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META-ANALYSIS AND SYSTEMATIC REVIEW

Systematic review of efficacy and outcomes of salvage liver transplantation after primary hepatic resection for hepatocellular carcinoma

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Abstract

Background and Aim: Upfront liver transplantation is the gold standard in the treatment of patients with hepatocellular carcinoma (HCC) and cirrhosis, but a shortage of donor organs negatively impacts on survival outcomes, with significant disease progression during long waiting lists. This systematic review evaluates the safety and efficacy of salvage liver transplantation (SLT) as treatment for recurrent HCC after initial hepatic resection.

Methods: Electronic searches of Pubmed, Embase, and Medline databases identified 130 abstracts, from which 16 eligible studies comprising 319 patients were selected for review. Studies adopting SLT following primary hepatic resection for recurrent HCC with more than five patients were included. Demographic details, morbidity and mortality indices, and survival outcomes were collected from each study and were tabulated.

Results: All patients included in the studies had liver cirrhosis, with the majority being Child-Pugh A (50%) and B (33%). The etiology of liver disease was hepatitis B in the majority of patients (84%). Disease recurrence occurred in 27–80% of patients at a median of 21.4 months (range 14.5–34) following initial resection. SLTs were performed on 41% of recurrences, and were associated with biliary complications (8%), infection (11%), bleeding (8%), and vascular complications (7%). There were 18 perioperative deaths (5.6%). The median 1-, 3-, and 5-year overall and disease-free survival was 89%, 80%, and 62%, and 86%, 68%, and 67%, respectively.

Conclusion: Synthesis of available observational studies suggests that SLT following primary hepatic resection is a highly applicable strategy with long-term survival outcomes that are comparable to upfront liver transplantation.

Introduction

Hepatocellular carcinoma (HCC) is the third leading cause of cancer-related death worldwide.[1] This burden of disease is excepted to increase in the future, with the high prevalence of hepatitis B virus infections in Asia and sub-Saharan Africa, and the incidence of hepatitis C virus infections and alcoholic liver cirrhosis rising in developed regions.[2]

The efficacy of liver transplantation for treatment of patients with HCC and cirrhosis was most notably described by Mazzaferro *et al*. in 1996 with the development of the Milan criteria.[3] In a cohort of 48 patients with a single tumor 5 cm or less in diameter, or no more than three tumor nodules each 3 cm or less in diameter, liver transplantation achieved a 4-year overall survival rate of 92% and a disease-free survival rate of 85%. Despite being the most effective treatment, the shortage of available donor organs significantly reduces the efficacy of this treatment, with patients on waiting lists suffering significant disease progression.[4]

Primary hepatic resection remains an accepted modality of treatment with 5-year overall survival rates of 55–71%.[5,6] The continuous improvement in surgical technique and perioperative management has also reflected an improved survival outcomes with this treatment.[5] However, recurrences are common, with almost 70% of patients developing intrahepatic or other disease recurrence within 5 years.[2,7]

More recently, primary hepatic resection with curative intent followed by salvage liver transplantation (SLT) for those with disease recurrence has been promoted as a potential treatment modality.[8] This strategy may potentially reduce disease progression for patients waiting for liver transplantation and reduce the number of transplants required. However, there remains concern

over the potential for increased difficulty of transplantation following a prior resection and postoperative complications to negate the benefits of an SLT.

We propose to evaluate the outcomes of SLT for patients with recurrent HCC following initial treatment with primary hepatic resection. In this review, we seek to investigate using a systematic literature examination the morbidity, mortality, and survival outcomes of this therapeutic strategy.

Methods

Literature search strategy. A literature search was last conducted on December 1, 2012 using Pubmed, Embase, and Medline databases (January 2000–November 2012). The search terms used to locate studies were "salvage," "secondary," "liver transplant," "liver transplantation," and "recurrent hepatocellular carcinoma." The search was limited to English-language articles and to humans. All relevant journal articles and conference abstracts identified were assessed with application of inclusion and exclusion criteria. Where there was insufficient information provided by the abstract or ambiguity of inclusion criteria, full-text articles were retrieved for further assessment. The reference lists of articles identified were manually searched to locate other articles of relevance.

Selection criteria. Selection criteria were as follows: (i) all studies > 5 patients, (ii) initially treated with hepatic resection, (iii) adopting SLT for recurrent HCC, and (iv) sufficient data to be included in either perioperative morbidity and mortality or longer-term survival tabulation. Where multiple treatments for primary disease recurrence was employed, reporting of outcome data must be separate. We excluded review articles, case reports, editorials, and letters. Where multiple publications from the same institution were identified, only the most recent update with the largest number of patients or longer follow-up group was included. Where conference abstracts and publications employed the same study cohort, the more recent was included. Studies were evaluated and categorized according to their level of evidence, where level I evidence: randomized controlled trials; level II evidence: nonrandomized controlled clinical trials or well-designed cohort studies; and level III evidence: observational studies, as described by the US Preventive Services Task Force.

Data extraction and critical appraisal. The studies were independently and critically appraised by two reviewers (DLC and TCC). Data of interest included study characteristics, patient demographics, disease characteristics, perioperative morbidity and mortality, disease recurrence, disease-free survival, and overall survival data. All data were extracted and tabulated from the relevant articles' texts, tables, and figures. Data were presented as median (range). Discrepancies were resolved by discussion and consensus. Meta-analysis was inappropriate due to the lack of a comparative arm in most studies.

Results

There were 120 articles identified from the literature search of three databases and an additional 10 articles from manual search of reference lists. Following removal of duplicates, 101 abstracts were screened and 74 papers were excluded. The remaining 27 articles were reviewed to assess for eligibility. Five articles had insufficient patient numbers of inclusion.[9–13] Two articles were excluded due to larger case series from same research group.[14,15] One article did not contain sufficient perioperative or long-term data for inclusion.[16] Two other articles were excluded for heterogeneous treatment of primary disease and disease recurrence, and failure to present hepatic resection and SLT results separately.[17,18] A retrospective case series from China contained large numbers from a data registry but had poor data quality, with almost 1000 of their 17 000 transplants excluded for this reason.[19] This article also included data from 54 transplant centers, even though only nine centers had a volume of > 20 transplants over a 10-year period. The remaining 16 articles were included for this review, as outlined in the PRISMA flow diagram (Fig. 1).[20–35] None of the studies reviewed were randomized trials. There was a combination of class II (nonrandomized comparative or well-designed cohort studies) and class III (observational studies) evidence in the available literature. Table 1 summarizes the data points included in relevant articles.

Patient demographics. In total, 319 patients from 16 different studies were reviewed. The median patient age was 51 years, range 44–63 years, and the majority were male (88%). The hepatitis B carrier status was positive in median 84% of patients, range 24–100%. The hepatitis C carrier status was positive in median 36%, range 0–33% of patients. Alcohol was the etiology of liver disease in median 9%, range 0–33% of patients. All patients reviewed had some degree of liver cirrhosis, Child-Pugh A (median 50%, range 28–100%), B (median 33%, range 0–54%), or C (median 12%, range 0–44%) (Table 2).

Primary disease and resection characteristics. The median tumor size was 3 cm, range 2.5–3.4 cm. The majority of tumors were solitary (median 81%, range 58–94%) and had well-differentiated histology (median 59%, range 0–94%). Microvascular involvement was more common than macrovascular (median 28%, range 0–53%, *vs* median 4%, range 0–13%) (Table 3). Only four studies (91 patients) published details on primary hepatic resection. Major hepatectomy was performed with 18–29% of patients. This was associated with minor morbidity in 19–41% of cases and a 0–6% mortality rate. Liver failure was noted in five patients (Table 4).

Recurrence and recurrent disease characteristics. Disease recurrence occurred in a median 54%, range 27–80% of patients following primary hepatic resection. Median time to recurrence was 21.4 months (range 14.5–34 months). The median tumor size was 2.6 cm (range 2–4.8 cm) at recurrence. Recurrences were solitary in 58% (range 27–89%) of patients and multiple in 42% (range 11–88%) of patients. The rate of SLT following recurrence was 41% (range 16–65%) (Table 5).

SLT morbidity and mortality. The median time from initial diagnosis of HCC to SLT was 35 months, range 19–47 months. Median operative time was 600 min, range 340–989 min,

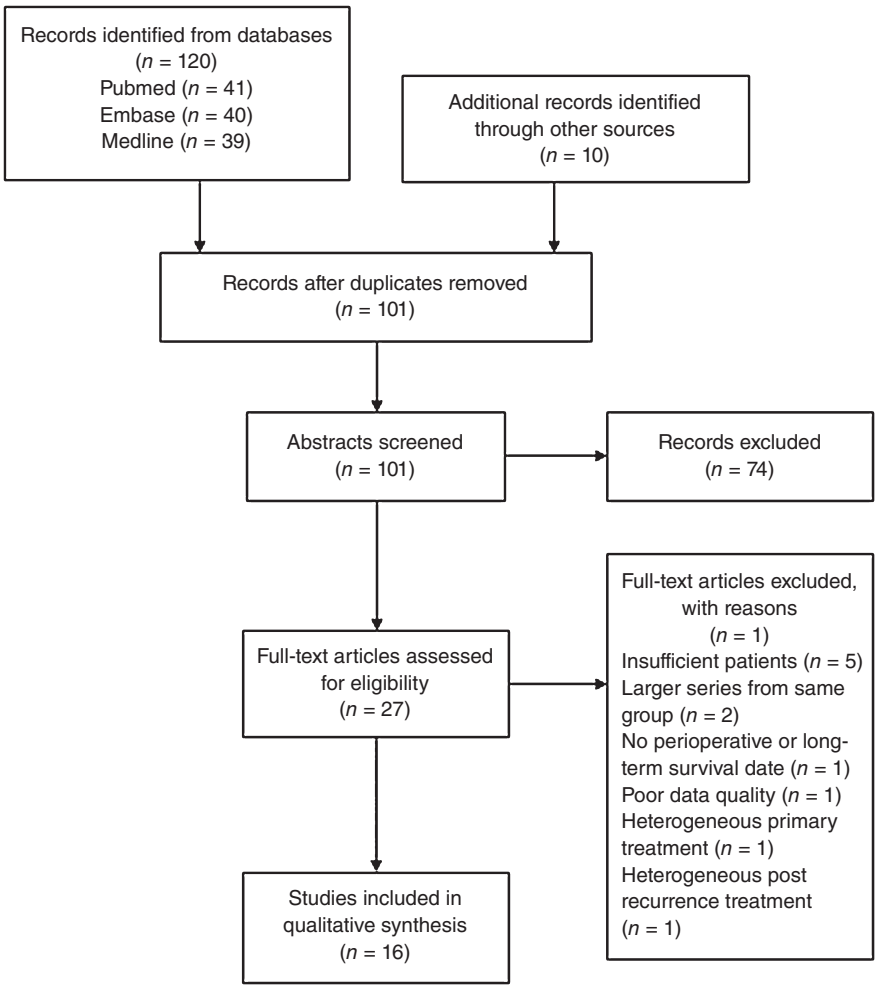

Figure 1 Literature search PRISMA flow diagram.

Table 1 Summary of data points presented in relevant clinical trials

Author	Year	Country	Level of evidence	SLT (*n* =)	Primary tumor details	Primary resection details	Time to recurrence	Recurrent tumor details	SLT details	Recurrence but no SLT and reason	Longer term survival
Adam *et al.*[20]	2003	France	Class II	17	Y	–	Y	Y	Y	Y	Y
Cherqui *et al.*[21]	2009	France	Class II	18	Y	Y	Y	Y	Y	Y	Y
Concejero *et al.*[22]	2008	Taiwan	Class III	7	Y	–	Y	Y	Y	–	Y
De Carlis *et al.*[23]	2013	Italy	Class II	26	–	–	–	Y	Y	–	Y
Del Gaudio *et al.*[24]	2008	Italy	Class II	16	Y	–	Y	Y	Y	Y	Y
Fuks *et al.*[25]	2012	France	Class II	39	Y	Y	Y	Y	Y	Y	Y
Hwang *et al.*[26]	2007	South Korea	Class III	17	–	Y	–	Y	Y	–	Y
Kaido *et al.*[27]	2012	Japan	Class III	19	–	–	–	Y	Y	–	Y
Kim *et al.*[28]	2008	Korea	Class III	15	–	–	Y	Y	Y	–	Y
Liu *et al.*[29]	2012	China	Class II	39	–	–	–	Y	Y	–	Y
Moon *et al.*[30]	2012	South Korea	Class III	17	–	–	–	Y	Y	–	Y
Ng *et al.*[31]	2008	Hong Kong	Class III	12	Y	–	Y	Y	Y	–	Y
Sapisochin *et al.*[32]	2010	Spain	Class II	17	Y	Y	Y	Y	Y	Y	Y
Shao *et al.*[33]	2008	China	Class III	15	Y	–	–	Y	Y	–	–
Vennarecci *et al.*[34]	2007	Italy	Class II	9	Y	–	Y	Y	Y	–	Y
Wu *et al.*[35]	2012	China	Class III	36	Y	–	–	Y	Y	–	Y

SLT, salvage liver transplantation; Y, recorded data available.

Table 2 Patient demographics

Author	SLT (*n* =)	Age (mean)	Male *n* (%)	Etiology of liver disease				Child-Pugh grading *n* (%)			Cirrhosis present *n* (%)
				Hepatitis B carrier *n* (%)	Hepatitis C carrier *n* (%)	Alcohol *n* (%)	Other *n* (%)	A	B	C	
Adam *et al.*[20]	17	55	16 (94)	13 (76)	–	1 (6)	3 (18)	6 (35)	9 (53)	2 (12)	17 (100)
Cherqui *et al.*[21]	18	63[†]	56 (84)[†]	16 (24)[†]	20 (30)[†]	20 (30)[†]	11 (16)	65 (97)[†]	2 (3)[†]	0 (0)[†]	18 (100)
Concejero *et al.*[22]	7	48[‡]	31 (89)[‡]	6 (86)	1 (14)	1 (3)[‡]	0 (0)	10 (28)[‡]	19 (54)[‡]	6 (17)[‡]	7 (100)
De Carlis *et al.*[23]	26	53	21 (81)	7 (29)	16 (62)	4 (15)	0 (0)	20 (76)	5 (21)	1 (3)	26 (100)
Del Gaudio *et al.*[24]	16	54	13 (81)	4 (25)	15 (94)	0 (0)	0 (0)	6 (37)	3 (19)	7 (44)	16 (100)
Fuks *et al.*[25]	39	57[§]	–	35 (25)[§]	56 (41)[§]	17 (12)[§]	30 (22)[§]	39 (100)	0 (0)	0 (0)	39 (100)
Hwang *et al.*[26]	17	49	12 (71)	17 (100)	–	–	–	–	–	–	17 (100)
Kaido *et al.*[27]	19	52	14 (74)	9 (48)	11 (58)	–	1 (5)	9 (47)	6 (32)	4 (21)	19 (100)
Kim *et al.*[28]	15	48	13 (87)	15 (100)	–	–	–	–	–	–	15 (100)
Liu *et al.*[29]	39	44	36 (92)	36 (92)	–	–	3 (8)	20 (51)	19 (49)[¶]	–	39 (100)
Moon *et al.*[30]	17	51	16 (94)	17 (100)	1 (6)	0 (0)	0 (0)	8 (47)	9 (53)[¶]	–	17 (100)
Ng *et al.*[31]	12	51	12 (100)	11 (92)	0 (0)	–	1 (8)	6 (50)	4 (33)	2 (17)	12 (100)
Sapisochin *et al.*[32]	17	57	15 (88)	–	12 (71)	–	5 (29)	17 (100)[††]	NR	0 (0)	17 (100)
Shao *et al.*[33]	15	50	14 (93)	15 (100)	–	5 (33)	0 (0)	7 (47)	6 (40)	2 (13)	15 (100)
Vennarecci *et al.*[34]	9	–	–	–	–	–	–	9 (100)	0 (0)	0 (0)	9 (100)
Wu *et al.*[35]	36	49	27 (75)	35 (97)	2 (6)	–	–	–	–	–	36 (100)
Median value (range)		51 (44–63)	88 (71–100)	84 (24–100)	36 (0–94)	9 (0–33)	7 (0–29)	50 (28–100)	33 (0–54)	12 (0–44)	100 (100)

[†]Combined data from 67 patients.
[‡]Combined data from 35 patients.
[§]Combined data from 138 patients.
[¶]Child-Pugh B and C.
[††]Child-Pugh A and B.
SLT, salvage liver transplantation.

Table 3 Primary disease characteristics

Author	SLT (*n* =)	Tumor characteristics			Histological grading (*n*, %)			Involvement (*n*, %)	
		Median tumor size cm	Single (*n*, %)	Multiple (*n*, %)	Well	Mod	Poor	Microvascular	Macrovascular
Adam *et al.*[20]	17	3.4[†]	16 (94)[‡]	1 (6)[‡]	–	–	–	–	–
Cherqui *et al.*[21]	18	–	63 (94)[§]	4 (6)	63 (94)[§,¶]	–	4 (6)[§]	13 (27)[§]	–
Concejero *et al.*[22]	7	–	4 (57)	3 (43)	4 (57)	2 (29)	1 (14)	0 (0)	–
Del Gaudio *et al.*[24]	16	2.4[†]	–	–	–	–	–	–	0 (0)
Fuks *et al.*[25]	39	3.5[††]	111 (80)[††]	27 (20)[††]	123 (89)[¶,††]	–	15 (11)[††]	52 (38)[††]	9 (7)[††]
Ng *et al.*[31]	12	2.7	8 (67)	4 (33)	–	–	–	3 (25)	–
Sapisochin *et al.*[32]	17	3	14 (82)	3 (18)	10 (59)	7 (41)[‡‡]	–	5 (29)	–
Shao *et al.*[33]	15	3	–	–	0 (0)	8 (53)	7 (47)	8 (53)	2 (13)
Vennarecci *et al.*[34]	9	2.5	8 (89)	1 (11)	5 (56)	3 (33)	1 (11)	3 (33)	–
Wu *et al.*[35]	36	–	21 (58)	15 (42)	28 (78)	0 (0)	8 (22)	2 (6)	0 (0)
Median value (range)		3 (2.5–3.4)	81 (58–94)	19 (6–43)	59 (0–94)	29 (0–53)	13 (6–47)	28 (0–53)	4 (0–13)

[†]Median value.
[‡]3 or less versus > 3 nodules.
[§]Combined data of 67 patients.
[¶]Well or moderately differentiated.
[††]Combined data of 138 patients.
[‡‡]Moderately or poorly differentiated.
SLT, salvage liver transplantation.

Table 4 Primary hepatic resection details

First author	HR (*n* =)	SLT (*n* =)	Major hepatectomy (*n*, %)	Median LOS	Morbidity and mortality				
					Minor morbidity (*n*, %)	Major morbidity (*n*, %)	Liver failure (*n*, %)	Infection (*n*, %)	Mortality (*n*, %)
Cherqui *et al.*[21]	67	18	12 (18)	–	13 (19)	9 (13)	1 (1)	2 (3)	3 (5)
Fuks *et al.*[25]	112	39	29 (21)	13	56 (41)	–	2 (3)	–	2 (1)
Hwang *et al.*[26]	NR	17	5 (29)	–	–	–	2 (12)	1 (6)	1 (6)
Sapisochin *et al.*[32]	100	17	–	8	5 (29)	–	–	–	0 (0)

HR, primary hepatic resection; SLT morbidity, not otherwise specified.
LOS, length of stay; NR, not reached; SLT, salvage liver transplantation.

and the length of stay was 19 days, range 15–38 days. Infection (median 11%, range 5–21%), biliary (median 5%, range 0–31%), bleeding (median 7%, range 0–33%), and vascular (median 7%, range 0–12%) complications were most commonly recorded. Two studies reported 23–24% reoperation rates, but no other reoperations occurred in any other study.[23,30] Acute rejection occurred in 4%, range 0–12%, of patients. Four patients required retransplantations. Median mortality rate was 5%, range 0–24% (Table 6).

Survival outcomes. The median follow-up was 29 months, range 11–77 months. Median disease-free survival was not yet reached in 10 of the studies. The median 1-year disease-free survival was 86%, range 47–100%; median 3-year disease-free survival was 68%, range 29–100%; and median 5-year disease-free survival was 67%, range 29–100%. Two studies reported a median overall survival of 45.6 and 61 months;[20,31] however, the remaining 14 studies had not yet reached median overall survival at publication of results. The median 1-year overall survival was 89%, range 59–100%; median 3-year overall survival was 80%, range 52–100%; and median 5-year overall survival was 62%, range 41–89% (Table 7).

Discussion

Primary liver transplantation is recognized as the most effective treatment of primary HCC within the Milan criteria, but is limited by organ shortage.[36] Efficacy of this treatment is affected by disease progression during prolonged waiting times.[8] Primary hepatic resection is a widely adopted modality of treatment for primary HCC with reasonable long-term survival outcomes but is associated with high rates of disease recurrence. Poon *et al.* suggest a treatment strategy of primary hepatic resection as the treatment of patients with HCC within the Milan criteria, with SLT reserved for those with disease recurrence.[8] This strategy may

Table 5 Recurrent disease characteristics following primary hepatic resection

Author	Primary hepatic resection (*n* =)	Recurrence (*n*, %)	Rate of SLT (*n*, %)	Median time to recurrence (months)	Tumor characteristics			Histological grading (*n*, %)			Involvement (*n*, %)
					Median size (cm)	Single (*n*, %)	Multiple (*n*, %)	Well	Mod	Poor	Microvascular
Adam *et al.*[20]	98	75 (77)	17 (23)	21.8	–	–	–	–	–	–	–
Cherqui *et al.*[21]	67	36 (54)	18 (50)	31.1	–	–	–	–	–	–	–
Concejero *et al.*[22]	–	–	7	24[†]	–	4 (57)	3 (43)	4 (57)	2 (29)	1 (14)	0 (0)
De Carlis *et al.*[23]	–	–	26	–	2.2	21 (81)[‡]	5 (19)	21 (81)[§]	–	5 (19)	2 (8)
Del Gaudio *et al.*[24]	80	39 (49)	16 (41)	21.8	2.4	–	–	–	–	–	–
Fuks *et al.*[25]	112	90 (80)	39 (65)	15.9	–	60 (67)	30 (33)	–	–	12 (13)	36 (40)
Hwang *et al.*[26]	–	–	17	–	2.6	5 (29)	12 (88)	–	–	–	3 (18)
Kaido *et al.*[27]	–	–	19	–	3.7[†]	–	–	1 (5)	13 (68)	5 (26)	7 (37)
Kim *et al.*[28]	–	–	15[¶]	16	2.3	4 (27)	9 (60)	–	–	–	7 (47)
Liu *et al.*[29]	380	86 (40)	39 (45)	12.9	–	22 (56)	17 (44)	10 (26)	20 (51)	9 (23)	20 (51)
Moon *et al.*[30]	–	–	17	–	–	11 (65)[‡]	6 (35)	17 (100)	–	0 (0)	13 (77)
Ng *et al.*[31]	277	75 (27)	12 (16)	34	3.0	9 (75)	3 (25)	–	–	–	3 (25)
Sapisochin *et al.*[32]	100	69 (69)	17 (25)	21	2.5	7 (41)	10 (59)	–	–	–	4 (24)
Shao *et al.*[33]	–	–	15	–	3.0	–	–	0 (0)	8 (53)	7 (47)	8 (53)
Vennarecci *et al.*[34]	–	–	9	14.5	2.5	8 (89)	1 (11)	5 (56)	3 (33)	1 (11)	3 (33)
Wu *et al.*[35]	–	–	36	–	4.8	21 (58)	15 (42)	28 (78)	–	8 (22)	2 (6)
Median value (range)		54 (27–80)	41 (16–65)	21.4 (14.5–34)	2.6 (2–4.8)	58 (27–89)	42 (11–88)	57 (0–100)	51 (29–68)	19 (11–47)	33 (0–77)

[†]Mean value.

[‡]One or two tumors

[§]Well-moderately differentiated.

[¶]Tumor characteristics and vascular involvement missing for two patients, percentages calculated from 13 patients.

SLT, salvage liver transplantation.

Table 6 Salvage liver transplantation (SLT) details

First author	SLT (*n* =)	Median time Dx to SLT (months)	Median Operative time (min)	Length of stay (days)	Morbidity and mortality							
					Biliary complication (*n*, %)	Infection (*n*, %)	Bleeding (*n*, %)	Vascular complication (*n*, %)	Reoperation (*n*, %)	Acute rejection (*n*, %)	Retransplant (*n*, %)	Mortality (*n*, %)
Adam *et al.*[20]	17	23.6	695	–	0 (0)	1 (6)	1 (6)	1 (6)	0 (0)	0 (0)	1 (6)	4 (24)
Cherqui *et al.*[21]	18	44.2	–	–	–	–	–	–	–	–	–	0 (0)
Concejero *et al.*[22]	7	36	–	–	0 (0)	–	–	–	0 (0)	0 (0)	0 (0)	0 (0)
De Carlis *et al.*[23]	26	–	430	19	1 (4)	5 (19)	4 (16)	1 (4)	6 (24)	3 (12)	1 (4)	1 (4)
Del Gaudio *et al.*[24]	16	47	–	–	5 (31)	3 (19)	0 (0)	1 (6)	0 (0)	0 (0)	0 (0)	0 (0)
Fuks *et al.*[25]	39	–	–	–	–	–	–	–	–	–	–	2 (5)
Hwang *et al.*[26]	17	35	989	–	4 (24)	9 (5)	5 (30)	2 (12)	0 (0)	0 (0)	0 (0)	1 (6)
Kaido *et al.*[27]	19	41.7	941	–	–	–	–	–	–	–	–	1 (5)
Kim *et al.*[28]	15	19	758	–	4 (27)	–	5 (33)	1 (7)	0 (0)	1 (7)	0 (0)	0 (0)
Liu *et al.*[29]	39	22	600	35	3 (8)	8 (21)	1 (3)	3 (8)	–	1 (3)	–	2 (5)
Moon *et al.*[30]	17	32	–	38	3 (18)	–	2 (12)	1 (6)	4 (23)	–	2 (12)	1 (6)
Ng *et al.*[31]	12	34	840	–	1 (8)	–	1 (8)	–	0 (0)	–	0 (0)	0 (0)
Sapisochin *et al.*[32]	17	44	370	19	–	–	–	–	–	–	–	1 (6)
Shao *et al.*[33]	15	27	480	–	–	–	–	1 (7)	–	1 (7)	–	3 (20)
Vennarecci *et al.*[34]	9	–	450	15	0 (0)	1 (11)	0 (0)	1 (11)	0 (0)	1 (11)	0 (0)	1 (11)
Wu *et al.*[35]	36	35	340	–	2 (6)	2 (6)	0 (0)	0 (0)	–	2 (6)	–	1 (3)
Median value (range)		35 (19–47)	600 (340–989)	19 (15–38)	8 (0–31)	11 (5–21)	7 (0–33)	7 (0–12)	0 (0–24)	4 (0–12)	0 (0–12)	5 (0–24)

Dx, initial diagnosis of hepatocellular carcinoma; SLT, salvage liver transplantation.

Table 7 Long-term survival outcomes after salvage liver transplantation (SLT)

First author	SLT (*n* =)	Median follow-up (months)	Disease-free survival				Overall survival			
			Median DF survival (months)	1-year survival (%)	3-year survival (%)	5-year survival (%)	Median overall survival (months)	1-year survival (%)	3-year survival (%)	5-year survival (%)
Adam *et al.*[20]	17	49[†]	21.8	47	29	29	45.6	71	53	41
Cherqui *et al.*[21]	18	57.6	31.1	82	52	44	NR	85	80	70
Concejero *et al.*[22]	7	41.9	NR	100	100	–	NR	100	100	–
De Carlis *et al.*[23]	26	–	NR	–	–	81	NR	–	–	82
Del Gaudio *et al.*[24]	16	26.2[†]	41	87	67	48	NR	90	80	62
Fuks *et al.*[25]	39	–	–	–	–	–	NR	94	81	71
Hwang *et al.*[26]	17	27	–	–	–	–	NR	88	65	54
Kaido *et al.*[27]	19	77	NR	92	88	78	NR	90	77	77
Kim *et al.*[28]	15	20	NR	–	–	–	NR	90	86	–
Liu *et al.*[29]	39	30	NR	86	76	67	NR	88	78	61
Moon *et al.*[30]	17	11	NR	67	67	67	NR	83	80	61
Ng *et al.*[31]	12	31	–	–	–	–	61	100	80	41
Sapisochin *et al.*[32]	17	21	NR	86	68	58	NR	59	52	52
Shao *et al.*[33]	15	20	NR	68	68	–	NR	80	80	–
Vennarecci *et al.*[34]	9	26.3	NR	100	100	100	NR	89	89	89
Wu *et al.*[35]	36	61	NR	97	88	74	NR	97	81	70
Median value (range)		29 (11–77)	(21.8–NR)	86 (47–100)	68 (29–100)	67 (29–100)	(45.6–NR)	89 (59–100)	80 (52–100)	62 (41–89)

Survival from time of salvage transplantation.

[†]Mean value.

NR, not reached.

potentially reduce disease progression for patients waiting for liver transplantation and reduce the number of transplantations required. The pathological specimen obtained from a primary resection can also assist surgeons in identifying those patients at high risk of recurrence, who would most likely benefit from an SLT.[16,37] The theoretical rate of patients eligible for SLT at recurrence has been reported to be as high as 60–80%.[8,38] Although early clinical studies demonstrated the relative safety of this treatment strategy,[14,20] there have been concerns about prior primary resection increasing the difficulty of SLT, negating potential outcome benefits.

Inclusion criteria for primary hepatic resection were generally consistent among studies. Initial resection was indicated in patients with good residual hepatic function, few tumor nodules (ideally solitary nodule), absence of intraoperative evidence of macrovascular invasion, absence of extrahepatic malignancy, and anatomically resectable disease. Early detection of recurrence is largely attributed to strict patient follow-up involving a combination of clinical history, examination, α-fetoprotein level, abdominal ultrasound, triple-phase CT scan, and magnetic resonance imaging at three to six monthly intervals for at least 12 months. Indications for SLT, as with primary transplantation, were consistent with disease within the Milan criteria.[3] In addition, several SLT were performed on patients without disease recurrence, in the setting of hepatic decompensation[20,24] and as a bridge transplantation.[21]

This systematic review demonstrated reasonable rates of morbidity of the SLT strategy. Cumulative data from available studies in a recent systematic review by Maggs *et al*. suggest comparable rates of morbidity between primary transplantation and SLT.[36] Of the studies included in our review, Moon *et al*. reported the largest series with results of 169 primary transplantations and 17 SLT.[30] This study compared postoperative complications between primary transplantation and SLT, and did not demonstrate any significant differences between the rates of biliary (10.1 *vs* 17.6%, $P = 0.401$), bleeding (8.9 *vs* 11.8%, $P = 0.658$), vascular complications (1.8 *vs* 5.9%, $P = 0.321$), and the need for reoperation or retransplantation (4.1 *vs* 11.8%, $P = 0.193$). The length of hospital stay was also not significantly different between the two groups (37 *vs* 38 days, $P = 0.566$). Although operative time of salvage transplantation was increased when compared with primary transplantation in a number of studies, this difference was generally not significant.[28,39,40] Kaido *et al*. reported a retrospective analysis of living donor liver transplantations and demonstrated significantly increased operative time of SLT versus primary transplantation (941 min *vs* 763 min, $P = 0.0024$); however, this did not translate into differences in survival outcomes.[27] Given the heterogeneous nature of studies included in this review and Maggs *et al*., it is difficult to draw further comparisons of morbidity results between primary transplantation and SLT without further studies with more consistent methodology.

The mortality rates associated with SLT following hepatic resection was significant (5%), but only three studies reporting mortality rates > 10%.[20,32,34] Shabahang *et al*. reported outcomes of primary hepatic resection versus primary liver transplantation and reported similar mortality rates (7 *vs* 7%).[41] The mortality rate following primary liver transplantation was recorded in four of the studies (median 4%, range 2.1–7.0%, $n = 744$) and was similar to SLT.[20,26,29,30] The rate of SLT following recurrence in our review was, however, significantly lower than the rates reported in theoretical studies.[8,38]

This systematic review also demonstrates comparable overall and disease-free survival outcomes of the strategy of primary hepatic resection followed by SLT (median 62%, range 41–89%; median 67%, range 29–100%, respectively) when compared with primary liver transplantation (range 61–80%, range 58–89%, respectively).[20,24,29,30,32,34,35] In general, primary liver transplantation was associated with improved 5-year overall and disease-free survival, but these findings were only statistically significant in two studies,[20,35] and disease-free survival but not overall survival was significantly improved with primary transplantation in two other studies.[30,32]

The heterogeneous nature of currently available studies is recognized, and the heterogeneous cohort of patients may limit the ability for the results of this review to be extrapolated and compared against outcome data of other therapeutic modalities reported in the literature. The included studies either analyzed patients having previously undergone primary hepatic resection and subsequently SLT for recurrence, or retrospectively analyzed all patients receiving SLT to identify those who had received hepatic resection as treatment of primary disease. This variation in study design is reflected in data reporting. Studies employing the former study design[20,21,24,25,29,31,32] reported much higher median SLT rates of 41%, range 16–65%, when compared with median SLT rate 17%, range 7–36%, of purely retrospective studies.[22,23,26–28,30,33–35] It is recognized that the lack of randomized trials examining this treatment strategy also increases the potential risk of bias of the current literature.

Interestingly, Cucchetti *et al*. recently developed the Markov model to investigate the risk–benefit balance between primary liver transplantation and the treatment strategy discussed in this review.[42] This model suggests that primary liver transplantation can produce improved survival outcomes when compared with primary hepatic resection and SLT if 5-year posttransplant survival remains higher than 60%. The balance between benefits and harm of SLT is clearly directly affected by the number of HCC candidates for transplantation and the expected waiting list time-to-transplant of local centers.

This review demonstrates that upfront primary hepatic resection is the treatment of choice in many centers with high incidence of HCC and significant organ shortage.[8] In centers where all patients with HCC initially undergo hepatic resection, perhaps SLT should be viewed as one of many salvage treatment options. The comparison of SLT to other salvage treatment options is then more clinically relevant than comparisons with primary liver transplantations in such centers. Repeat hepatic resection is the only other potentially curative salvage therapy for recurrent HCC. A recent systematic review by our group on repeat hepatic resection as a salvage treatment option for recurrent HCC following primary resection demonstrates lower rates of morbidity and mortality, but worse disease-free and overall survival outcomes of repeat hepatic resection compared with SLT.[43] The relationship between these two salvage treatment therapies is also mirrored in comparisons between hepatic resection and liver transplantation for primary disease.[36]

The role of loco-regional therapy, in particular with the use of radiofrequency ablation (RFA), in recurrent HCC is still emerging. There is no evidence to support RFA as an alternative to SLT or

repeat hepatic resection in patients with recurrent HCC, except in those unsuitable for operative management. Chan *et al*. reported a single-center retrospective series and demonstrated significantly poorer 5-year overall and disease-free survival outcomes with RFA compared with SLT or repeat hepatic resection (11% *vs* 50%, 48%).[44] The role of RFA as neoadjuvant or adjuvant loco-regional therapy in relation to SLT is also unclear. Certainly for patients with disease exceeding the Milan criteria, RFA may be effective in downstaging the tumor;[45] however, the limited evidence available does not currently support improved disease-free or overall survival in this setting.[46]

Synthesis of available observational studies suggests that SLT following primary hepatic resection is a highly applicable treatment option with long-term survival outcomes and acceptable low rates of morbidity and mortality. Although no randomized studies between the two treatment strategies currently exist, the results of this review suggest that the tolerance and efficacy of these two treatment strategies may be comparable. The treatment strategy of primary hepatic resection followed by SLT may present an alternative to upfront liver transplantation with several potential benefits and is a clinical practice strategy that warrants further well-conducted randomized comparison study.

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