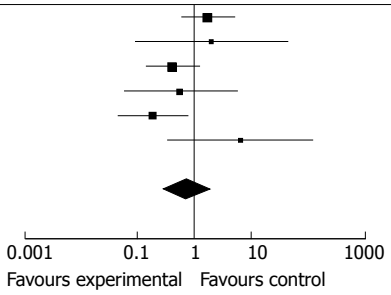


Figure 2 Fixed-effect model of odds ratio for 1-year disease-free survival rates (A); random-effect model of odds ratio for 3-year disease-free survival rates (B) and 5-year disease-free survival rates (C) after salvage liver transplantation and primary liver transplantation (Experimental: Salvage liver transplantation; Control: Primary liver transplantation). SLT: Salvage liver transplantation; PLT: Primary liver transplantation.

group (74.1%) were seen in the 3-year survival rate (OR: 0.89, 95% CI: 0.58-1.37, P = 0.61, Figure 1B).

5-year survival after SLT and PLT: A total of 853 patients were included in 8 articles. According to χ^2 test of heterogeneity (P = 0.53), a fixed-effect model was used. No difference between SLT group (57.5%) and PLT group (65.3%) were seen in the 5-year survival rate (OR: 0.72, 95% CI: 0.46-1.11, P = 0.13, Figure 1C).

1-year disease-free survival after SLT and PLT: A total of 620 patients were included in 8 articles. According to χ^2 test of heterogeneity (P = 0.60), a fixed-effect model was used. No difference between SLT group (80.0%) and PLT group (83.4%) were seen in the 1-year disease-free survival rate (OR: 0.56, 95% CI: 0.31-1.00, P = 0.05, Figure 2A).

3-year disease-free survival after SLT and PLT: A total of 620 patients were included in 8 articles. According to χ^2 test of heterogeneity (P = 0.0001), a random-effect model was used. No difference between SLT group (67.8%) and PLT group (67.6%) were seen in the 3-year disease-free survival rate (OR: 0.98, 95% CI: 0.27-3.47, P = 0.97, Figure 2B).

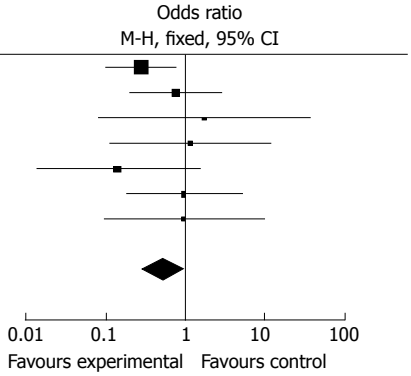
5-year disease-free survival after SLT and PLT: A total of 506 patients were included in 6 articles. According

A Review: SLT *vs* PLT; Comparison: SLT *vs* PLT; Outcome: 1-year disease-free survival rates for DDLT recipients

Study or subgroup	SLT Events	SLT Total	PLT Events	PLT Total	Weight %	Odds ratio M-H, fixed, 95% CI
Adam *et al*[6]	8	17	148	195	45.9	0.28 (0.10, 0.77)
Del Gaudio *et al*[9]	13	16	125	147	16.8	0.76 (0.20, 2.90)
Facciuto *et al*[10]	5	5	28	32	2.7	1.74 (0.08, 37.08)
Margarit *et al*[13]	4	5	28	36	5	1.14 (0.11, 11.72)
Sapisochin *et al*[14]	14	17	33	34	14.2	0.14 (0.01, 1.48)
Shao *et al*[15]	13	15	54	62	10.2	0.96 (0.18, 5.08)
Vennarecci *et al*[16]	8	9	33	37	5.2	0.97 (0.09, 9.90)
Total (95% CI)		84		543	100.0	0.53 (0.29, 0.95)
Total events	65		449			

Heterogeneity: χ^2 = 4.76, df = 6 (P = 0.58), I^2 = 0%

Test for overall effect: Z = 2.12 (P = 0.03)



B Review: SLT *vs* PLT; Comparison: SLT *vs* PLT; Outcome: 5-year disease-free survival rates for DDLT recipients

Study or subgroup	SLT Events	SLT Total	PLT Events	PLT Total	Weight %	Odds ratio M-H, fixed, 95% CI
Adam *et al*[6]	5	17	113	195	37	0.30 (0.10, 0.89)
Del Gaudio *et al*[9]	8	16	104	147	29.5	0.41 (0.15, 1.17)
Margarit *et al*[13]	1	5	11	36	6.2	0.57 (0.06, 5.69)
Sapisochin *et al*[14]	10	17	30	34	23.8	0.19 (0.05, 0.79)
Vennarecci *et al*[16]	8	9	27	37	3.4	2.96 (0.33, 26.79)
Total (95% CI)		64		449	100.0	0.42 (0.23, 0.74)
Total events	32		285			

Heterogeneity: χ^2 = 4.62, df = 4 (P = 0.33), I^2 = 13%

Test for overall effect: Z = 2.96 (P = 0.003)

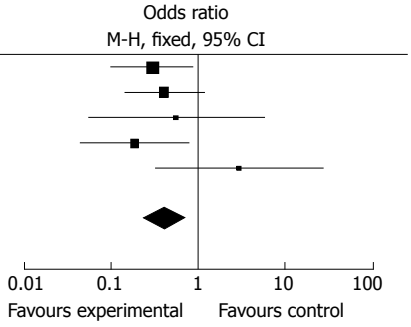


Figure 3 Fixed-effect model of odds ratio for 1-year (A) and 5-year (B) disease-free survival rates for deceased-donor liver transplantation recipients after salvage liver transplantation and primary liver transplantation (Experimental: Salvage liver transplantation; Control: Primary liver transplantation). DDLT: Deceased-donor liver transplantation; SLT: Salvage liver transplantation; PLT: Primary liver transplantation.

to χ^2 test of heterogeneity (P = 0.08), a random-effect model was used. No difference between SLT group (65.7%) and PLT group (65.0%) were seen in the 5-year disease-free survival rate (OR: 0.75, 95% CI: 0.29-1.96, P = 0.56, Figure 2C).

When stratifying for the donor source, compared with deceased-donor liver transplantation (DDLT) recipients, we found that living-donor liver transplantation (LDLT) recipients had significantly higher 1-year survival rate (OR: 1.02, 95% CI: 0.26-4.10, P = 0.97), lower 3-year survival rate (OR: 0.54, 95% CI: 0.20-1.47, P = 0.23) and lower 5-year survival rate (OR: 0.54, 95% CI: 0.21-1.35, P = 0.19). DDLT recipients had significantly lower 1-year survival rate (OR: 0.66, 95% CI: 0.38-1.15, P = 0.14), higher 3-year survival rate (OR: 0.99, 95% CI: 0.62-1.59, P = 0.97) and higher 5-year survival rate (OR: 0.77, 95% CI: 0.47-1.26, P = 0.30). No useable data about disease-free survival rates can be extracted from LDLT researches. And in DDLT recipients they had better 1-year disease-free survival rate (OR: 0.53, 95% CI: 0.29-0.95, P = 0.03, Figure 3A) and better 5-year disease-free survival rate (OR: 0.42, 95% CI: 0.23-0.74, P = 0.003, Figure 3B) in SLT group. No difference between SLT group and PLT group were seen in the 3-year disease-free survival rate (OR: 0.95, 95% CI: 0.26-3.52, P = 0.94).

When stratifying for Milan criteria, we found that no difference was seen in 1-year survival rates (OR: 0.26, 95% CI: 0.01-4.94, P = 0.37), 3-year survival rates (OR: 0.41, 95% CI: 0.01-24.54, P = 0.67) and 5-year survival rates (OR: 0.55, 95% CI: 0.07-4.48, P = 0.57) between SLT group and PLT group who beyond Milan criteria at the time of liver transplantation (LT). No usable data for patients who met Milan criteria at the time of LT.

Publication bias

Publication bias may exist when no significant findings remain unpublished, thus artificially inflating the apparent magnitude of an effect. Funnel plots of our study results are shown in Figure 4. The funnel plots on survival and disease-free survival following SLT or PLT for the treatment of HCC showed basic symmetry, which suggested no publication bias.

DISCUSSION

As one of the radical treatments for HCC, LT is nowadays limited by organ shortage. Due to the prolonged waiting times before transplantation, tumor progression and deterioration of liver function may counteract its benefit[2]. The outcome of liver resection is mainly influenced by a high rate of recurrence that limits long-term survival rates. But previous research noted that most of patients with recurrence after primary liver resection were still eligible for LT[2]. Hence, hepatectomy and LT should be considered as complementary, not competitive, treatments for HCC in cirrhotic patients with well-preserved

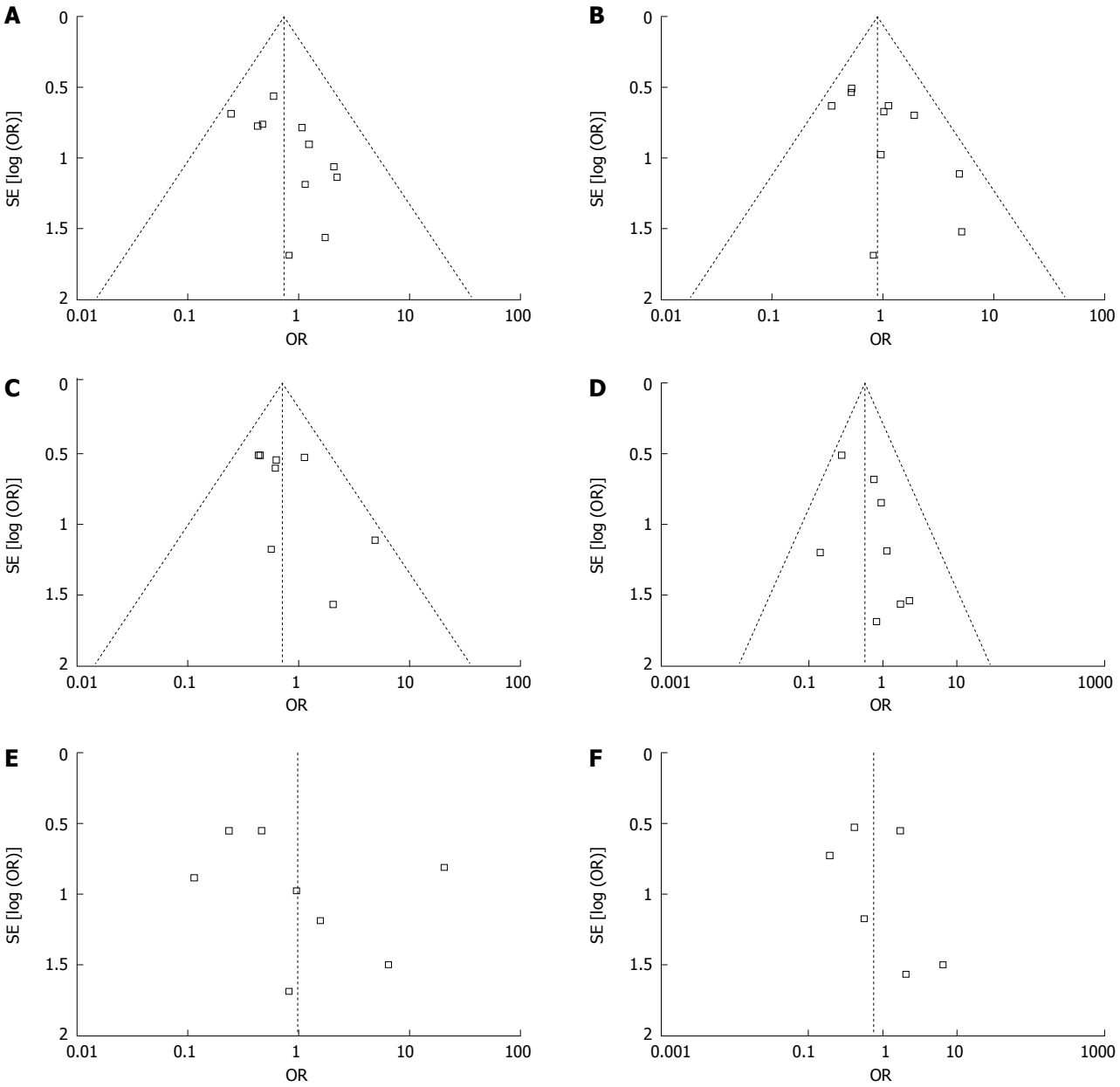


Figure 4 Funnel plot. A: 11 articles in the meta-analysis of 1-year survival after treatment; B: 10 articles in the meta-analysis of 3-years survival after treatment; C: 8 articles in the meta-analysis of 5-years survival after treatment; D: 8 articles in the meta-analysis of 1-year disease-free survival after treatment; E: 8 articles in the meta-analysis of 3-year disease-free survival after treatment; F: 6 articles in the meta-analysis of 5-year disease-free survival after treatment. SE: Standard error; OR: Odds ratio.

liver function. Resection of the liver tumor is an optional bridge treatment[17-19]. SLT was proposed in order to reduce the impact of a long waiting times, donor shortage and tumor recurrence after resection in HCC patients.

The increased technical difficulty during SLT and the risk for impaired posttransplant survival worried most of surgeons. Heavy adhesions and portal hypertension are often encountered after prior liver resection. Inattentive dissection of perihepatic adhesions could result in uncontrollable bleeding at the dissection surface. Also due to heavy adhesions, the relationship between hepatic vein and inferior vena cava are hard to identify. Hwang *et al*[11] found that SLT did not increase the operative risks or postoperative complications. The two major technical concerns-bleeding and reconstruction of the hepatic vein outflow can be solved successfully by steady and meticulous sharp dissection and sufficient dissection of the recipient inferior vena cava. Kim *et al*[12] showed that end-to-end anastomosis for bile ducts and hepatic artery was feasible, too. Our study showed that SLT had no bad effect on overall survival and disease-free survival in comparison with PLT.

Considering different surgical methods may have an effect on survival rates, the whole patients were stratified to LDLT recipients and DDLT recipients. In each subgroup, no difference between SLT group and PLT group were seen in 1-year survival rates, 3-year survival rates and 5-year survival rates. But LDLT recipients may have

a significant higher 1-year survival rates than DDLT recipients, while a significant lower 3-year survival rates and 5-year survival rates. This may be a result of improvement of surgical technique and perioperative management. However, because of a relatively higher incidence (up to 30%) of biliary complication after LDLT[20-23], LDLT recipients may have a lower long-term survival rates than DDLT recipients. Different results in DDLT recipients' disease-free survival rates seem hard to explain. We consider a better tumor stage at the time of transplantation (meet Milan criteria) may contribute to better 1-year disease-free survival rates and 5-year disease-free survival rates. A lager sample and more randomized controlled studies may resolve this conflict and draw a right conclusion.

The tumors' stage at the time of resection and LT is another risk factor for postoperative overall survival and disease-free survival. Some studies were theoretical and assessed the salvage transplantability according to the pattern of recurrence after resection for HCC within Milan criteria and found that 76% to 87% of recurrences were considered eligible for SLT on imaging grounds[2,12,24,25]. For HCC patients not meeting Milan criteria, SLT could be applied for those cases with less aggressiveness, namely tumor size less than 6 cm and pathological well differentiation. For those cases meeting Milan criteria, PLT seems to be the first option. SLT could be performed for those patients with recurrence within Milan criteria after primary resection and without delay before recurrence with advanced disease manifestations. But there is no consensus about the survival rates for patients with recurrence beyond Milan criteria. Our result reveals that SLT group has similar survival rates compared with PLT group beyond Milan criteria at the time of LT. Unfortunately, data extracted from our including studies are not enough to do further meta-analysis on patients' survival rates meeting Milan criteria at the time of LT and the corresponding disease-free survival rates.

Moreover, in countries with a higher incidence of HCC, a higher proportion of HCC patients on the waiting list and/or a longer median time-to-transplant, SLT could offer a gain in life-expectancy to the remaining waiting-list patients[26].

This review has some limitations. Although funnel plots may be suggestive of publication bias with lack of negative small RCTs, a firm conclusion about bias is difficult to make as the asymmetry of the funnel plots is minimal. And funnel plots can show asymmetry for other reasons. Therefore, our pooled OR might be an overestimate of the true effect. Due to data constraints, this meta-analysis could not analyze the quality of life score and was unable to carry out stratified analyses of other possible confounding factors. The method need to be more effective. Larger samples and randomized controlled studies with longer follow-up are required. Our conclusions also need more detailed data to confirm the results. The search language was limited. The integrity of the data was affected to a certain extent.

In conclusion, this new strategy SLT can be effectively performed for patients with recurrence or deterioration of liver function after hepatectomy for HCC. It does not increase the perioperative mortality and has a similar long-term survival rates compared to PLT. When surgical technique is no longer a problem for SLT, more patients will benefit from it.

COMMENTS

Background

Due to shortage of available donors, salvage liver transplantation (SLT) has been proposed and performed for the patients who undergo primary liver resection for hepatocellular carcinoma (HCC) or HCC recurrence or deterioration of liver function. This meta-analysis was designed to evaluated survival and recurrence after SLT for the treatment of HCC compared with primary liver transplantation (PLT).

Research frontiers

The study evaluated survival and recurrence after SLT for the treatment of HCC compared with PLT using a meta-analysis of all relevant controlled studies.

Innovations and breakthroughs

This is the first systematic review and meta-analysis on the survival and recurrence after SLT for the treatment of HCC compared with PLT. The author made a comprehensive search of studies. Several important conclusions might be used for future selection in SLT or PLT for HCC patients' treatments.

Applications

This meta-analysis shows that SLT has a similar survival rates in comparison with PLT. SLT offers an alternative treatment method for HCC patients in facing a shortage of available donors.

Terminology

SLT was defined as a liver transplantation performed for recurrent HCC or deterioration of liver function after primary liver resection.

Peer review

The article should be published as it is a nice overview on the topic after some revisions are performed.

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S- Editor Shi ZF **L- Editor** A **E- Editor** Zhang DN