A meta-analysis of adjuvant therapy after potentially curative treatment for hepatocellular carcinoma

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BACKGROUND: The high recurrence rate of hepatocellular carcinoma (HCC) after potentially curative treatment determines the long-term prognosis.

OBJECTIVE: To evaluate the efficacy and safety of adjuvant therapies in patients with HCC who have undergone hepatic resection, transplantation or locoregional ablation therapy.

METHODS: Several databases were searched to identify randomized controlled trials (RCTs) fulfilling the predefined selection criteria. Meta-analyses were performed to estimate the effects of adjuvant therapies of any modality on recurrence-free survival (RFS) and overall survival (OS).

RESULTS: Eight adjuvant modalities were identified from 27 eligible RCTs conducted predominantly in Asian populations comparing adjuvant with no adjuvant therapy. Adjuvant chemotherapy, internal radiation and heparanase inhibitor PI-88 therapy failed to improve RFS or OS, while interferon (IFN) therapy yielded significant survival results. The findings of adjuvant vitamin analogue therapy required further examination. Adjuvant adoptive immunotherapy conferred significant benefit for RFS but not for OS. Although cancer vaccine therapy and radioimmunotherapy may improve survival after radical surgery, the results were from single, small-scale trials. Severe side effects were observed in the studies of adjuvant chemotherapy and of IFN therapy.

CONCLUSIONS: Adjuvant IFN therapy can improve both RFS and OS; however, the benefits of using this agent should be weighed against its side effects. Combination of systemic and transhepatic arterial chemotherapy is not recommended for HCC after potentially curative treatment. Other adjuvant therapies produce limited success for survival. Additional RCTs with proper design are required to establish the role of adjuvant therapies for HCC.

Key Words: *Adjuvant therapy; Hepatocellular carcinoma; Recurrence; Survival*

Une méta-analyse de la thérapie adjuvante après un traitement au potentiel curatif contre le carcinome hépatocellulaire

HISTORIQUE : Le taux élevé de récurrence de carcinome hépatocellulaire (CCH) après un traitement au potentiel curatif en détermine le pronostic à long terme.

OBJECTIF : Évaluer l'efficacité et l'innocuité des thérapies adjuvantes chez des patients atteints d'une CCH qui ont subi une résection hépatique, une transplantation ou une ablation locorégionale.

MÉTHODOLOGIE : Les auteurs ont fait des recherches dans plusieurs bases de données pour en extraire les essais aléatoires et contrôlés (EAC) qui respectaient les critères de sélection prédéfinis. Ils ont procédé à des méta-analyses pour évaluer les effets des thérapies adjuvantes, quelles que soient leurs modalités, sur la survie sans récurrence (SSR) et la survie globale (SG).

RÉSULTATS : Les chercheurs ont établi huit modalités tirées des 27 EAC admissibles menés surtout auprès de populations asiatiques, qui comparaient la thérapie adjuvante à l'absence de thérapie adjuvante. La chimiothérapie adjuvante, la radiation interne et la thérapie par inhibiteur de l'héparanase PI-88 n'amélioraient pas la SSR et la SG, mais la thérapie à l'interféron (IFN) donnait des résultats significatifs sur le plan de la survie. L'immunothérapie adjuvante adoptive avait d'importants avantages pour la SSR, mais par pour la SG. Même si la thérapie du cancer par la vaccination et la radio-immunothérapie peuvent accroître la survie après une chirurgie radicale, les résultats provenaient d'essais uniques à petite échelle. Les chercheurs ont observé des effets secondaires marqués dans les études sur la chimiothérapie adjuvante et la thérapie à l'IFN.

CONCLUSIONS : La thérapie à l'IFN adjuvante peut améliorer la SSR et la SG, mais il faudrait soupeser les avantages de cet agent par rapport à ses effets secondaires. Il n'est pas recommandé de dispenser une association de chimiothérapie systémique et artérielle transhépatique du CCH après un traitement au potentiel curatif. Les autres thérapies adjuvantes avaient peu de succès sur le plan de la survie. D'autres EAC bien conçus s'imposent pour établir le rôle des thérapies adjuvantes du CCH.

Worldwide, hepatocellular carcinoma (HCC), the most common primary cancer of the liver, ranks sixth among malignant tumours in incidence and is the third leading cause of cancer-related death (1). In China, owing to the high prevalence of hepatitis B viral infection and associated liver cirrhosis, HCC accounts for >54% of the world annual incidence, with an estimated 372,079 mortalities in 2008 (1-3).

For many years, surgery (hepatic resection and transplantation) has been considered the only curative option for HCC. Locoregional ablation therapy, particularly percutaneous radiofrequency ablation (RFA), was recently demonstrated to have similar efficacy to surgical resection for small HCC nodules (<3 cm in diameter) (4). Although these

treatments offer a possibility of cure for HCC, the long-term outcomes after surgery or ablation therapy are disappointing because of the high frequency of recurrence. HCC often recurs as a result of intrahepatic dissemination of primary cancer cells or the development of a de novo tumour in the cirrhotic liver, which, in total, complicates 70% of cases at five years (5-7). However, because it is difficult to distinguish the two types of HCC recurrence in routine clinical practice, the presence of tumour originating from either primary or metachronous multicentric carcinogenesis is regarded as a recurrence (8). Therefore, adjuvant therapy that aims to reduce or delay the incidence of recurrence by eradicating the growth of pre-existing minute tumour foci not detected before initiation of adjuvant therapy, or by inhibiting the occurrence

of metachronous multicentric tumours, is essential to improve the efficacy of curative treatment of HCC.

Several adjuvant modalities have been developed in the past decades; nevertheless, the clinical use of these therapies is either controversial or requires further evaluation (9). To date, there have been five reviews or meta-analytic studies (10-14) published between 2002 and 2009 assessing the role of neoadjuvant and/or adjuvant therapy for HCC. While the early analyses (10-12) had achieved modest survival benefits from some adjuvant therapies, two recent studies with updated evidence (13,14) only applied qualitative descriptive approaches for therapeutic evaluation. Furthermore, these studies (10-14) neither considered modalities other than surgical resection as potentially curative treatment for HCC, nor quantitatively measured the effects of adjuvant therapies on survival using time-to-event outcomes. On the other hand, although previous individual meta-analyses have also shown encouraging results with adjuvant chemotherapy (15,16), adjuvant immunotherapy (17-23) and vitamin analogue chemoprevention (24), some of these may be inconclusive or of doubtful accuracy because of bias due to limited sample size and statistical methodological flaws (15,16,24). Nevertheless, emerging evidence from randomized controlled trials (RCTs) of novel adjuvant modalities and from trials with updated information is currently available. Given that no therapies after potentially curative treatments have been accepted as standard of care in HCC to date, the effects of adjuvant therapies on recurrence and survival are even less clear. Using currently available RCT evidence and knowledge of survival analysis (25-27), the aim of the present study was to evaluate the efficacy of adjuvant therapies of any modality in terms of the hazard ratio (HR) of recurrence-free survival (RFS) and overall survival (OS), and the safety of these adjuvant therapies after potentially curative treatment with surgical resection, liver transplantation or ablation therapy for HCC.

METHODS

Literature search
The Cochrane Library, MEDLINE (via PubMed) and Embase were searched using the keywords "hepatocellular carcinoma" and "recurrence". Both medical subject and text terms were used and combined, and the search strategy was not restricted to languages or publication date. However, only RCTs were considered in the present meta-analysis, for which searches in MEDLINE and Embase were limited by study type. The searches were performed mainly in June 2011, and the result was updated in November 2011. In addition, published meta-analyses and reviews of relevance were scrutinized for other potential studies, and reference lists of included trials were manually searched.

Inclusion and exclusion criteria
RCTs published as full text assessing adjuvant therapy in patients with HCC who had undergone potentially curative treatment with surgical resection, hepatic transplantation or locoregional ablation therapy were eligible if recurrence-related outcomes were analyzed using survival analysis. However, to guarantee that adjuvant therapy was truly adjuvant, only trials in which randomization was performed after patients had been treated with initially curative treatment were considered. Trials concurrently comparing sequential combinations of curative and adjuvant therapies versus curative treatment alone were excluded because adjuvant effects in such trials could not be separately evaluated due to the presence of initially curative treatment. Similarly, given the nature of neoadjuvant trials for which patient allocation is achieved before curative treatment, neoadjuvant therapy was not included in the present study. Furthermore, because no well-accepted adjuvant therapeutic modality has been currently established, the meta-analysis only compared adjuvant therapy with no active adjuvant therapy (no treatment or concurrent placebo). Other exclusions were trials with nonrandomized design, studies involving noncurative or palliative treatment for HCC, and trials comparing different adjuvant therapies or different schedules of one adjuvant therapy.

Study selection and outcomes measurement
All references records retrieved from the searches were stored in an EndNote (Thomson Reuters, USA) file and duplicates were removed. Two authors independently assessed eligibility against the inclusion criteria by scanning the title and abstract of each record, with disagreement resolved by discussion. Where studies had multiple publications, the most recent report was included and secondary articles were also considered. Trials containing three or more study groups were retained if at least two groups addressed an eligible comparison.

The primary outcome was RFS, which is also referred to as disease-free survival (DFS). However, for studies in which neither of the two outcomes was reported, time to recurrence (TTR) was used as a surrogate outcome. The secondary outcomes were OS and side effects.

Data extraction and analysis
Information regarding adjuvant therapy protocols of each trial was extracted and tabulated, along with tumour histological factors (size, number and vascular invasion) and staging of HCC, and underlying liver disease, which are the variables that are the most important predictors of recurrence and survival (28-30). Details of methodological quality assessment of the included RCTs were also abstracted. The number of patients developing events (recurrence or death) during follow-up was recorded. Locations and types of recurrence, and reasons for death were also presented. Furthermore, to determine the risk of patients developing events, recurrence and survival rates at various time points (one, two, three, four and five years) for patients in the control group (did not receive an active adjuvant therapy) were reported.

The HR of time-to-event outcomes (ie, RFS, TTR and OS) was directly extracted from trial publication, if available, or was estimated indirectly using the reported number of events and the corresponding P value for the log-rank statistics, or by reading survival curves, as described by Parmar et al (25). An Excel spreadsheet (Microsoft, USA) developed by the Meta-analysis Group of the MRC Clinical Trials was used for the calculations (26).

A pooled analysis was performed for RCTs testing a similar modality of adjuvant therapy, for which all trials included were analyzed in several subgroups to assess their effects on RFS and OS. Sensitivity analyses were performed to examine effects of excluding extraordinary studies with either quality concerns or confounding data. In the safety analyses, however, because the criteria for assessment varied across trials, only side effects requiring a discontinuation of adjuvant therapy were reported. All outcomes data were extracted on worksheets and were cross-checked for accuracy by two authors before combining for analysis.

Quality assessment
The methodological quality of RCTs was assessed independently by two authors, using the criteria outlined in *Cochrane Handbook for Systematic Reviews of Interventions* (Version 5) (31). Any disagreement was resolved by discussion or by consulting a third author. Six items assessing components of internal validity of RCTs were applied: generation of random sequence, allocation concealment, completeness of outcomes data reporting, whether free of selective reporting, and other bias including whether balanced in baseline characteristics and whether there was a priori sample size calculation. Blinding was, however, removed in the assessment of risk of bias, given the impracticability to mask adjuvant therapy in most trials using no treatment as a comparator. Each item was scored as 'yes' for low risk of bias, 'unclear' for either lack of information or uncertainty over the potential for bias, and 'no' for high risk of bias.

Statistical analysis
Time-to-event outcomes were combined using the inverse variance method in Review Manager Software (Version 5.1.1, The Nordic Cochrane Centre, The Cochrane Collaboration) with a fixed-effect model. A pooled HR represents the overall risk of an event on adjuvant therapy over control, in which HR <1.0 favoured adjuvant therapy and HR ≥1.0 favoured control. Respective 95% CIs were calculated for each estimate. Statistical heterogeneity of the results of
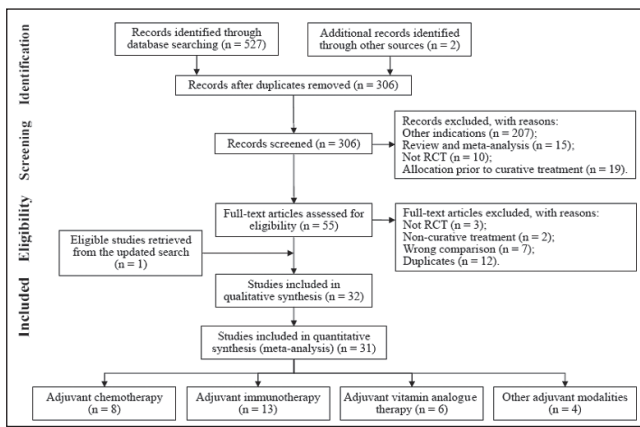
Figure 1) *PRISMA flow diagram for randomized controlled trials (RCT)*

the trials was assessed using the χ^2 statistic and the proportion of variation due to heterogeneity was expressed as I^2, where $I^2<25\%$ is considered to be low-level heterogeneity, 25% to 50% as moderate-level, and $I^2>50\%$ as high-level heterogeneity (32). Recurrence and survival rates were expressed as median values with the minimum to maximum range.

RESULTS

Search results and characteristics of the included RCTs

The databases searches indentified 527 records, and another two were obtained from references lists. Of these, 474 were initially judged as irrelevant, yielding 55 potential study reports that were assessed for eligibility at full-text level, resulting in retrieval of another prospective trial. Finally, 32 publications corresponding to 28 RCTs met the inclusion criteria, from which 31 publications (33-63) of 27 trials, involving a total of 2614 randomized patients, were eligible for analysis (one study [64] was excluded due to insufficient reporting of survival outcomes data). Figure 1 summarizes the study identification flow according to the recommendations of the PRISMA statement (65).

From the 31 trial publications assessing adjuvant therapy, eight modalities were indentified, including chemotherapy in eight (three [33-35] involved oral, three [36-38] transhepatic arterial and two [39,40] a combination of systemic and transhepatic arterial approaches), interferon (IFN) therapy in nine (eight [42-49] used IFN-α and one [41] IFN-β), vitamin analogue therapy in six (two [50,51] tested polyprenoic acid, a vitamin A [VA] analogue; and four [52-55] menatetrenone, a vitamin K2 [VK2] analogue), adoptive immunotherapy in three (one [56] involved lymphokine-activated killer [LAK] and two [57,58] cytokine-induced killer [CIK] cells), cancer vaccine therapy with autologous HCC fragments in one (59), internal radiation therapy using transhepatic arterial infusion of iodine 131-labelled lipiodol (^{131}I-lipiodol) in two (60,61), antibody-targeted radioimmunotherapy with ^{131}I-lipiodol metuximab (Licartin, Chengdu Hoist Hitech Co. Ltd, China; and the Fourth Military Medical University, Xi'an, China) in one (62), and molecular targeted therapy with heparanase inhibitor PI-88 in one study (63) (Table 1). Most of the trials were conducted or presented in the past decade, and all except one (47) were performed among Asian populations (Japan and China). The sample size of the RCTs varied from 15 (38) to 548 (55), and the range of median follow-up duration was between 12.3 (62) and 66 (61) months. Randomization was done after curative treatment for HCC in all of these adjuvant trials, and the delay between curative and the first adjuvant therapy was usually scheduled to commence after one month. Of the RCTs included, 24 trials compared adjuvant therapy with no active adjuvant therapy, while the other three (50,55,62) used a concurrent control group involving placebo.

With regard to modes of initially curative treatment, 26 RCTs used hepatic resection, or locoregional ablation therapy (percutaneous

TABLE 1
General information regarding the included studies

Item	RCTs (publications), n (n)
Total	27 (31)
Years of publication	
1990–2000	9 (11*)
2001–2010	17 (19)
2011–present	1 (1)
Countries involved (investigator affiliations)	
Japan	15 (18)
China	11 (12)
Italy	1 (1)
Adjuvant therapeutic modality	
Chemotherapy	8 (8)
Interferon therapy	7 (9)
Adoptive immunotherapy	3 (3)
Cancer vaccine therapy	1 (1)
Vitamin analogue therapy	5 (6)
Internal radiation therapy	1 (2)
Antibody targeted radioimmunotherapy	1 (1)
Heparanase inhibitor PI-88 therapy	1 (1)
Curative treatment modality for hepatocellular carcinoma	
Hepatic resection	17 (20)
Locoregional ablation therapy†	3 (3)
Hepatic resection or locoregional ablation therapy†	6 (7)
Liver transplantation	1 (1)
Sample size‡	
<30 patients per study group	13 (16)
≥30 patients per study group	14 (15)
Duration of follow-up, years§	
<2	8 (8)
≥2	19 (23)
Outcomes of interest	
Recurrence-free survival or disease-free survival	18 (21)
Time to recurrence	9¶ (10)
Overall survival	22 (26)

Two reports from one trial were presented in 1999 and in 2008, respectively; †Includes ablation therapy with or without transhepatic arterial therapy; ‡In terms of patients analyzed; §One study reported time to second primary hepatocellular carcinoma; ¶According to presented recurrence curves. RCT Randomized controlled trial

ethanol/acetic acid injection or RFA) given with or without transarterial chemoembolization, while the remaining RCT (62) involved liver transplantation. Nevertheless, among the individual trials in which surgical resection or ablation therapy was used as initial treatment for HCC (41,50,52-55), the proportion of patients receiving either of the treatments was balanced between the compared groups. Curative treatment was performed for primary HCC in all trials except for one (55), in which 21% of the enrolled patients had undergone hepatic resection or ablation therapy for their first intrahepatic recurrence of HCC. Of the 27 RCTs, 22 (33,35-37,39,40,44-50,52-54,56-59,61,63) specified curativity of initial treatment, which was usually on the basis of defining a completed tumour-eliminating surgical or ablation procedure and/or identifying a postprocedural imaging findings indicative of no demonstrable residual tumour.

The searches identified three publications of one trial by Kubo et al and others (42-44). Although the latest report (44) provided final outcomes data, the previous two publications (42,43) were also considered for analysis because they reported other important information of the trial accrual. The polyprenoic acid study by Muto et al (50,51) and internal radiation study by Lau et al (60,61) also presented two

TABLE 2
Summary of study results regarding recurrence and survival

Study* (reference)	Overall recurrence, n	Intrahepatic recurrence, %	Recurrence rates for patients without adjuvant therapy, %					Overall death, n	Death due to recurrence, %	Survival rates for patients without adjuvant therapy, %				
			1-year	2-year	3-year	4-year	5-year			1-year	2-year	3-year	4-year	5-year
Izumi et al (36)	40	93	57	78	88	94	94	31	87	81	65	53	37	29
Yamamoto et al (33)	35	83	28	48	66	71	82	22	68	82	78	67	52	48
Ono et al (40)	38	97	19	30	59	71	84	23	83	92	81	77	56	56
Lai et al (39)	40	80	31	47	52	52	NA	20	95	94	88	64	64	NA
Muto et al (50,51)	34	NA	28†	36†	50†	NA	NA	NA	NA	98	86	77	67	60
Ueno et al (37)	NA	NA	56	78	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Lau et al (60,61)	24	88	41	64	64	68	68	26	81	86	62	46	36	36
Ikeda et al (41)	8	NA	63	100	NA	NA	NA	0‡	NA	NA	NA	NA	NA	NA
Takayama et al (56)	102	90	40	55	67	73	78	52	92	95	85	74	68	62
Kubo et al (42–44)	22	100	19	47	74	80	87	12	100	94	87	80	58	47
Shiratori et al (45)	NA	NA	24	70	76	85	92	41	100	96	88	84	62	48
Lin et al (46)	18	NA	40	70	90	90	NA	9	78	NA	NA	NA	NA	NA
Kuang et al (59)	16	94	53	60	NA	NA	NA	9	100	72	50	NA	NA	NA
Tanaka et al (38)	NA	NA	63	88	NA	NA	NA	NA	NA	75	25	25	NA	NA
Hasegawa et al (34)	115	NA	29	38	63	66	71	NA	NA	99	98	92	83	73
Sun et al (48)	138	87	42	54	60	65	65	98	92	78	62	52	44	44
Mazzaferro et al (47)	100	NA	34	51	63	77	94	61	67	NA	NA	NA	NA	NA
Mizuta et al (52)	40	NA	55	83	92	NA	NA	11	73	96	81	64	NA	NA
Lo et al (49)	43	79	30	45	50	53	55	21	76	85	72	70	70	61
Hotta et al (53)	19	NA	33	47	73	NA	NA	NA	NA	88	82	82	NA	NA
Kakizaki et al (54)	34	NA	28	64	90	NA	NA	11	82	96	90	66	NA	NA
Xu et al (62)	25	32	57	NA	NA	NA	NA	15	NA	62	NA	NA	NA	NA
Weng et al (57)	46	93	30	NA	NA	NA	NA	0‡	NA	NA	NA	NA	NA	NA
Hui et al (58)	77	83	17	69	79	82	89	63	73	87	85	65	54	37
Liu et al (63)	42	NA	68	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Xia et al (35)	39	90	37	50	70	77	77	27	NA	84	70	57	50	40
Yoshida et al (55)	56	98	30	NA	NA	NA	NA	NA	NA	97	NA	NA	NA	NA

*Listed according to year of publication; †Recurrence rate of second primary hepatocellular carcinoma; ‡No patients died during follow-up. NA Not available.

unduplicated articles; hence, data from both reports of each of the studies were used, separately (50,51) or in combination (60,61), in the outcomes analysis. Six RCTs (33,46,49,55,58,59) involved three or more study groups. In two of these (46,55), because no difference in recurrence rates and in RFS was found between two adjuvant groups, respectively, data from both adjuvant groups were combined for analysis. However, for the other four trials (33,49,59,63), due to the lack of combined outcomes data, only selected adjuvant groups were compared with control. The HR of RFS, TTR or OS was estimated using indirect methods (25,26) for most of the RCTs, because only a few studies (34,35,55,59) directly provided data for these time-to-event outcomes.

Overall, 13 trials (33,35-37,46,49,50,52,54,56-59) found adjuvant therapy could confer a significant advantage in RFS or TTR, and six (38,44,48,51,59,62) indentified a significant OS gain with adjuvant therapy. In four other trials (34,39,40,55), however, adjuvant therapy demonstrated worse outcomes compared with no adjuvant therapy, although differences in RFS or OS were insignificant.

Summary of study results on recurrence and survival
A total of 1151 patients from both adjuvant and control groups of 24 trials (33-36,39-41,44,46-50,52-59,61-63) reported recurrence of HCC during follow-up, and the proportion of intrahepatic recurrence among 14 studies (33,35,36,39,40,44,48,49,55-59,61) was in the range of 79% (49) to 100% (44) (Table 2). In the only trial involving liver transplantation as initial curative treatment (62), more patients developing extrahepatic recurrence were observed (68%). With regard to types of recurrence, although most of the studies failed to specify the

distinction between intrahepatic metastasis and de novo tumour for recurrent disease, it was noteworthy the incidence of second primary HCC characterized by multicentric carcinogenesis in the only study (50,51) was 79% (27 of 34 recurrences). Of 525 deaths noted from 18 RCTs (33,35,36,39,40,44-49,52,54,56,58,59,61,62), 67% (47) to 100% (44,45,59) of cases were the result of recurrent HCC that occurred predominantly in residual liver.

As illustrated in Table 2, for patients receiving no active adjuvant therapy after potentially curative treatment for HCC, the median one-, two-, three-, four- and five-year recurrence rates were 36% (range 17% to 68%), 58% (range 30% to 100%), 69% (range 50% to 92%), 73% (range 52% to 94%) and 82% (range 55% to 94%), respectively; and that for survival rates at the corresponding time point were 88% (range 62% to 99%), 81% (range 25% to 98%), 67% (range 25% to 92%), 57% (range 36% to 83%) and 48% (range 29% to 73%), respectively.

Efficacy and safety evaluation of adjuvant therapy
For assessment and analysis of adjuvant therapies for which there was potential for clinical benefit, these 27 RCTs were classified into five categories: chemotherapy, IFN therapy, vitamin analogue therapy, adoptive immunotherapy and other therapies (each therapy was tested in a single trial) including cancer vaccine therapy, internal radiation therapy, radioimmunotherapy and heparanase inhibitor PI-88 therapy. A detailed description of treatment protocols, study characteristics and methodological quality assessment of the RCTs are presented in Tables 3 to 12.

TABLE 3
Characteristics of the randomized controlled trials evaluating adjuvant chemotherapy

Study (reference)	Adjuvant protocol and number of patients	Patients' baseline characteristics		
		Tumour characteristics	Liver disease	Follow-up
Oral chemotherapy				
Yamamoto et al (33)	Study arm: oral HCFC 200 mg twice daily until recurrence or severe side effects developed; n=35	UICC stage II	LCSGJ stage I–II; cirrhosis 65%	NR
	Control arm: no adjuvant therapy; n=32			
Hasegawa et al (34)	Study arm: oral UFT 300 mg/day for 1 year; n=79	Single nodule 70%; median tumour size 33 mm for study arm and 34 mm for control arm; vascular invasion 22%	C-P A 87%; cirrhosis 50%	Median 4.8 years
	Control arm: no adjuvant therapy; n=80			
Xia et al (35)	Study arm: oral CAP 1000 mg/m^2 twice daily for 4–6 courses (1 course consisted of 2 weeks of CAP followed by a 1-week interval); n=30	pTNM stage I–III; single nodule 70%; tumour size >5 cm 57%; microvessels invasion 63%	C-P A 100%; cirrhosis 33%	Median 47.5 months
	Control arm: no adjuvant therapy; n=30			
Transhepatic arterial chemotherapy				
Izumi et al (36)	Study arm: L-TAC (ADM 20 mg/m^2 + MMC 10 mg/m^2) with or without embolization once; n=23	Tumour size >5 cm 76%; vascular invasion and/or intrahepatic metastasis 100%	Cirrhosis 82%	NR
	Control arm: no adjuvant therapy; n=27			
Ueno et al (37)	Study arm: TAC (CDDP 50–80 mg/body + MMC 10 mg/body) 2–3 times (1-month intervals); n=10	NR	NR	NR
	Control arm: no adjuvant therapy; n=11			
Tanaka et al (38)	Study arm: TAC (CDDP 10 mg + 5-FU 250 mg) for 4 courses (one course consisted of daily TAC for 5 consecutive days and a 2-day interval); n=7	Portal vein invasion and/or intrahepatic metastasis 100%	NR	NR
	Control arm: no adjuvant therapy; n=8			
Systemic and transhepatic arterial chemotherapy				
Lai et al (39)	Study arm: L-TAC (CDDP 10 mg) 3 times (2-month intervals), and iv EPI 40 mg/m^2, 8 doses (6-week intervals); n=30	LCSGJ stage I–III; single nodule 60%; tumour size >5 cm 65%; vascular invasion 45%	Cirrhosis 55%	Median 28.3 months
	Control arm: no adjuvant therapy; n=36			
Ono et al (40)	Study arm: TAC (EPI 40 mg/m^2) once, followed by iv EPI 40 mg/m^2 (3-month interval) and daily oral HCFC 300 mg/day for 2 years; n=29	Mean tumour number 4.2 for study arm and 3.7 for control arm; Mean tumour size 1.4 cm for study arm and 1.2 cm for control arm vascular invasion 34%	C-P A 75%; cirrhosis 68%	NR
	Control arm: no adjuvant therapy; n=27			

5-FU 5-Fluorouracil; ADM Adramycin (doxorubicin); CAP Capecitabine; CDDP Cisplatin; C-P Child-Pugh class; *EPI Epirubicin; HCFC 1-hexylcarbamoyl-5-fluorouracil (carmofur); iv Intravenous; LCSGJ Liver Cancer Study Group of Japan; L-TAC Transarterial chemotherapy and lipiodolization; MMC Mitomycin c; NR Not reported; pTNM Pathological tumour-node metastasis; TAC Transarterial chemotherapy; UFT Uracil-tegafur; UICC Union for International Cancer Control*

RFS
The outcome of RFS or DFS was reported in 18 trials (33-40,44,47-49, 55-59,61), four (35,56,57,59) of which also included TTR as a primary outcome. However, for the other nine trials (41,45,46,50,52-54,62,63) that reported recurrence or recurrence-free rates, TTR was used as surrogate outcome. Eight subgroup analyses were performed for RFS (Figure 2).
Chemotherapy: The meta-analysis for eight trials (33-40) demonstrated that adjuvant chemotherapy failed to improve RFS compared with no treatment (HR 0.94 [95% CI 0.81 to 1.10]). Nevertheless, a significant statistical heterogeneity among the trials was found (I^2=55%). After excluding any of these eight trials by sensitivity analysis, heterogeneity was consistently high (data not shown). Therefore, the eight trials were further subdivided according to the different administration routes of chemotherapy (Figure 3), and the results showed that adjuvant oral chemotherapy (HR 0.91 [95% CI 0.77 to 1.09]; I^2=77%) and transhepatic arterial chemotherapy (HR 0.69 [95% CI 0.41 to 1.16]; I^2=0%) did not improve RFS, while the pooled HR for two trials (39,40) testing the combination of systemic and transhepatic arterial chemotherapy marginally favoured no adjuvant therapy (HR 1.51 [95% CI 0.94 to 2.40]; I^2=11%).
IFN therapy: Seven RCTs (41-49) of adjuvant IFN therapy were pooled for RFS, and the result favoured IFN therapy (HR 0.72 [95% CI 0.59 to 0.88]; data not shown) but with an obvious heterogeneity

(I^2=60%). After carefully examining the characteristics of each trial, the RCT by Ikeda et al (41) appeared to be the source of the heterogeneity. This was the only trial identified that used IFN-β, and the sample sizes were small (10 patients each in IFN and control groups); it was also restricted by methodological limitations. The sensitivity analysis excluding the study (41) showed that pooled HR was 0.75 (95% CI 0.61 to 0.92; Figure 2), significantly favouring adjuvant IFN therapy with acceptable heterogeneity (I^2=5%).
Vitamin analogue therapy: The pooled analysis for five trials testing polyprenoic acid (50,51) or menatetrenone (52-55) indentified a significant RFS gain with these vitamin analogues (HR 0.76 [95% CI 0.60 to 0.96]; data not shown). However, an elevated heterogeneity was observed across the studies (I^2=78%), which was likely due to the inclusion of the VK2 study by Yoshida et al (55). Despite having the largest sample size (n=548), this trial (55) enrolled 21% patients with first intrahepatic recurrence of HCC and was terminated after a maximum follow-up of only 36 months, all of which may confound the combined result. Nevertheless, restricting the analysis to the other four RCTs (50-54) did not change the effects of adjuvant vitamin analogue therapy on RFS (HR 0.43 [95% CI 0.30 to 0.62]; Figure 2), while heterogeneity was eliminated (I^2=0%).
Adoptive immunotherapy: The meta-analysis of RFS for the three RCTs (56-58) showed a significant difference favouring adoptive immunotherapy, compared with no adjuvant therapy (HR 0.55 [95%

TABLE 4
Methodological quality assessment of the randomized controlled trials evaluating adjuvant chemotherapy

Study (reference)	Random sequence generation	Allocation concealment	Incomplete outcome data	Selective reporting	Other bias	
					Balanced in baseline characteristics	Sample size calculation
Yamamoto et al (33)	Unclear: only stated as random	Yes: by central office telephone	Yes: analysis by ITT	Unclear: the study protocol was unavailable	Yes	No
Hasegawa et al (34)	Yes: minimization randomization	Unclear: by an independent investigator	Unclear: ITT analysis excluded 1 patient randomly assigned to the treatment arm	Yes: all expected outcomes were reported in accordance with the study protocol	Yes	Yes
Xia et al (35)	Unclear: only stated as random	Unclear: unspecified sealed envelope procedure	Yes: analysis by ITT	Unclear: the study protocol was unavailable	Yes	No
Izumi et al (36)	Unclear: only stated as random	Unclear: only stated as random	Unclear: 2 patients dropped out of the treatment arm were reported, but not resolved	Unclear: the study protocol was unavailable	Yes	No
Ueno et al (37)	Unclear: unspecified block randomization	Unclear: unspecified sealed envelope procedure	Yes: analysis by ITT	Unclear: the study protocol was unavailable	Yes	No
Tanaka et al (38)	Unclear: only stated as random	Unclear: only stated as random	Yes: analysis by ITT	Unclear: the study protocol was unavailable	Yes	No
Lai et al (39)	Unclear: only stated as random	Unclear: only stated as random	Yes: analysis by ITT	Unclear: the study protocol was unavailable	Yes	Yes
Ono et al (40)	Unclear: only stated as random	Unclear: unspecified sealed envelope procedure	Yes: analysis by ITT	Unclear: the study protocol was unavailable	Yes	No

ITT Intention-to-treat

TABLE 5
Characteristics of the randomized controlled trials evaluating adjuvant interferon therapy

Study (reference)	Adjuvant protocol and number of patients	Patients' baseline characteristics		
		Tumour characteristics	Liver disease	Follow-up
Ikeda et al (41)	Study arm: IFN-β 6 MU twice a week for 36 months; n=10 Control arm: no adjuvant therapy; n = 10	Single nodule 90%; median tumour size 22 mm for study arm and 20 mm for control arm; vascular invasion 0%	HCV 100%; cirrhosis 85%	Median 25 month
Kubo et al (42-44)	Study arm: daily IFN-α 6 MU for 2 weeks, then three times per week for 14 weeks, followed by twice weekly for 88 weeks; n=15 Control arm: no adjuvant therapy; n=15	Single tumour 100%; tumour size ≤5 cm 100%	HCV 100%; C-P A 77%; cirrhosis 50%	5.0 years for study arm and 4.1 years for control arm
Shiratori et al (45)	Study arm: IFN-α 6 MU three times a week for 48 months; n=49 Control arm: no adjuvant therapy; n=25	Single tumour 65%; tumour size ≤30 mm 100%	HCV 100%; C-P A 100%; cirrhosis 100%	Mean 7.1 years
Lin et al (46)	Study arm 1: IFN-α 3 MU thrice a week for 24 months; n=11 Study arm 2: IFN-α 3 MU 10 times a month for 6 months, followed by 3 MU 10 times every 3 months for 18 months; n=9 Control arm: no adjuvant therapy; n=10	Single tumour 83%; median tumour size 20–25 mm	HBV 53%; C-P A 87%; cirrhosis 93%	Median 27 months
Mazzaferro et al (47)	Study arm: IFN-α-2b 3 MU thrice a week for 48 weeks; n=76 Control arm: no adjuvant therapy; n=74	pTNM stage III–IV 39%; single tumour 76%; median tumour size 35 mm; vascular invasion 21%	HCV 100%; C-P A 93%; cirrhosis 100%	Median 45 months
Sun et al (48)	Study arm: IFN-α-1b 3 MU twice a week for two weeks, followed by 5 MU thrice a week for 18 months; n=118 Control arm: no adjuvant therapy; n=118	Single tumour 87%; tumor size ≤5 cm 69%; microvessel invasion 76%	HBV 100%; cirrhosis 86%	Median 36.5 months
Lo et al (49)	Study arm 1: IFN-α-2b 10 MU three times per week for 16 months; n=40 Study arm 2: IFN-α-2b 30 MU three times per week for 16 months; n=6 Control arm: no adjuvant therapy; n=40	pTNM stage III–IVA 51%; single tumour 79%; Tumour size >5 cm 51%; vascular invasion 44%	HBV 91%; cirrhosis 50%	30–71 months

C-P Child Child-Pugh class; HBV Hepatitis B virus; HCV Hepatitis C virus; IFN Interferon; MU Million units; pTNM Pathological tumour-node-metastasis

TABLE 6
Methodological quality assessment of the randomized controlled trials evaluating adjuvant interferon therapy

Study (reference)	Random sequence generation	Allocation concealment	Incomplete outcome data	Selective reporting	Other bias	
					Balanced in baseline characteristics	Sample size calculation
Ikeda et al (41)	Unclear: only stated as random	Unclear: only stated as random	Yes: analysis by ITT	Unclear: the study protocol was unavailable	Yes	No
Kubo et al (42-44)	Yes: from a random-numbers table	Unclear: assignments were withheld from the investigators	Yes: analysis by ITT	Unclear: the study protocol was unavailable	Yes	Yes
Shiratori et al (45)	Unclear: from an unspecified random list (2:1 assignment ratio)	Unclear: by an independent investigator	Yes: analysis by ITT	Unclear: the study protocol was unavailable	Yes	Yes
Lin et al (46)	Unclear: only stated as random	Unclear: only stated as random	Yes: analysis by ITT	Unclear: the study protocol was unavailable	Yes	No
Mazzaferro et al (47)	Yes: computer-generated random number	Yes: by central office telephone	Unclear: ITT analysis excluded 1 patient randomized to the treatment arm	Yes: all expected outcomes were reported in accordance with the study protocol	Yes	Yes
Sun et al (48)	Yes: computer-generated random number	Unclear: unspecified sealed envelope procedure	Yes: analysis by ITT	Unclear: the study protocol was unavailable	Yes	Yes
Lo et al (49)	Unclear: only stated as random	Yes: sealed envelope procedure, ensured by a research assistant	Yes: analysis by ITT	Unclear: the study protocol was unavailable	Yes	Yes

ITT Intention-to-treat

TABLE 7
Characteristics of the randomized controlled trials evaluating adjuvant vitamin analogue therapy

Study (reference)	Adjuvant protocol and number of patients	Patients' baseline characteristics		
		Tumour characteristics	Liver disease	Follow-up
Vitamin A analogue				
Muto et al (50,51)	Study arm: oral polyprenoic acid 600 mg/day for 12 months; n=44 Control arm: the same dosage of placebo; n=45	LCSGJ stage I–III; mean tumour number 1.5 for study arm and 1.4 for control arm; mean tumour size 2.9 cm for study arm and 3.0 cm for control arm	HCV 75%	Median 38 or 62 months
Vitamin K2 analogue				
Mizuta et al (52)	Study arm: oral menatetrenone 45 mg/day until recurrence; n=32 Control arm: no adjuvant therapy; n=29	LCSGJ stage I–III; mean tumour number 1.5; mean tumour size 18 mm^2 for study arm and 19 mm^2 for control arm; vascular invasion 0%	C-P A 79%; HCV 89%	Median 28.9 months for study arm and 27.7 months for control arm
Hotta et al (53)	Study arm: oral menatetrenone 45 mg/day until recurrence; n=21 Control arm: no adjuvant therapy; n=24	Single tumour 44%; mean tumour size ≤3 cm 80%	C-P A 60%; HCV 73%	Median 19.5 months for study arm and 16.5 months for control arm
Kakizaki et al (54)	Study arm: oral menatetrenone 45 mg/day until recurrence; n=30 Control arm: no adjuvant therapy; n=30	LCSGJ stage I–III; single tumour 68%; mean tumour size 20 mm for study arm and 25 mm for control arm; vascular invasion 0%	C-P A 73%; HCV 100%	NR
Yoshida et al (55)	Study arm 1: oral menatetrenone 45 mg/day until recurrence; n=182 Study arm 2: oral menatetrenone 90 mg/day until recurrence; n=185 Control arm: the same dosage of placebo; n=181	Single tumour 71%; median tumour size 19 mm; vascular invasion 0%	C-P A 87%; cirrhosis 78%; HCV 83%	NR

C-P Child Child-Pugh class; HCV Hepatitis C virus; LCSGJ Liver Cancer Study Group of Japan; NR Not reported

CI 0.42 to 0.71]). There was no heterogeneity among these studies (I^2=0%).

Other therapeutic modalities: Cancer vaccine therapy (59) and radioimmunotherapy (62) achieved significantly higher RFS (HR 0.19 [95% CI 0.05 to 0.69]) and longer TTR (HR 0.28 [95% CI 0.12 to 0.66]) compared with control, respectively; adjuvant therapy with ^{131}I-lipiodol (60,61) or PI-88 (63) tended to decrease the risk of recurrence, although difference in RFS (HR 0.58 [95% CI 0.25 to 1.32]) or TTR (HR 0.63 [95% CI 0.34 to 1.15]) between adjuvant and no adjuvant therapy groups failed to reach statistical significance.

TABLE 8
Methodological quality assessment of the randomized controlled trials evaluating adjuvant vitamin analogue therapy

Study (reference)	Random sequence generation	Allocation concealment	Incomplete outcome data	Selective reporting	Other bias	
					Balanced in baseline characteristics	Sample size calculation
Muto et al (50,51)	Unclear: unspecified block randomization	Yes: by sequentially numbered drug containers of identical appearance	Yes: analysis by ITT	Unclear: the study protocol was unavailable	Yes	Yes
Mizuta et al (52)	Yes: from a table of random permutations	Unclear: only stated as random	Yes: analysis by ITT	Unclear: the study protocol was unavailable	No: patients in the treatment arm had significantly lower serum DCP level	No
Hotta et al (53)	Unclear: from an unspecified random list	Unclear: only stated as random	Yes: analysis by ITT	Unclear: the study protocol was unavailable	Yes	No
Kakizaki et al (54)	Unclear: only stated as random	Unclear: only stated as random	Unclear: ITT analysis for patients treated rather than randomized	Unclear: the study protocol was unavailable	Yes	No
Yoshida et al (55)	Yes: minimization randomization	Yes: by sequentially numbered drug containers of identical appearance	Yes: efficacy analysis by ITT	Yes: all expected outcomes were reported in accordance with the study protocol	No: patients in the two treatment arms had significantly higher serum TBIL and AST levels	Yes

AST Aspartate aminotransferase; DCP Des-gamma-carboxy prothrombin; ITT Intention-to-treat; TBIL Total bilirubin

TABLE 9
Characteristics of the randomized controlled trials evaluating adjuvant adoptive immunotherapy

Study (reference)	Adjuvant protocol and number of patients	Patients' baseline characteristics		
		Tumor characteristics	Liver disease	Follow-up
Takayama et al (56)	Study arm: iv LAK cell-based immunotherapy for 5 times (at weeks 2, 3, 4, 12, and 24 after curative treatment); n=76	Single tumour 69%; tumour size ≥3 cm 53%; intrahepatic metastasis or vascular invasion 56%	C-P A 69%; cirrhosis 51%; HCV 66%	Median 4.4 years
	Control arm: no adjuvant therapy; n=74			
Weng et al (57)	Study arm: Transhepatic arterial CIK cell-based immunotherapy for 8-10 times (2-week intervals); n=45	Tumour size ≥5 cm 56%; vascular invasion 0%	C-P A 81%	18 months
	Control arm: no adjuvant therapy; n=40			
Hui et al (58)	Study arm 1: iv CIK cell-based immunotherapy for 3 times (2-week intervals); n=41	Single tumour 100%; tumour size ≥5 cm 55%; vascular invasion 46%	C-P A 80%; cirrhosis 80%; HBV 76%	5–7 years
	Study arm 2: iv CIK cell-based immunotherapy for 6 times (2-week intervals); n=43			
	Control arm: no adjuvant therapy; n=43			

C-P Child Child-Pugh class; *CIK Cytokine-induced killer; HBV Hepatitis B virus; HCV Hepatitis C virus; iv Intravenous; LAK Lymphokine activated killer;*

TABLE 10
Methodological quality assessment of the randomized controlled trials evaluating adjuvant adoptive immunotherapy

Study (reference)	Random sequence generation	Allocation concealment	Incomplete outcome data	Selective reporting	Other bias	
					Balanced in baseline characteristics	Sample size calculation
Takayama et al (56)	Unclear: unspecified block randomization	Unclear: only stated as random	Yes: analysis by ITT	Unclear: the study protocol was unavailable	Yes	Yes
Weng et al (57)	Unclear: only stated as random	Unclear: only stated as random	Yes: analysis by ITT	Unclear: result of TTR was not presented	Yes	Yes
Hui et al (58)	Yes: by drawing of lots	Unclear: only stated as random	Yes: analysis by ITT	Unclear: the study protocol was unavailable	Yes	No

ITT Intention-to-treat; TTR Time to recurrence

OS

Twenty-two trials (33-36,38-40,44,45,47-50,52-56,58,59,61,62) provided OS data. Nevertheless, due to the insufficient data reporting for the calculation of HR, three (47,53,55) of these 22 studies were further excluded from the analysis of the outcome. Seven subgroup analyses were performed for OS (Figure 4).

Chemotherapy: The meta-analysis for seven (33-36,38-40) trials assessing adjuvant chemotherapy yielded a nonsignificant but heterogeneous result (HR 1.01 [95% CI 0.76 to 1.35]; I^2=64%). The separate subgroup analysis (Figure 5) in terms of different routes of administration demonstrated that adjuvant oral (HR 1.01 [95% CI 0.70 to 1.47]; I^2=75%) or transhepatic arterial chemotherapy (HR 0.59 [95% CI 0.31 to 1.14]; I^2=62%) did not indentify an OS gain, while the combination of systemic and transhepatic arterial chemotherapy had a trend favouring no adjuvant therapy (HR 1.67 [95% CI 0.88 to 3.16]; I^2=12%).

IFN therapy: The pooled HR of 0.52 (95% CI 0.38 to 0.71) among four (44,45,48,49) trials in favour of adjuvant group demonstrated a convincing benefit of IFN therapy over no adjuvant therapy in OS. There was no heterogeneity among trials (I^2=0%).

TABLE 11
Characteristics of the randomized controlled trials evaluating other adjuvant therapies

Study (reference)	Adjuvant protocol and number of patients	Patients' baseline characteristics		
		Tumour characteristics	Liver disease	Follow-up
Cancer vaccine therapy				
Kuang et al (59)	Study arm: intradermal injection of autologous formalin-fixed tumour vaccine for 3 courses (one course consisted of 5 injections of the tumour vaccine followed by a two-week interval); n=18	TNM stage I–IIIA; single tumour 95%; tumour size ≥5 cm 51%; intrahepatic metastasis or vascular invasion 33%	C-P A 92%; cirrhosis 54%; HBV 90%	Median 15 months
	Control arm: no adjuvant therapy; n=21			
Internal radiation therapy				
Lau et al (60, 61)	Study arm: transhepatic arterial infusion of iodine 131-labelled lipiodol (1850 MBq) for one time; n=21	Median tumour size 4.4 cm for study arm and 3.8 cm for control arm; vascular invasion 5%	Okuda stage I-II; HCV 88%	Median 34.6 or 66 months
	Control arm: no adjuvant therapy; n=22			
Antibody targeted radioimmunotherapy				
Xu et al (62)	Study arm: iv h*Licartin**† 15.4 MBq/kg for 3 times (28-day intervals); n=30	TNM stage III–IV; single lesion with tumour size >5 cm 72%; multiple lesion with tumour size >3 cm 28%; portal vein cancer thrombi 45%	C-P A 43%; cirrhosis 100%; HBV 88%	Median 12.3 months
	Control arm: the same dosage of placebo; n=30			
Heparanase inhibitor PI-88 therapy				
Liu et al (63)	Study arm 1: subcutaneous injection of PI-88 160 mg/day for 9 courses (one course consisted of consecutive 4 days of daily PI-88 for 3 weeks and a one-week interval); n=56	Single tumour 85%; mean tumour size 4.9 cm for study arm 1, 5.1 cm for study arm 2 and 5.5 cm for control arm; vascular invasion 23%	C-P A 96%; cirrhosis 56%; HBV 73%	379–381 days
	Study arm 2: PI-88 250 mg/day given with the same protocol as arm 1; n=54			
	Control arm: no adjuvant therapy; n=58			

*Iodine 131-labelled metuximab (HAb18 F[ab']2). †Chengdu Hoist Hitech Co Ltd, China; and the Fourth Military Medical University, Xi'an, China. C-P Child Child-Pugh class; iv Intravenous.

TABLE 12
Methodological quality assessment of the randomized evaluating other adjuvant therapies

Study (reference)	Random sequence generation	Allocation concealment	Incomplete outcome data	Selective reporting	Other bias	
					Balanced in baseline characteristics	Sample size calculation
Kuang et al (59)	Unclear: unspecified block randomization	Unclear: by an independent investigator	Unclear: ITT analysis excluded 2 randomized patients.	Unclear: the study protocol was unavailable	Yes	Yes
Lau et al (60,61)	Yes: computer-generated random number	Unclear: only stated as random	Yes: analysis by ITT	Unclear: the study protocol was unavailable	Yes	Yes
Xu et al (62)	Unclear: randomization by doctors	Yes: by sequentially numbered drug containers of identical appearance	Yes: analysis by ITT	Unclear: the study protocol was unavailable	Yes	Yes
Liu et al (63)	Unclear: unspecified block randomization	Yes: pharmacy-controlled randomization	Unclear: ITT analysis excluded 1 patient randomized to the treatment group	Unclear: the study protocol was unavailable	Yes	Yes

ITT Intention-to-treat

Vitamin analogue therapy: The meta-analysis for three trials (51,52,54) showed that adjuvant therapy with VK2 analogue significantly improved OS compared with control, with no heterogeneity across the trials (HR 0.48 [95% CI 0.29 to 0.82]; I^2=0%).

Adoptive immunotherapy: The pooled HRs for two trials (56,58) testing adoptive immunotherapy demonstrated there was no significant difference between adjuvant and no adjuvant groups in terms of OS (HR 0.79 [95% CI 0.55 to 1.14]). An acceptable heterogeneity was observed between the trials (I^2=25%).

Other therapeutic modalities: The HR of OS for the trial of cancer vaccine therapy (59) was 0.07 (95% CI 0.02 to 0.27), and that for the radioimmunotherapy study (62) was 0.26 (95% CI 0.08 to 0.83), each of which significantly favoured adjuvant therapy. However, OS in the internal radiation trial (60,61) did not differ significantly between adjuvant and the control groups (HR 0.68 [95% CI 0.30 to 1.55]).

Side effects
All except one trial (37) reported data on side effects. In the studies of chemotherapy (33-36,38-40) and of IFN therapy (41-49), 24% (50 of 212) and 11% (35 of 328) patients in adjuvant group, respectively, developed severe toxicity or treatment-related side effects requiring a discontinuation of adjuvant therapy, while cancer vaccine (59), adoptive immunotherapy (56-58) and heparanase inhibitor PI-88 therapy (63) caused frequent but mild adverse effects. Other adjuvant modalities such as vitamin analogue therapy (50-55), internal radiation therapy (60,61) and radioimmunotherapy (62) appeared to be safe, because side effects of these therapies were barely reported in the publications.

DISCUSSION

HCC is a major health problem in hepatitis-prevalent countries such as China (1-3). Despite great improvement in diagnostic and
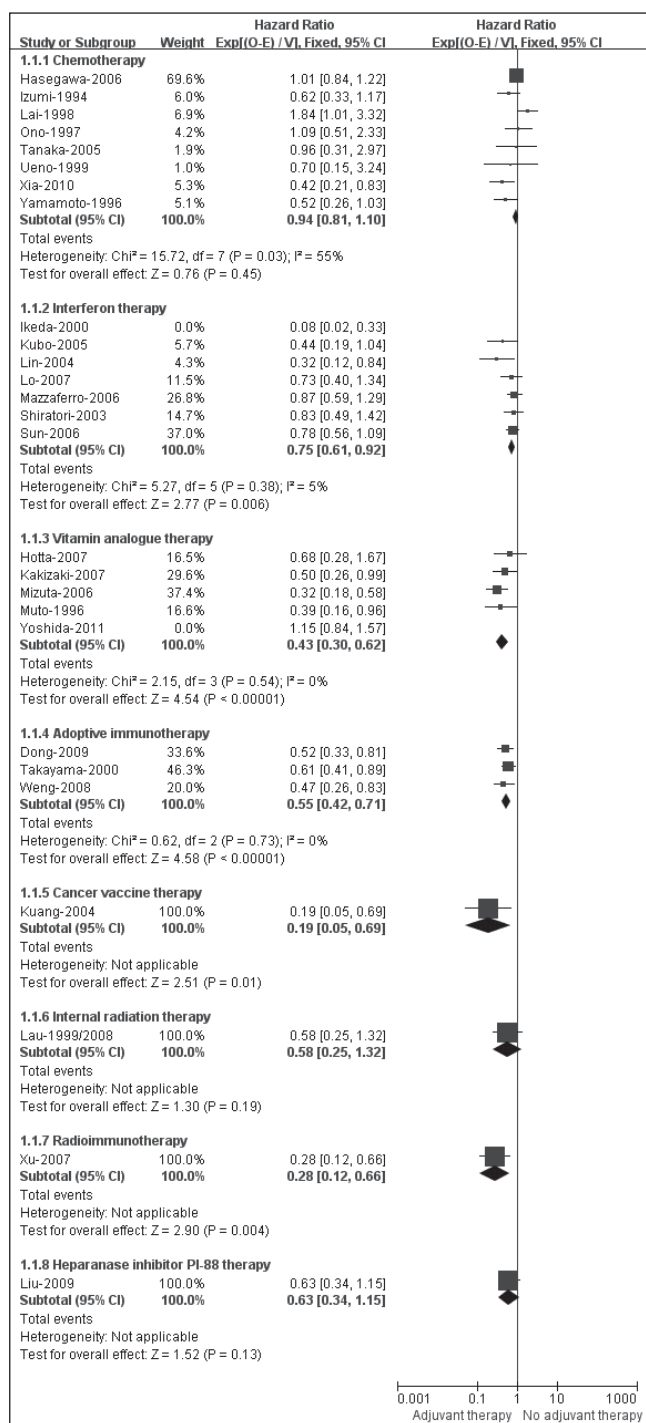
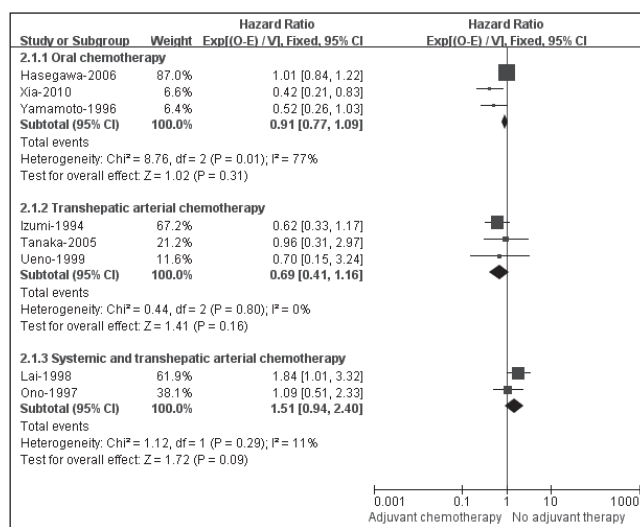**Figure 2)** *Meta-analysis (sensitivity analysis) of recurrence-free survival in randomized controlled trials evaluating adjuvant therapy*

Figure 3) *Subgroup analysis of recurrence-free survival in randomized controlled trials evaluating adjuvant chemotherapy*

therapeutic techniques, the long-term outcomes of HCC remain unsatisfactory, even after treatment with cure intent. From our analysis for patients receiving no active adjuvant therapy, the median five-year recurrence rate after surgical resection, liver transplantation or ablation therapy was up to 82% (range 55% to 94%), and that for survival rate at five years was 48% (range 29% to 75%). The high recurrence rate was explained by intrahepatic metastasis of primary HCC, which accounted for >79% of recurrence cases; the main cause of death after these potentially curative treatments was recurrent HCC (67% to 100%) that occurred mostly in residual liver.

The current meta-analysis included a broad spectrum of adjuvant therapies with either antitumour or chemopreventive effects to be evaluated. Adjuvant chemotherapy failed to confer any benefit to RFS and OS, regardless of what agents or administration modes were used. On the contrary, the combination of systemic and transarterial chemotherapy may have a deleterious effect on patient prognosis. Although the efficacy results of the adjuvant IFN studies were encouraging, one caveat is that the survival benefits from IFN therapy should be weighed against the risks of adverse effects. The findings of chemoprevention with vitamin analogues require further examination because the meta-analysis of RFS and of OS was performed only in a limited number of small RCTs with methodological weaknesses. Adoptive immunotherapy with either LAK or CIK cells may be as promising a strategy as adjuvant therapy for HCC because it increased the RFS by 45% and resulted in few adverse effects, although the approaches are too cumbersome and costly for use in large clinical trials. Nevertheless, follow-up periods in these trials (56-58) were too short to confer a statistically significant benefit in OS. Postoperative adjuvant therapy using either transhepatic arterial ^{131}I-lipiodol infusion or subcutaneous injection of heparanase inhibitor PI-88 did not appear able to decrease recurrence and to improve survival, while cancer vaccine therapy and Licartin radioimmunotherapy showed some promise after radical surgery for HCC. However, each of these modalities was examined in single trial with small-scale and preliminary settings.

The results of the current meta-analysis suggest that the effectiveness of an adjuvant modality depends largely on front-line therapy for HCC. In fact, because the cancer is insensitive to chemotherapy and radiotherapy (66), adjuvant use of any chemotherapeutic agent or radioactive material may not be effective. Furthermore, the beneficial effects of adjuvant IFN therapy on recurrence and survival may contribute to its efficacy in preventing hepatitis from developing into HCC (67,68). On the other hand, the lack of effective therapeutic agents remains the main challenge in the provision of adjuvant therapy for HCC (9) because the presence of underlying cirrhosis limits the capability of remnant liver insulted by initially curative treatment to tolerate any adjuvant cytotoxic therapy. Nevertheless, because intrahepatic recurrence can either represent metastasis from primary HCC or de novo tumour formation in a cirrhotic liver, an agent or regimen with both tumouricidal and chemopreventive effects, but less toxicity, may be effective to prevent recurrence after curative treatment for HCC (7,61,69). In the current analysis, however, the effect of adjuvant therapy on metachronous de novo carcinogenesis may have been obscured because of the presence of recurrence resulting from intrahepatic metastases of HCC, and because most of the trials lacked a precise description of the difference between primary metastasis and de novo HCC. For future trials, therefore, measures for
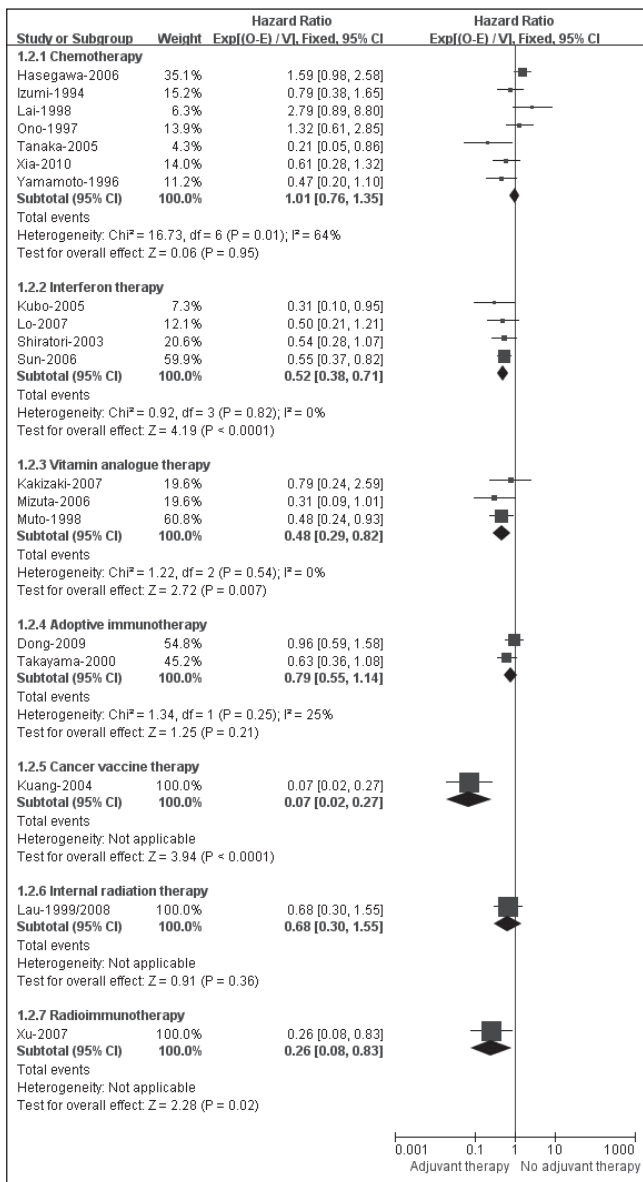
Figure 4) *Meta-analysis of overall survival in randomized controlled trials evaluating adjuvant therapy*

Figure 5) *Subgroup analysis of overall survival in randomized controlled trials evaluating adjuvant chemotherapy*

randomization was performed before patients underwent mainly curative resection for HCC (Figure 1). Although postoperative recurrence was addressed, these studies were not considered for inclusion because adjuvant effects in treatment group may have been confounded by the introduction of initially curative treatment. Also, it is crucial to distinguish recurrent disease after a curative treatment from residual tumour after a palliative therapy when testing an adjuvant therapy that aims primarily to decrease the recurrence of HCC. Therefore, proper documentation of curability of initial treatment for HCC is necessary. The curability in most of the trials included was defined as the complete elimination or necrosis of all macroscopically detectable tumours, with no demonstrable evidence of residual or recurrent tumours on image studies before initiation of adjuvant therapy. However, it was either not described at all, or insufficiently described by other trials (34,38,41,55,62), which may have resulted in inadvertent enrollment of patients with residual HCC before randomization. Nevertheless, given that there have been no established assessment criteria of curability after surgical resection or ablation therapy, a more stringent definition of curability is required.

One of the major weakness of the present meta-analysis is that the generalizability of the results was limited by predominantly including RCTs conducted among Japanese and Chinese patients. Conceivably, there could be differences in the natural history of HCC among geographical regions, although these potential differences have not been well understood. Therefore, it is possible that the findings of the current meta-analysis may not be extrapolated to the non-Asian population.

Another limitation is that the study failed to detect the impact of underlying liver disease, particularly cirrhosis, on survival outcomes. A meta-regression analysis could be helpful to capture the effect of liver cirrhosis on survival. Nevertheless, it is hardly believable that a meta-regression analysis using cirrhosis as a covariate could affect the overall results of the current study because the majority of deaths were due to HCC recurrence rather than to liver cirrhosis (Figure 2). On the other hand, the use of RFS as primary outcome could potentially confound effects of adjuvant therapies on survival by involving death from liver failure. In the current meta-analysis, we initially planned to include TTR as the primary outcome. However, because only a few studies reported TTR (35,56,57,59) or presented data for estimating the HR of the outcome (41,45,46,52-54,62), RFS was used as a surrogate. Furthermore, we found the difference in the estimates of the HR between TTR and RFS in the trials (35,56,57,59) that reported either of the outcomes was minor (data not shown). Again, RFS or DFS may be preferable to TTR as a correlate of OS, because it is able to capture

metastatic recurrence in the residual liver may be necessary, and molecular diagnostic techniques, such as comparative genomic hybridization, integration pattern of HBV, or DNA fingerprinting using loss of heterozygosity assays or microarray analysis (70-72) are recommended, if feasible, to differentiate the two types of recurrence.

Theoretically, reduced recurrence is expected to improve survival. Nevertheless, several trials (38,44,48) found an improvement in OS but not in RFS. These were studies that had relatively small number of participants and insufficient follow-up, and there was little consideration of statistical power in the design. These limitations, however, may prevent or delay recognition of potentially beneficial therapies. Furthermore, effects of adjuvant therapy may differ over time. This was apparent in studies involving polyprenoic acid (50,51) and internal radiation therapy (60,61), in which the benefits in decreasing recurrence became more evident or were lost after expending follow-up visits. Therefore, larger sample sizes and longer periods of observation are emphasized for future trials.

For trials testing adjuvant therapy, any adjuvant effect should be evaluated independently from other potential effects. The database searches initially identified 19 reports on adjuvant therapies in which
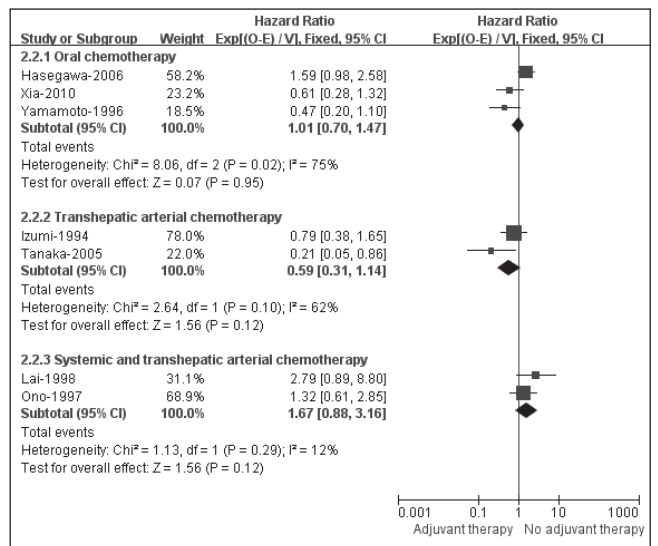
fatal toxicity in trials where the majority of deaths are expected to be related to cancer (73). Nevertheless, given the confounding composite nature of RFS that concerns not only recurrence but also death from any cause, death resulting from the natural history of cirrhosis may confound detection of potential benefits from adjuvant therapy (8,74). Therefore, the overall results of RFS in the meta-analysis should be interpreted with care, and TTR is recommended for further adjuvant trials in HCC.

Third, the present study has the typical weakness of an aggregated data meta-analysis of time-to-event outcomes. Of the 31 study reports included, only four (34,35,55,59) directly presented HR and associated 95% CIs for RFS or OS, while results of these outcomes for most of the trials were obtained by performing calculations using other statistics or data extracted from published survival curves (25,26). Bias may have been produced in estimating the HR with the use of these indirect methods, which may, however, partially explain the statistical heterogeneity among individual comparisons. Nevertheless, in the absence of necessary statistics, a meta-analysis based on data from published curves can be the only practical alternative (25). Future publications reporting time-to-event outcomes should, therefore, provide more detailed statistical information, preferably in the form of the results of log HRs and their variances, or their estimators (75).

The current meta-analysis assessed methodological quality of the included RCTs using rigorous criteria proposed by the Cochrane

systematic review (31). As a result, only nine RCTs included were assessed as having adequate quality (34,44,47-50,55,61,62), while nearly one-half of the trials were subject to methodological weakness. Hence, the overall results of the present meta-analysis were prone to bias that was incurred from the bias of these original studies. Therefore, more prospective studies of good methodological quality are needed for adjuvant HCC clinical trials.

CONCLUSIONS

The prognosis of patients with HCC after potentially curative treatment is poor. Adjuvant IFN therapy can improve both RFS and OS, but the benefits of using this agent should be weighed against side effects. Combination of systemic and transhepatic arterial chemotherapy is not currently recommended for patients with HCC after potentially curative treatment. Other adjuvant therapies produce limited success for survival. Further well-designed RCTs with sufficient sample size and follow-up are required to establish the role of adjuvant therapies for HCC, and new agents or regimens with both antitumor and chemopreventive effects are expected.

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