Systematic review

Meta-analysis of determinants of survival following treatment of recurrent hepatocellular carcinoma

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Background: **Intrahepatic recurrence of hepatocellular carcinoma (HCC) following resection is common. However, no current consensus guidelines exist to inform management decisions in these patients. Systematic review and meta-analysis of survival following different treatment modalities may allow improved treatment selection. This review aimed to identify the optimum treatment strategies for HCC recurrence.**

Methods: **A systematic review, up to September 2016, was conducted in accordance with MOOSE guidelines. The primary outcome was the hazard ratio for overall survival of different treatment modalities. Meta-analysis of different treatment modalities was carried out using a random-effects model, with further assessment of additional prognostic factors for survival.**

Results: **Nineteen cohort studies (2764 patients) were included in final data analysis. The median 5-year survival rates after repeat hepatectomy (525 patients), ablation (658) and transarterial chemoembolization (TACE) (855) were 35·2, 48·3 and 15·5 per cent respectively. Pooled analysis of ten studies demonstrated no significant difference between overall survival after ablation *versus* repeat hepatectomy (hazard ratio 1·03, 95 per cent c.i. 0·68 to 1·55; $P = 0·897$). Pooled analysis of seven studies comparing TACE with repeat hepatectomy showed no statistically significant difference in survival (hazard ratio 1·61, 0·99 to 2·63; $P = 0·056$).**

Conclusion: **Based on these limited data, there does not appear to be a significant difference in survival between patients undergoing repeat hepatectomy or ablation for recurrent HCC. The results also identify important negative prognostic factors (short disease-free interval, multiple hepatic metastases and large hepatic metastases), which may influence choice of treatment.**

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Introduction

Hepatocellular carcinoma (HCC) is currently the third leading cause of cancer-related mortality worldwide[1,2]. Partial hepatectomy is the recommended first-line treatment for primary HCC, where curative treatment is deemed possible[2]. Despite this, however, local recurrence rates as high as 70 per cent at 5 years following primary resection with curative intent have been reported[3].

The incidence of HCC is rising, with a reported fivefold increase over the past 30 years, from 1·51 to 6·20 per 100 000 between 1973 and 2011[4]. Consequently, it is to be expected that the number of patients requiring treatment for local recurrence will continue to undergo a similar increase. Risk factors for recurrence, such as the presence of satellites, cirrhosis and increased tumour size, are well established, and it is now increasingly accepted that a large proportion of patients diagnosed with HCC even at an early stage will potentially require repeated intervention[5]. In the event of recurrence of HCC, a number of treatment options may be considered. These consist most commonly of repeat hepatectomy (RH), radiofrequency ablation (RFA) or transarterial chemoembolization (TACE)[6–8]. The exact selection criteria determining treatment modality may vary between centres, although there are broad indications for each. RH is typically used to treat

single hepatic recurrence in the presence of Child–Pugh grade A liver disease and minimally deranged liver function and platelet count[6,9]. Ablation and TACE may be considered in local HCC recurrence with Child–Pugh grade A or B liver disease. For multiple recurrences, RFA may be considered if the lesions are few in number and size, with TACE more appropriate for recurrence with involvement of greater liver volumes in terms of tumour size or number[6,9]. Finally, some patients may also be considered for liver transplantation[6,9–11], typically in the setting of decompensated liver disease, local HCC recurrence and absence of other contraindications[6,9,11].

Although there are recognized European[2] and American[3] expert guidelines for the management of primary HCC, similar guidelines do not exist for HCC recurrences, despite their relatively common nature. The aim of this meta-analysis was to compare the overall survival associated with different treatment modalities and to identify prognostic factors for survival to determine optimum treatment strategies.

Methods

Search strategy

A literature search was conducted in line with the MOOSE guidelines[12]. The search involved online MEDLINE and Embase databases up to September 2016. A free-text search was carried out using the terms 'hepatocellular carcinoma', 'HCC', 'recurrence' and 'recurrent'. Boolean operators AND and OR were used to widen the search. References of the articles identified by the search were analysed by hand to identify any relevant citations missed on the initial search. Two independent researchers performed search and data extraction, and any discrepancies were resolved by consensus.

Selection criteria

Observational studies were included if they assessed factors for survival following failed initial curative treatment by hepatectomy. As the authors sought to include only patients treated with curative intent, studies were excluded if they involved patients with extrahepatic disease or lacked *post hoc* analysis of determinants of survival. Studies published in languages other than English with no translation readily available were also excluded.

Assessment of quality

The quality of cohort studies was assessed using the Newcastle–Ottawa Scale (NOS)[12]. This comprises a score ranging from 0 to 9, with points assigned on the basis of appropriateness of patient selection, comparability of cohorts, and adequate assessment of the final outcome to control for potential sources of bias.

Outcome measures

The primary outcome measure was the hazard ratio (HR) for overall survival. The relative effect of RH, ablation and TACE on overall survival was evaluated alongside the median 5-year overall survival rate for each intervention. Secondary outcomes included the additional prognostic factors for survival. Demographic details were extracted. All data was entered into an Excel™ (Microsoft, Redmond, Washington, USA) spreadsheet for analysis.

Statistical analysis

The logarithm of the HR with 95 per cent c.i. was used in comparison of the interventions. Where possible, data were extracted directly from the original study. When this information was not available, HRs were estimated from the data presented on overall survival or from Kaplan–Meier curves, using the method of Parmar and colleagues[13].

Meta-analysis was conducted using STATA/SE12® (StataCorp, College Station, Texas, USA). A random-effects model was used to identify subject-specific events with regard to treatment modalities. Funnel plots were used to assess publication bias. Heterogeneity between studies was evaluated using the χ^2 statistic and the I^2 value. Heterogeneity was defined as low, moderate or high, based on an I^2 value of less than 25 per cent, between 25 and 75 per cent, and over 75 per cent, respectively. Statistical significance was set at $P < 0{\cdot}050$.

Results

Search results

The original database search returned 7549 entries. Forty-nine candidate articles were retrieved and full-text versions reviewed following a search of titles and abstracts. A total of 19 studies[7–11,14–27] were included in the final data synthesis (*Fig. 1*). The included studies evaluated a total of 2764 patients with intrahepatic recurrence of HCC. All of these were single-centre retrospective cohort studies. The majority of patient data originated from centres in Asia (2499 of 2764 patients, 90·4 per cent).

Treatment modality

The included reports demonstrated great heterogeneity in procedures, and the outcomes reported. There was a marked difference in the algorithms for allocation

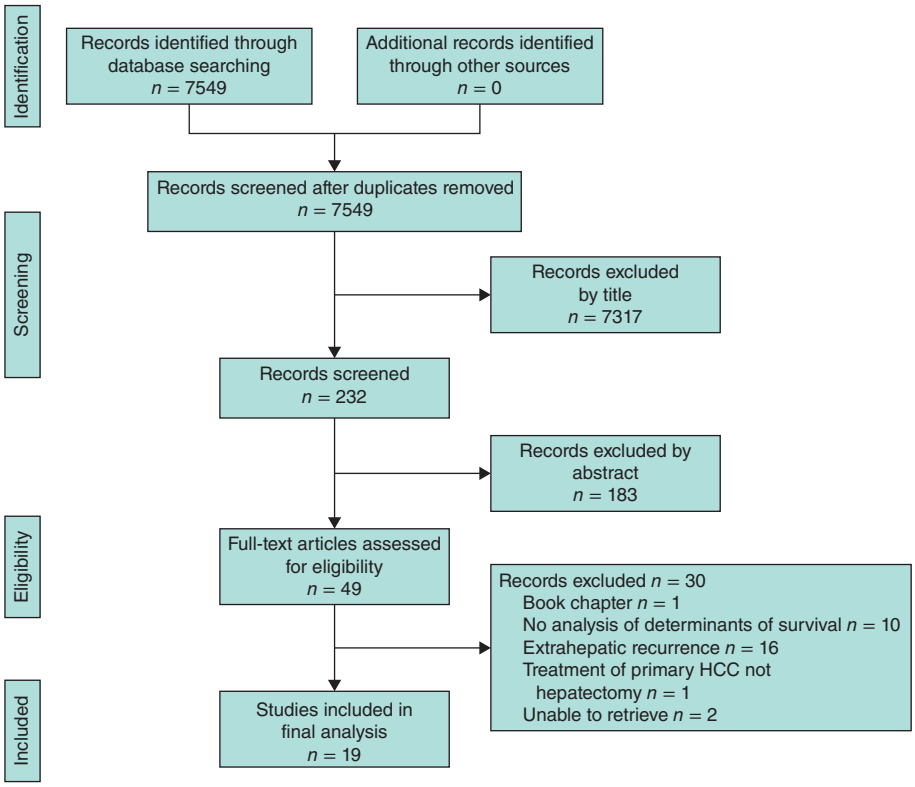

Fig. 1 PRISMA diagram showing selection of articles for review. HCC, hepatocellular carcinoma

of treatment between centres. Typically, the treatment options consisted of no treatment, RH, TACE, RFA or liver transplantation. However, the inclusion of one, some or all of these treatment options varied across the included studies (*Table 1*). Some studies offered multiple treatment modalities but chose to report only a given treatment subgroup; four studies[17,23–25] looked at RH alone. Centres offering ablation reported mostly RFA only[7,8,14–16,19,22]; however, three studies[11,18,20] used both RFA and ethanol ablation, combining these into a single ablation group. Additional ablation techniques, such as holminum[10] and microwave coagulation[21], were reported in single studies. No study reported the survival outcomes of patients treated with radiotherapy.

Patient demographics

Patient demographics between studies and treatment modalities were broadly similar, with no discernible differences in age and sex of the patients. Across the studies, the median age of those undergoing RH, TACE and ablation was 54·1 (range 44–66), 57·0 (51–72) and 59 (52·7–68) years respectively. The median proportions of men in each treatment arm were also similar: 80 (44–96), 83 (62–89) and 80 (74–100) per cent respectively.

The prevalence of hepatitis B virus (HBV) and hepatitis C virus (HCV) positivity, and cirrhosis is shown in *Table 1*. Their incidence differed greatly between studies. The prevalence of HBV ranged from 15 per cent[24] to 93 per cent[22]. There were no reasons given for the difference in HBV prevalence, and it most likely representative of local prevalence and treatment guidelines for HCC in the presence of HBV. Sun and colleagues[23] described a population of patients with recurrent HCC in the presence of HBV infection, and so all included patients were HBV-positive. The prevalence of HCV ranged from 0 per cent[14] to 89 per cent[21]; again, no immediately apparent reasons could be ascertained for this variation in rate of infection.

There was heterogeneous reporting with regard to length of follow-up, which was documented in ten studies[8–10,15,17,21–23,25,26]. Median follow-up in these was 26·2 (range 19–93) months.

Study quality

The overall quality of the included studies was high, with all but three[21,23,27] assigned a NOS score of 7 or greater. All were cohort studies and drew on local databases with good follow-up, with a low risk of selection or reporting bias.

Table 1 Study demographics

Reference	Country	*n*	Treatment (% of patients)	Underlying disease (% of patients)			Study quality (NOS score)
				HBV	HCV	Cirrhosis	
Koh *et al.*[14]	China	102	Ablation 41·2	67	0	12	9
			TACE 58·8	62	2	12	
Song *et al.*[15]	Korea	217	RH 18·0	92	3	59	9
			Ablation 82·0	90·0	3·8	59·0	
Wang *et al.*[7]	China	629	RH 20·3	36·4			9
			TACE 53·9	46·5			
			Ablation 25·8	60·2			
Chan *et al.*[16]	China	179	RH 16·2	90	4		7
			Ablation 25·1	89	7		
Ho *et al.*[8]	Taiwan	435	No therapy/supportive 18·0	73	26	41	8
			RH 12·4	72	32	48	
			TACE 58·0	63·0	34·2	47·6	
			Ablation 12·0	54	46	56	
Huang *et al.*[17]	China	82	RH 100	85	2	84	9
Li *et al.* [18]	China	99	No therapy/supportive 20	–			7
			RH 30	–			
			TACE 27	–			
			Ablation 10	–			
			PC ethanol injection 7	–			
Umeda *et al.*[19]	Japan	125	RH 23·2	28	66		8
			TACE 30·4	11	82		
			Ablation 46·4	19	70		
Roayaie *et al.*[9]	USA	179	RH 19·6	57	26		7
			Listed for transplant 44·1	–			
			TACE 19·0	–			
			Ablation 6·7	–			
Kawano *et al.*[20]	Japan	147	No therapy/supportive 12·2	–			9
			RH 8·8	–			
			TACE 56·5	–			
			Ablation 22·4	–			
Ueno *et al.*[21]	Japan	32	RH 28		89		6
			TACE 41		85		
			Ablation 31		60		
Choi *et al.*[10]	Korea	97	RH 9	–			7
			Listed for transplant 6	–			
			TACE 70	–			
			Ablation 14	–			
Liang *et al.*[22]	China	110	RH 40·0	93			9
			Ablation 60·0	91			
Kubo *et al.*[27]	China	51	RH 100		100		6
Shah *et al.*[11]	Canada	86	No therapy/supportive 38	–			9
			RH 13	–			
			Listed for transplant 4	–			
			TACE 9	–			
			Ablation 36	–			
Sun *et al.*[23]	China	57	RH 100	100			6
Shimada *et al.*[24]	Japan	41	RH 100	15	83		8
Hu *et al.*[25]	Taiwan	59	RH 100	–			8
Lee *et al.* [26]	Taiwan	37	RH 68	68	32	76	8
			TACE 32	58	33	75	

HBV, hepatitis B virus-positive; HCV, hepatitis C virus-positive; NOS, Newcastle–Ottawa Scale; TACE, transarterial chemoembolization; RH, repeat hepatectomy; PC, percutaneous.

Table 2 Factors affecting survival

	Reference	Outcome	Effect size
Treatment	Wang *et al.*[7]	OS	Ablation *versus* RH: HR 1·44 (0·94, 2·19) TACE *versus* RH: HR 2·95 (2·02, 4·31)‡
	Ho *et al.*[8]	OS	RH *versus* supportive: HR 0·14 (0·06, 0·34)* Ablation *versus* supportive: HR 0·1 (0·03, 0·29)* TACE *versus* supportive: HR 0·33 (0·19, 0·58)*
	Umeda *et al.*[19]	OS	RH *versus* TACE: HR 0·07 (0·02, 0·24)‡ Ablation *versus* TACE: HR 0·17 (0·06, 0·44)‡
	Shah *et al.*[11]	OS	Supportive *versus* any potentially curative treatment: HR 3·9 (2·1, 7·2)*
	Lee *et al.*[26]	OS	TACE *versus* RH: HR 0·98 (n.a.)*
Time to recurrence	Wang *et al.*[7]	OS	≤ 1 *versus* > 1 year: HR 1·59 (1·19, 2·14)†
	Huang *et al.*[17]	OS	≤ 18 *versus* > 18 months: HR 2·19 (1·07, 4·47)
	Shah *et al.*[11]	OS	≤ 1 *versus* > 1 year: HR 6·8 (3·3, 14·0)*
	Choi *et al.*[10]	OS	≤ 1 *versus* > 1 year: RR 6·75 (2·14, 21·29)‡
	Sun *et al.*[23]	OS	≤ 3 *versus* > 3 years: RR 4·57 (1·06, 19·61)*
	Huang *et al.*[17]	DFS	≤ 18 *versus* > 18 months: HR 2·32 (1·35, 3·98)†
No. of recurrent tumours	Wang *et al.*[7]	OS	Multiple *versus* single: HR 1·32 (1·03, 1·70)*
	Umeda *et al.*[19]	OS	≥ 3 *versus* < 3: HR 3·78 (1·69, 8·58)*
	Kawano *et al.*[20]	OS	Multiple *versus* single: HR 1·50 (1·16, 1·96)†
	Song *et al.*[15]	DFS	Multiple *versus* single: HR 2·78 (1·54, 5·03)‡
Tumour size	Ho *et al.*[8]	OS	≥ 5 *versus* < 5 cm: HR 1·11 (1·01, 1·22)*
	Umeda *et al.*[19]	OS	> 3 *versus* ≤ 3 cm: HR 4·01 (1·28, 12·7)*
	Huang *et al.*[17]	DFS	≥ 5 *versus* < 5 cm: HR 2·26 (1·30, 3·95)†
AFP	Koh *et al.*[14]	OS	> 400 *versus* ≤ 400 ng/ml: HR 2·36 (1·28, 4·36)†
	Wang *et al.*[7]	OS	> 20 *versus* ≤ 20 ng/ml: HR 1·66 (1·26, 2·20)†
Child grade	Ho *et al.*[8]	OS	B *versus* A: HR 2·15 (1·27, 3·65)* C *versus* A: HR 3·61 (1·63, 8·01)*
	Umeda *et al.*[19]	OS	B *versus* A: HR 3·84 (1·15, 16·6)*
	Choi *et al.*[10]	OS	≥ B *versus* A: RR 8·63 (1·76, 42·40)†
Initial Edmondson–Steiner stage	Wang *et al.*[7]	OS	III–IV *versus* I–II: HR 1·70 (1·20, 2·40)†
Microvascular invasion	Huang *et al.*[17]	OS	Yes *versus* no: HR 3·13 (1·38, 7·12)†
	Huang *et al.*[17]	DFS	Yes *versus* no: HR 4·07 (2·00, 8·29)†
Vascular invasion	Shah *et al.*[11]	OS	Yes *versus* no: HR 2·9 (1·4, 5·7)*
	Sun *et al.*[23]	OS	Yes *versus* no: RR 3·49 (1·36, 8·94)*
Primary portal vein invasion	Shimada *et al.*[24]	OS	Yes *versus* no: RR 3·26; †Cox's coefficient 1·180(s.e. 0·422)
ALT	Song *et al.*[15]	DFS	> 40 *versus* ≤ 40 units/l: HR 1·52 (1·03, 2·24)*
Varices at initial diagnosis	Wang *et al.*[7]	OS	Yes *versus* no: HR 1·61 (1·23, 2·10)†
Intraoperative blood transfusion	Kawano *et al.*[20]	OS	Yes *versus* no: HR 1·49 (1·19, 1·88)†
Sex	Hu *et al.*[25]	OS	Women *versus* men: HR 3·56 (n.a.)*
Recurrent tumour grade	Hu *et al.*[25]	OS	G2 *versus* G1: HR 0·14 (n.a.)† G3 *versus* G1: HR 0·56 (n.a.)
Albumin	Choi *et al.*[10]	OS	≤ 3·5 *versus* > 3·5 g/dl: RR 4·59 (1·80, 11·80)†
Second recurrence	Koh *et al.*[14]	OS	Recurrence treated by ablation *versus* no recurrence: HR 11·73 (1·46, 94·39)* Recurrence treated by TACE *versus* no recurrence: HR 7·79 (1·05, 57·74)*
Age at recurrence (patients with late recurrence)	Li *et al.*[18]	OS	> 52 *versus* ≤ 52 years: HR 2·19 (1·20, 4·01)*
Vascular invasion (patients with early recurrence)	Li *et al.*[18]	OS	Yes *versus* no: HR 3·03 (1·06, 8·60)*
ALT (patients with early recurrence)	Li *et al.*[18]	OS	> 40 *versus* ≤ 40 units/l: HR 3·20 (1·28, 8·03)*

Values in parentheses are 95 per cent confidence intervals. OS, overall survival; RH, repeat hepatectomy; HR, hazard ratio; TACE, transarterial chemoembolization; n.a., not available; RR, risk ratio; DFS, disease-free survival; AFP, α-fetoprotein; ALT, alanine aminotransferase. *$P < 0{\cdot}050$; †$P < 0{\cdot}010$; ‡$P < 0{\cdot}001$.

Factors determining survival

There was great variation between studies in factors found to be predictive of improved survival. *Table 2* summarizes effect sizes determined by multivariable analysis of prognostic factors found to be significant. The four factors most frequently identified as predictors of better prognosis were RH or ablation over TACE or no treatment[7,8,11,19,26], increased time to recurrence[7,11,17], and having fewer recurrent tumours[7,19,20]. In adjusted regression analyses, RH conferred the greatest survival in comparison to TACE, with a HR of as low as 0·07[19].

Table 3 Five-year overall survival

	RH		TACE		Ablation	
Reference	*n*	5-year survival (%)	*n*	5-year survival (%)	*n*	5-year survival (%)
Koh *et al.*[14]	–	–	60	26	42	24
Song *et al.*[15]	39	84	–	–	178	71·0
Wang *et al.*[7]	128	43·0	339	8·3	162	26·7
Chan *et al.*[16]	29	35	–	–	45	29
Ho *et al.*[8]	54	72	254	56·0	50	83
Huang *et al.*[17]	82	22	–	–	–	–
Umeda *et al.*[19]	29	56	38	0	58	48
Roayaie *et al.*[9]	35	67	–	–	–	–
Kawano *et al.*[20]	13	25	83	23	33	78
Ueno *et al.*[21]	9	29	13	0	10	57
Choi *et al.*[10]	6	n.a.	68	16	14	n.a.
Liang *et al.*[22]	44	28	–	–	66	40
Sun *et al.*[23]	57	31	–	–	–	–
Overall*	525	35·2	855	15·5	658	48·3

*Overall 5-year survival rates are median values. RH, repeat hepatectomy; TACE, transarterial chemoembolization; n.a., not available.

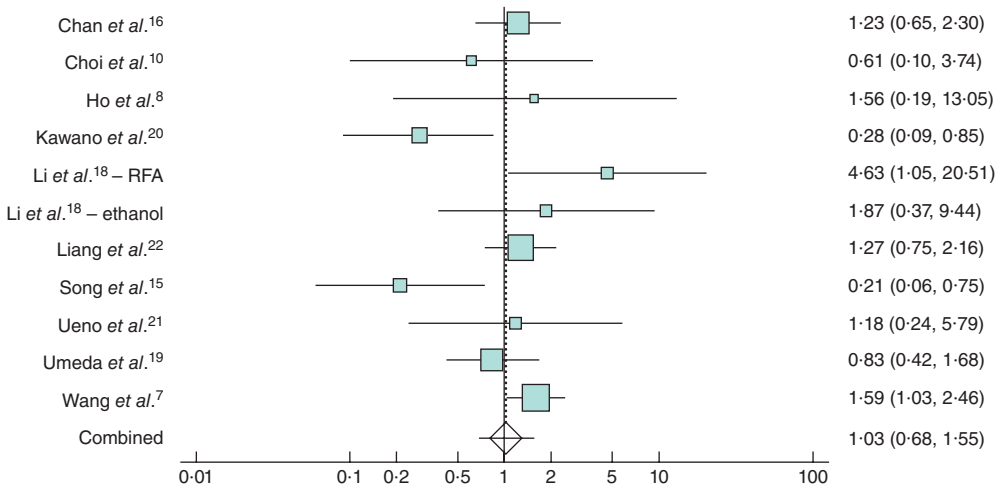

Fig. 2 Forest plot comparing 5-year overall survival after ablation *versus* repeat hepatectomy. A random-effects model was used for meta-analysis. Hazard ratios are shown with 95 per cent confidence intervals. RFA, radiofrequency ablation. $P = 0{\cdot}897$

Rapid recurrence of the tumour within 1 year was reported to have the greatest effect in reducing survival (HR 6·8, 95 per cent c.i. 3·3 to 14·0; $P < 0{\cdot}050$)[11], in addition to having more than three recurrent tumours (HR 3·78, 1·69 to 8·58; $P < 0{\cdot}050$)[19] and recurrent tumours larger than 3 cm in diameter (HR 4·01, 1·28 to 12·7; $P < 0{\cdot}050$)[19].

Numerous other factors predictive of survival were identified (*Table 2*), such as serum α-fetoprotein level and Child grade. However, these were almost invariably confined to single studies or analyses.

Overall survival

Median 1-year overall survival rates were 89·7 (range 69·0–94·5), 87·1 (76·6–94·7) and 79·7 (76·6–93·6) per cent for RH, ablation and TACE respectively. Corresponding 3-year survival rates were 61·2 (40·8–71·5), 48·4 (39·7–75·1) and 38·2 (22·5–68·1) per cent. The available data on 5-year overall survival were also pooled (*Table 3*). Reported 5-year survival rates following TACE were particularly poor (median 15·5 (range 0–56·0) per cent). Survival rates were better following RH (35·2 (22–84) per cent) or ablation (48·3 (24–83) per cent).

Meta-analysis of comparative studies

Ablation versus *repeat hepatectomy*

Pooled analysis of ten studies included 1020 patients, 633 (62·1 per cent) treated by ablation and 387 (37·9 per cent) by RH. Median follow-up ranged from 21·1 to

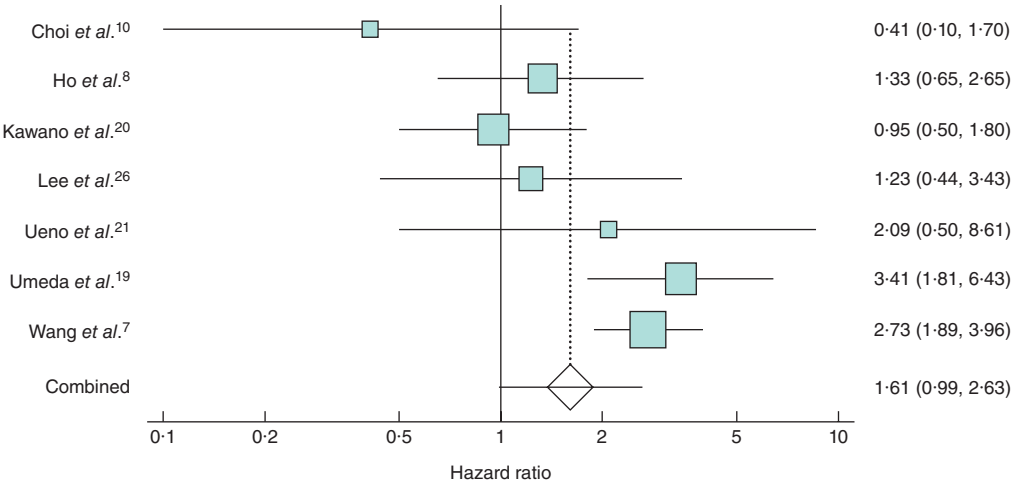

Fig. 3 Forest plot comparing 5-year overall survival after transarterial chemoembolization *versus* repeat hepatectomy. A random-effects model was used for meta-analysis. Hazard ratios are shown with 95 per cent confidence intervals. $P = 0{\cdot}056$

93·0 months. The pooled analysis showed no statistically significant difference in survival between the two treatments (ablation *versus* RH: HR 1·03, 95 per cent c.i. 0·68 to 1·55; $P = 0{\cdot}897$) (*Fig. 2*). There was a moderate level of statistical heterogeneity for this result ($I^2 = 51{\cdot}2$ per cent).

Transarterial chemoembolization versus *repeat hepatectomy*

Pooled analysis of seven studies included 1074 patients, 807 (75·1 per cent) treated with TACE and 267 (24·9 per cent) with RH. Median follow-up ranged from 24 to 93 months. There was no statistically significant difference in overall survival between TACE and RH (HR 1·61, 0·99 to 2·63; $P = 0{\cdot}056$) (*Fig. 3*). The level of statistical heterogeneity for this result was moderate ($I^2 = 65{\cdot}9$ per cent).

Transarterial chemoembolization versus *ablation*

There were too few studies with survival curves comparing TACE *versus* ablation for formal analysis of these two treatment modalities.

Bias exploration

Funnel plots allowed both combined and subgroup analysis of bias, and demonstrated symmetry. Sensitivity analyses for subgroups were performed by exploring the effect of removal of an individual study from the meta-analysis; this did not lead to any significant changes in HRs (data not shown).

Discussion

This review summarizes the currently available literature on treatments for recurrent HCC. The evidence suggests that in the context of locally recurrent HCC, despite best treatment with curative intent, 5-year survival rates are relatively moderate to poor, with median 5-year survival across the included studies ranging from 48·3 per cent (ablation) to as low as 15·5 per cent (TACE). This variation in outcomes partially reflects the heterogeneity between treatment practices across the world, which may be due in part to differences in local populations.

The overall survival associated with each procedure is comparable to that of the same treatments in primary HCC. Llovet and co-workers[28] described an expected 5-year overall survival of greater that 50 per cent in recent studies involving primary resection of HCC, whereas the median 5-year survival rate after resection of recurrence was 35·2 per cent in the present study. Lencioni *et al.*[29] reported overall survival at 5 years after radiofrequency ablation as primary treatment of 41 per cent, compared with 48·3 per cent after treatment of recurrence in the present study. O'Suilleabhain and colleagues[30] documented an overall survival rate of 8·0 per cent at 5 years after primary TACE, in comparison with 15·5 per cent 5 years after TACE for recurrent HCC found in this review. The results are far superior to those of systemic therapies, such as sorafenib. In patients with advanced HCC, Llovet and co-workers[31] reported that sorafenib increased overall survival from 7·9 to 10·1 months.

The present analysis found no difference in overall survival of patients treated with ablation *versus* RH. RH is often used as the primary modality to achieve curative resection of primary HCC among patients with small, solitary tumours but no significant disease. Recent RCTs[32,33] have questioned whether surgery provides a true survival advantage over ablation for patients with these primary tumours.

None of the studies included in this review detailed the survival outcomes following radiotherapy for HCC recurrence. Selective internal radiation therapy is used in primary HCC to downstage tumours or for palliation in patients with a life expectancy below 3 months[34]. It is likely to have similar applications in recurrent HCC. Stereotactic body radiotherapy has similarly revolutionized HCC radiotherapy[35].

A large proportion (90·4 per cent) of the patients included in this review were treated in Asian centres where the prevalence of HCC is far greater than in the West. This can in part be attributed to the high prevalence of HBV in southeast Asia[26,27]. However, the incidence of HCC is rising in Western nations; this has been attributed in part to increasing obesity and consumption of alcohol[36]. Such disease differences, as well as other patient-, culture- and health system-related differences should be taken into account when interpreting the findings of this review in a global context.

In an attempt to address such underlying confounders, this review has also summarized data on patient-, treatment- and tumour-related factors that have been found to have significant associations with long-term survival. Multivariable regression analyses conducted in the included studies controlled for other confounding factors, such as variations in population characteristics. The most significant factors in reducing patient survival are treatment modality, time to recurrence, number of tumours and size of tumours. Increased tumour invasiveness correlated negatively with prognosis. Recurrence within 1 year of primary resection can increase the probability of death up to sevenfold[11]. Although there was heterogeneity in the reported parameters for number and size of tumours, all studies reported a significant negative relationship between these factors and survival. Many other factors were also identified, but without consensus across studies. More research is required to strengthen the evidence before these prognostic factors can be considered when planning treatment.

Although a short interval to recurrence is associated with poor survival, it remains uncertain whether early monitoring may also influence rates of cure. In other malignancies, enhanced surveillance programmes have led to earlier identification of recurrence or metastases with no effect on long-term survival. The recent FACS trial[37] of follow-up after surgery for colorectal cancer demonstrated that intensive screening had limited effects on mortality, even though it increased early diagnosis and treatment rates.

This review is limited by the quality of the included studies. Although study quality was acceptable, the studies were relatively small observational series with incomplete follow-up. This makes it difficult to determine the true effects of treatment, as patients with less severe disease were more likely to have undergone RH. Patients who had TACE may have had more severe co-morbidities. However, five separate studies[7,8,11,19,26] demonstrated in multivariable analysis that treatment modality is a prognostic factor independent of patient and tumour factors. Many studies did not report the algorithm by which treatment was assigned, and it was not all-encompassing in those that did. Moreover, there were tangible differences between the populations in different studies and, in the absence of standardized reporting of treatment algorithms, it is difficult to draw definitive conclusions about the treatment in relation to patient- and disease-specific characteristics. For example, 84 per cent of the patients undergoing RH described by Huang and colleagues[17] had cirrhosis, compared with 48 per cent of those in the RH cohort reported by Ho and co-workers[8]. This may be responsible for the discrepancy in 5-year survival data between the two cohorts. The creation of a tumour board review in the management of recurrent HCC may help in standardizing treatment selection[38].

The significant heterogeneity between individual studies in populations, treatment protocols and reporting of endpoints prevented the implementation of formal meta-regression to further identify prognostic factors. Despite these limitations, this systematic review provides valuable insights into outcomes after treatment of recurrent HCC and suggests important further steps. The introduction of an international registry for recurrent HCC would allow collation of the ever-increasing volumes of data, and permit deeper insights into the natural history and course of this disease. The Korean Liver Cancer Study Group and Asian Pacific Association for the Study of the Liver have provided some guidance on treatment modalities in recurrent HCC[39,40]. However, there is currently no evidence available of hierarchical level greater than IIb, and no formal guidelines are available from any recognized expert body. This stands in stark contrast to the management of other hepatic malignancies[2,41]. Additionally, recurrence following ablation is of concern, but studies describing this have not been included in the present review. There is a paucity of published data regarding recurrence after ablation and it was decided to focus on outcomes after hepatectomy to improve the homogeneity between the included studies. Finally, it is important to consider, especially in the treatment of cancer, outcomes beyond pure survival benefit. Quality-of-life outcomes are important in guiding clinical practice, but were not addressed in this review because few studies have examined the impact of treatments for recurrent HCC on patient-reported outcomes. The formulation

of treatment guidelines would also benefit from studies analysing the effect of these treatments on quality of life, in addition to survival.

Disclosure

The authors declare no conflict of interest.

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