Conventional Oral Systemic Chemotherapy for Postoperative Hepatocellular Carcinoma

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Abstract: *Background*: The findings of randomized clinical trials (RCTs) about the efficacy of adjuvant conventional oral systemic chemotherapy (COSC) for patients with hepatocellular carcinoma (HCC) after curative hepatic resection (HR) are contradictory. Therefore, a systematic review of clinical trials is needed to evaluate the clinical efficacy of adjuvant COSC.

Methods: Sources such as MEDLINE, EMBASE and the Cochrane Library were systematically searched. All clinical trials comparing curative HR with HR plus COSC for HCC were identified. Odds ratios (ORs) and 95% confidence intervals (95% CIs) were calculated.

Results: Five RCTs and one non-RCT involving a total of 461 patients were included. No treatment-related deaths were reported in the including trials. The adverse effects of COSC were generally mild. However, included studies and meta-analysis showed that adjuvant COSC did not demonstrate statistically significant improvement for the 1-, 3-, and 5-year overall survival. For the 1-, 3-, and 5-year tumor recurrence and recurrence-free survival rates, adjuvant COSC also did not show statistically significant less incidence.

Conclusion: Adjuvant COSC provides no survival benefits for HCC patients after curative HR. Considering the efficacy of sorafenib for advanced HCC and the results of this systematic review, no more trials should be carried out to explore the efficacy of adjuvant COSC.

Keywords Adjuvant, hepatocellular carcinoma, oral, systemic chemotherapy, systematic review.

INTRODUCTION

As a malignancy with poor prognosis, hepatocellular carcinoma (HCC) has a heterogeneous composition with multiple variables that vary from region to region. Though many new treatments are explored and used to clinic, resection remains the primary treatment for HCC. However, even after curative resection, recurrence is common and is the main cause of patient deaths. The 3 year tumor recurrence rate is more than 60% after hepatic resection (HR) [1-2]. And the 5 year overall survival (OS) rate is between 39-50% [3-4]. Consequently, adequate and effective adjuvant therapy is essential to improve the OS.

Various types of postoperative therapies, such as transarterial therapy with or without embolization, systematic therapy, interferon, lamivudine, vitamin A and K2 analog, adoptive immunotherapy, etc, have been reported for HCC patients following curative treatment. Nevertheless, interferon is frequently associated with various adverse effects [5]. Postoperative transarterial chemoembolization seems promising only for HCC patients with high risk of recurrence [6]. Adoptive immunotherapy, while associated with lower recurrence after HCC surgery, does not appear to increase OS [7], and the manufacturing operation and therapeutic process are fussy. The efficacy of adjuvant vitamin A or K2 analog and lamivudine therapy is not yet definite in randomized clinical trials (RCTs). Oral administration chemotherapy is one kind of systematic therapies. As a convenient and noninvasive therapy, oral chemotherapeutic drug therapy is easily adopted for patients.

Though conventional systemic chemotherapy is well tolerated by patients with inoperable HCC [8-9], it is widely considered chemotherapy resistant, with response rates about 20%, irrespective for single or combination chemotherapy [10]. Doxorubicin and 5-fluorouracil (capecitabine, uracil-tegafur, and carmofur) are two of the most widely used chemotherapeutic agents. Even so, many investigators attempted to improve the survival of HCC patients postoperatively by conventional oral systemic chemotherapy (COSC) with 5-fluorouracil in the recent decades. However, these trials have contradictory findings. Therefore, a systematic review is needed to provide a more comprehensive analysis to better understand the efficacy of COSC.

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METHODS

Identification of Trials

The electronic databases of MEDLINE, EMBASE and the Cochrane Library were systematically searched through October 2013. Comparative studies comparing curative HR with and without COSC were identified using any of the following key words: hepatocellular carcinoma, hepatic tumor, liver tumor, postoperative, adjuvant, chemotherapy, oral. The search was not limited to controlled or randomized trials for minimizing the chances of missing a study. Manual search of relevant references and review articles was also performed. There were no date and language restrictions. RCTs and non-RCTs which assessed the effect of COSC for postoperative HCC were included.

Studies dealing with liver metastases or postoperative recurrent HCC were excluded. Patients in control group did not receive COSC. Studies identified by the search were screened independently by two reviewers. Any disagreements were resolved by discussion.

Types of Outcome Measures

The primary outcomes evaluated in this systematic review were OS and recurrence rates. The secondary outcome was incidence of adverse events attributable to COSC.

Quality Assessment

Two reviewers independently evaluated the quality of each retrieved trial in terms of randomization by sequence generation, allocation concealment, blinding of outcome assessors and reporting of intention-to-treat analysis. Trials were considered to be of low quality if they reported none of the items, of moderate quality if they reported on one or two items and of good quality if they reported on three or four. The reporting of this systematic review is in accordance with the QUOROM statement [11]. Non-RCTs were considered as low quality.

Data Extraction

Two reviewers independently extracted data concerning author details, methodological quality, number of patients, patient characteristics, interventions and outcomes. Discrepancies were resolved by consensus. When multiple publications of the same trial were identified, data were extracted from the multiple publications and reported as a single trial.

Statistical Analysis

Data from each study were analyzed using the software package RevMan 5.1. Odds ratios (ORs) with 95% confidence intervals (CIs) were calculated for overall survival and recurrence rate outcomes. A fixed-effect model and a random-effect model were applied in an 'intention-to-treat' analysis, i.e. all patients were evaluated according to their group allocation. Patients whose endpoint was unknown were considered dead or to have suffered tumor recurrence. Homogeneity between trials was analyzed by the χ^2-test with significance set at $P > 0.1$, and the extent of heterogeneity was assessed by calculating I^2. The point estimate of the OR was considered statistically significant at the $P < 0.05$ level if the 95% CI did not include the value 1.

RESULTS

Identification and Characteristics of Studies

From 432 citations identified by database searches, five eligible RCTs [12-16] and one non-RCT [17] involving a total of 461 patients were included in this systematic review (Figure **1**). One study was conducted in China [12], five in Japan [13-17]. A definite diagnosis of HCC was made based on histological evidence or a combination of several imaging modalities, e.g. hepatic angiography, enhanced CT, and magnetic resonance imaging. All HCC patients underwent curative hepatic resection. No patient in the control group received any type of chemopreventive therapy before the discovery of recurrent HCC in five studies [12-17]. Three studies did not report the follow-up in detail [15-17]. Among the included studies, recurrence was measured and assessed the same way by at least two imaging methods. All the HCC patients of these trials were underwent curative HR. Patients in the control group of five trials only received supportive care after HR [12-14,16-17]. On the contrast, patients in the treated group received adjuvant COSC with or without other type of chemotherapy. The characteristics of the studies included in the review are shown in Tables **1** and **2**.

Quality of the Included RCTs

The risks of bias in the studies included in this systematic review are detailed in Table **3**. The methodological quality was high in the first study [12],

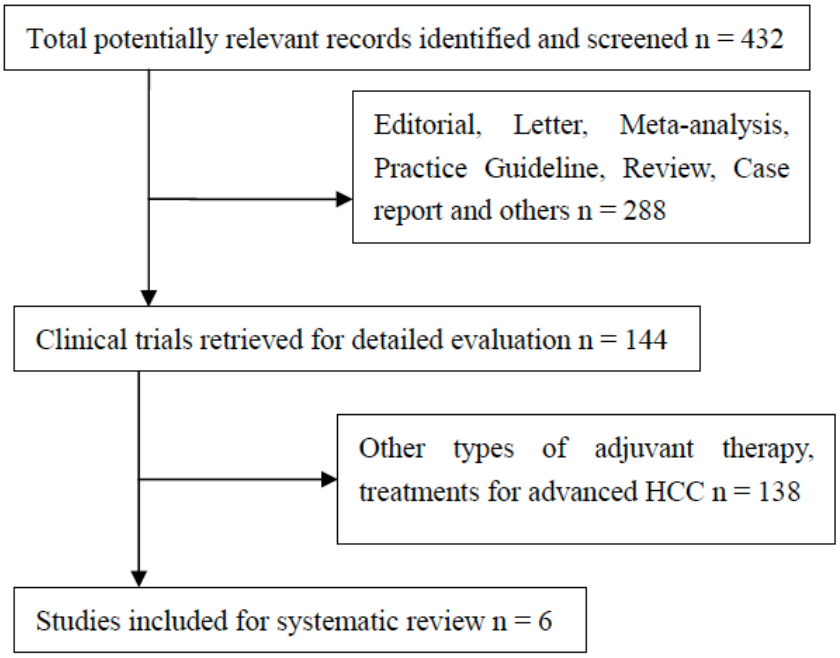

Figure 1: Flow chart of articles identified, included and excluded.
Abbreviations: HCC, hepatocellular carcinoma.

Table 1: Baseline Characteristics of Clinical Trials Included into Systematic Review

Study	Mean follow-up (years)	Child-Pugh classification (A/B)	Sample size (n)	Tumor size (median, cm)	Hepatitis (n) (HBV/HCV)	Cirrhosis (%)	Vascular invasion (n)
Xia *et al*. [12]	4.0 (range 0.3-5.4)	60/0	T:30	7.27	26/ NR	63.3	12
			C:30	6.34	24/ NR	70.0	10
Hasegawa *et al*. [13]	4.8 (range 0.5-7.9)	138/21	T:79	3.3	14/58	53.2	18
			C:80	3.4	15/56	47.5	17
Yamamoto *et al*. [14]	4-6	NR	T:35	NR	NR	100	NR
			C:32	NR	NR	100	NR
Kohno *et al*. [15]	NR	NR	T:40	NR	NR	NR	NR
			C:48	NR	NR	NR	NR
Ono *et al*. [16]	NR	42/14	T:29	4.2	9/NR	65.5	9
			C:27	3.7	7/NR	70.4	10
Takenaka *et al*. [17]	NR	NR	T:12	3.6	1/10	66.7	1
			C:19	1.9	5/9	84.2	1

C, control group; NR, not reported; T, treated group.

moderate in two studies [13,16] and low in the remaining studies [14-15,17].

Efficacy

The efficacy of the included RCTs [12-16] and non-RCT [17] of adjuvant COSC for HCC patients are summarized in Table **2**. Considering the treated group patients of three RCTs [12-14] only receiving HR plus COSC (fluorouracil drugs), while the control group with supportive care, meta-analysis of these three RCTs were conducted.

OS

All the trials [12-17] described the OS. In the study by Xia *et al*. [12], the median OS time was longer in the

Table 2: Results of clinical trials of Adjuvant Conventional Oral Systemic Chemotherapy for HCC

Study	Drugs and dose of the treated and control groups	Outcomes	Treated group (%)	Control group (%)	*p*-value
Xia *et al*. [12]	Two weeks of Capecitabine (1000 mg/m^2) twice a day, followed by 1 week of rest, 4–6 cycles	5-year DFS	46.7	23.3	< 0.05
	Supportive care	5-year OS	62.5	39.8	> 0.05
Hasegawa *et al*. [13]	Oral Uracil-tegafur (300 mg/d) for 1 year	5-year DFS	29	29	> 0.05
	Supportive care	5-year OS	58	73	> 0.05
Yamamoto *et al*. [14]	Oral Carmofur (200 mg) twice daily for as long as possible	5-year DFS§	50	19	< 0.05
	Supportive care	5-year OS§	72	49	< 0.05
Kohno *et al*. [15]	Oral Uracil-tegafur (300 mg/d) for 1 year, plus once transarterial chemotherapy (Epirubicin 40 mg/m^2)	5-year DFS	17	14	> 0.05
	Oral Uracil-tegafur (300 mg/d) for 1 year	5-year OS	35	30	> 0.05
Ono *et al*. [16]	Transarterial chemotherapy (Epirubicin 40 mg/m^2); then intravenous chemotherapy (Epirubicin 40 mg/m^2), once every 3 months for 2 years, in addition, oral Carmofur (300 mg/d) for 2 years	5-year DFS	32	22.5	> 0.05
	Supportive care	5-year OS	31.5	57	> 0.05
Takenaka *et al*. [17]	Oral Uracil-tegafur or Carmofur (300 ~ 400 mg/d) for 18 months	3-year DFS	50	15	> 0.05
	Supportive care	3-year OS	100	84	> 0.05

DFS, disease-free survival; OS, overall survival; §, patients with stage I disease.

Table 3: Methodological Quality Assessment: Internal Validity of the Included Trials

Study	Random allocation	Concealment of random allocation	Blinding of persons who assess treatment effects	Intention-to-treat analysis
Xia *et al*. [12]	+	+	-	+
Hasegawa *et al*. [13]	+	-	-	+
Yamamoto *et al*. [14]	+	-	-	-
Kohno *et al*. [15]	+	-	-	-
Ono *et al*. [16]	+	+	-	-
Takenaka *et al*. [17]	-	-	-	-

capecitabine group (60.0 vs. 52.5 months), but the difference was not statistically significant (p = 0.216). The study by Yamamoto and co-workers [14] concluded that the OS of patients with stage I disease was higher in the oral carmofur group than in the control group (p = 0.08). However, in patients with stage II disease no significant difference was observed (p = 0.77). Interestingly, Hasegawa and co-workers [13] drew an opposite conclusion, reporting that OS was slightly but not significantly worse in the uracil-tegafur group than in the control group (p =0.08). There were no significant differences between the two groups in relation to long-term survival in the study by Kohno *et al*. [15] (p = 0.2162), the study by Ono *et al*. [16] (p = 0.144), and the study by Takenaka *et al*. (p $>$ 0.05) [17].

Meta-analysis of three RCTs [12-14] showed that adjuvant COSC did not statistically reduced the 1-, 3- and 5-year OS, with pooled ORs of 1.43 (95% CI 0.58-3.56, p = 0.44), 1.39 (95% CI 0.75-2.55, p = 0.29) and 1.20 (95% CI 0.46-3.16, p = 0.71), respectively (Figure **2**).

Recurrence Rates and Recurrence-Free Survival Rates

All the trials [12-17] reported the recurrence rate. Comparing with supportive care, capecitabine

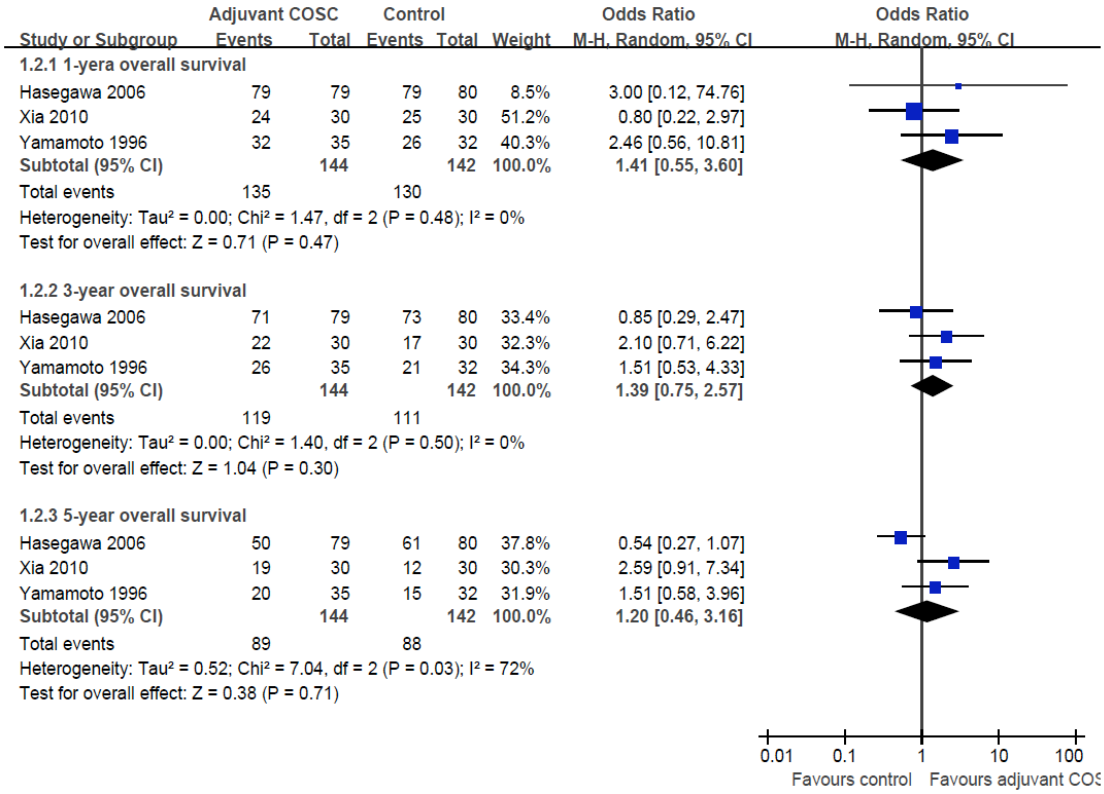

Figure 2: Meta-analysis of hepatocellular carcinoma patients' overall survival in randomized trials comparing hepatic resection plus conventional oral systemic chemotherapy versus hepatic resection alone. CI, confidence interval.

significantly decreased recurrence rate (p = 0.046) [12]. Carmofur also improved the recurrence-free survival rates of patients with stage I disease (p = 0.04). However, in patients with stage II disease no significant difference was observed (p = 1.00) [14]. Then, Yamamoto and co-workers [14] concluded that the potential benefits of carmofur on tumor recurrence should be weighed against the risks of adverse reactions in patients with mild liver dysfunction. In the third study, the recurrence-free survival curves in the groups were similar (p = 0.87) [13]. However, all the three trials [15-17] showed that no statistical difference in the disease-free survival curves between the control and COSC with or without other type of chemotherapy groups was observed.

The meta-analysis of three RCTs [12-14] also did not revealed statistically significant less incidence of the 1-, 3- and 5-year HCC recurrence rate, with pooled ORs of 0.92 (95% CI 0.62-1.35, p = 0.66), 0.82 (95% CI 0.66-1.01, p = 0.06) and 0.84 (95% CI 0.71-1.01, p = 0.06), respectively (Figure **3**).

Adverse Effects of Adjuvant COSC

There were no treatment-related deaths. In the study by Xia and coworkers [12], adverse reactions were generally mild. Nausea (23.3%) and diarrhea (16.7%) were the most common adverse effects of oral capecitabine. Two patients (7%) withdrew from capecitabine therapy because of repeated grade III nausea or low white blood cell and platelet counts. Though treatment with uracil-tegafur was temporarily or permanently discontinued in 41% patients because of adverse effects, negligible toxicity on liver function was observed. Moreover, all adverse events responded to conservative therapy [13]. However, carmofur intake was suspended due to side-effects in nine of 21 (42.9%) patients with clinical stage I and in three of six (50%) with stage II cirrhosis, although the symptoms resolved within 2 months since of the drug. Most of the adverse effects were neuropathy (18.5%) or liver dysfunction (18.5%) [14].

DISCUSSION

The aim of this systematic review was to assess the evidence of the impact of HR plus COSC on OS and tumor recurrence or recurrence-free survival rates for HCC patients. On the whole, adjuvant COSC with capecitabine, uracil-tegafur, or carmofur was well tolerated by most HCC patients. Two included RCTs indicated that adjuvant COSC significantly decreased the recurrence rate of HCC patients after curative HR

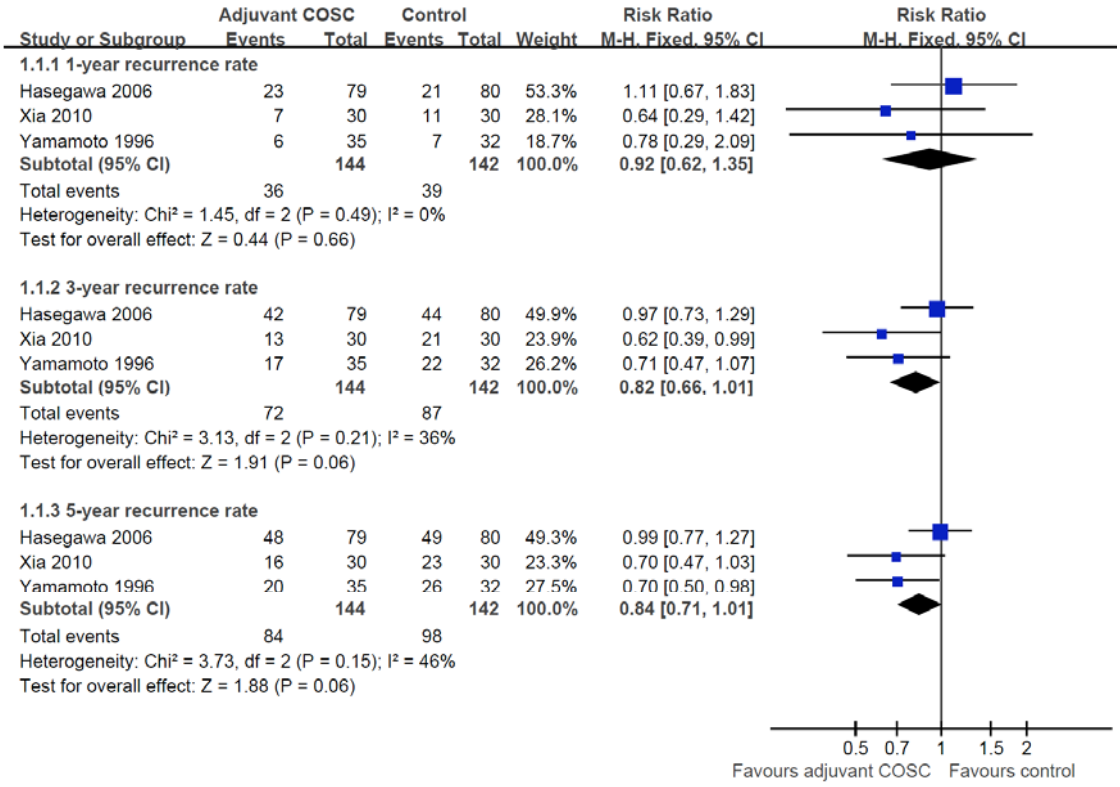

Figure 3: Meta-analysis of hepatocellular carcinoma recurrence in randomized trials comparing hepatic resection plus conventional oral systemic chemotherapy versus hepatic resection alone. CI, confidence interval.

[12,14]. However, meta-analysis showed that there was no statistical significance for OS and tumor recurrence. Moreover, other two RCTs [15,16] which explored the efficacy of adjuvant COSC plus transarterial chemotherapy and one case-control trial [17] also did not reveal statistical benefit of adjuvant COSC. The results were consistent with the former studies which evaluated the efficacy of COSC [9,18] and systemic intravenous chemotherapy for advanced HCC [19-22]. Therefore, conventional systemic therapy with single or combination agents did not provide survival benefits.

Theoretically, adjuvant COSC may prevent metastatic recurrence caused by HCC cells present in the microcirculation which were not identified by preoperative imaging, with fewer severe side effects on the liver. It is said that tumoricidal effects on lesions in the precancerous stage will be achieved by oral intake of anticancer agents which induces a high portal drug concentration [14]. As a matter of fact, systemic chemotherapy is often difficult to carry out on cirrhotic HCC patients after HR. First, most of the HCC patients were with cirrhosis. Anticancer drugs may lead to more impaired liver function. Hence, cirrhosis has a significant impact on the pharmacokinetics of systemic therapy for HCC. Unlike other cancers, most of deaths in HCC patients are due to liver disease rather than to HCC [13]. In cirrhosis patients, adjuvant chemotherapy is associated with worse disease-free survival and OS by negatively affecting liver function [14,23]. Secondly, some drug resistance genes of HCC cells, such as p-glycoprotein, glutathione-S-transferase, heat shock proteins, and mutations in p53, are over-expressed [24,25]. These genes may reduce the effect of the drugs. Even more, accelerated repopulation of surviving tumor cells can occur after sequential chemotherapy [26]. Marginally higher incidence of advanced recurrence in the adjuvant COSC group is observed in the study by Hasegawa and co-workers [13]. Lai *et al*. [27] reported that adjuvant chemotherapy was associated with more frequent extrahepatic recurrences and a worse outcome. These reasons lead to the systemic chemotherapy not widely used. On the other hand, few trials with small sample size is another reason leading to controversial trials results. Meta-analysis showed that adjuvant COSC was likely to decrease the recurrence rate and improve the OS. However, no statistical benefit was observed.

Most of the included HCC patients in this systematic review were with hepatitis B/C virus and/or cirrhosis. In addition, all included patients underwent HR. However, hepatitis, cirrhosis, and HR may not affect the efficacy of chemotherapy by itself.

Nowadays, some double-blind, multicenter, Phase III RCTs indicate that oral sorafenib is effective for the treatment of advanced HCC [28-30]. A Phase III trial is ongoing to evaluate the safety and efficacy of adjuvant sorafenib compared to placebo in the treatment of HCC. Hopefully, oral sorafenib may be an appropriate option for the treatment of HCC after curative HR.

A major drawback of this review is that the number of the included patients, who all may be Asian, was relatively small. Though we systematically searched Medline, Embase and the Cochrane Library databases, it may lead to risk of random errors. Besides, some of the important characteristics of patients, such as tumor size and hepatitis status, were not described. In addition, the randomization procedure and allocation concealment remained unclear in some studies. Because of these limitations, the results and the conclusions should be interpreted with caution.

In summary, though adjuvant COSC was well tolerated, our results offer no benefits of adjuvant COSC in HCC patients undergoing curative HR. Further trials should be conducted to explore new ways of adjuvant therapies, such as multikinase inhibitor.

COMPETING INTERESTS

The authors declare that they have no competing interests.

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REFERENCES

[1] Imamura H, Matsuyama Y, Tanaka E, *et al*. Risk factors contributing to early and late phase intrahepatic recurrence of hepatocellular carcinoma after hepatectomy. J Hepatol 2003; 38: 200-207. http://dx.doi.org/10.1016/S0168-8278(02)00360-4

[2] Zhong C, Guo RP, Li JQ, *et al*. A randomized controlled trial of hepatectomy with adjuvant transcatheter arterial chemoembolization versus hepatectomy alone for Stage III A hepatocellular carcinoma. J Cancer Res Clin Oncol 2009; 135: 1437-1445. http://dx.doi.org/10.1007/s00432-009-0588-2

[3] Capussotti L, Muratore A, Amisano M, *et al*. Liver resection for hepatocellular carcinoma on cirrhosis: analysis of mortality, morbidity and survival--a European single center experience. Eur J Surg Oncol 2005; 31: 986-993. http://dx.doi.org/10.1016/j.ejso.2005.04.002

[4] Lang H, Sotiropoulos GC, Brokalaki EI, *et al*. Survival and recurrence rates after resection for hepatocellular carcinoma in noncirrhotic livers. J Am Coll Surg 2007: 205: 27-36. http://dx.doi.org/10.1016/j.jamcollsurg.2007.03.002

[5] Zhong JH, Li H, Li LQ, *et al*. Adjuvant therapy options following curative treatment of hepatocellular carcinoma: a systematic review of randomized trials. Eur J Surg Oncol 2012; 38: 286-295. http://dx.doi.org/10.1016/j.ejso.2012.01.006

[6] Zhong JH, Li LQ. Postoperative adjuvant transarterial chemoembolization for participants with hepatocellular carcinoma: A meta-analysis. Hepatol Res 2010; 40: 943-953. http://dx.doi.org/10.1111/j.1872-034X.2010.00710.x

[7] Zhong JH, Ma L, Wu LC, *et al*. Adoptive immunotherapy for postoperative hepatocellular carcinoma: a systematic review. Int J Clin Pract 2012; 66: 21-27. http://dx.doi.org/10.1111/j.1742-1241.2011.02814.x

[8] Llovet JM, Ruff P, Tassopoulos N, *et al*. A phase II trial of oral eniluracil/5-fluorouracil in patients with inoperable hepatocellular carcinoma. Eur J Cancer 2001; 37: 1352-1358. http://dx.doi.org/10.1016/S0959-8049(01)00100-9

[9] Benson AB 3rd, Mitchell E, Abramson N, *et al*. Oral eniluracil/5-fluorouracil in patients with inoperable hepatocellular carcinoma. Ann Oncol 2002; 13: 576-581. http://dx.doi.org/10.1093/annonc/mdf079

[10] Johnson PJ. Hepatocellular carcinoma: is current therapy really altering outcome? Gut 2002; 51: 459-462. http://dx.doi.org/10.1136/gut.51.4.459

[11] Moher D, Cook DJ, Eastwood S, *et al*. Improving the quality of reports of meta-analyses of randomised controlled trials: the QUOROM statement. QUOROM Group. Br J Surg 2000; 87: 1448-1454. http://dx.doi.org/10.1046/j.1365-2168.2000.01610.x

[12] Xia Y, Qiu Y, Li J, *et al*. Adjuvant therapy with capecitabine postpones recurrence of hepatocellular carcinoma after curative resection: a randomized controlled trial. Ann Surg Oncol 2010: 17: 3137-3144. http://dx.doi.org/10.1245/s10434-010-1148-3

[13] Hasegawa K, Takayama T, Ijichi M, *et al*. Uracil-tegafur as an adjuvant for hepatocellular carcinoma: a randomized trial. Hepatology 2006; 44: 891-895. http://dx.doi.org/10.1002/hep.21341

[14] Yamamoto M, Arii S, Sugahara K, *et al*. Adjuvant oral chemotherapy to prevent recurrence after curative resection for hepatocellular carcinoma. Br J Surg 1996; 83: 336-340. http://dx.doi.org/10.1002/bjs.1800830313

[15] Kohno H, Nagasue N, Hayashi T, *et al*. Postoperative adjuvant chemotherapy after radical hepatic resection for hepatocellular carcinoma (HCC). Hepatogastroenterology 1996; 43: 1405-1409.

[16] Ono T, Nagasue N, Kohno H, *et al*. Adjuvant chemotherapy with epirubicin and carmofur after radical resection of hepatocellular carcinoma: a prospective randomized study. Semin Oncol 1997; 24: S6-18-S16-25.

[17] Takenaka K, Yoshida K, Nishizaki T, *et al*. Postoperative prophylactic lipiodolization reduces the intrahepatic recurrence of hepatocellular carcinoma. Am J Surg 1995; 169: 400-404. http://dx.doi.org/10.1016/S0002-9610(99)80184-6

[18] Patt YZ, Hassan MM, Aguayo A, *et al*. Oral capecitabine for the treatment of hepatocellular carcinoma, cholangiocarcinoma, and gallbladder carcinoma. Cancer 2004; 101: 578-586. http://dx.doi.org/10.1002/cncr.20368

[19] Edeline J, Raoul JL, Vauleon E, *et al*. Systemic chemotherapy for hepatocellular carcinoma in non-cirrhotic liver: a retrospective study. World J Gastroenterol 2009; 15: 713-716. http://dx.doi.org/10.3748/wjg.15.713

[20] Zhu AX. Systemic treatment of hepatocellular carcinoma: dawn of a new era? Ann Surg Oncol 2010; 17: 1247-1256. http://dx.doi.org/10.1245/s10434-010-0975-6

[21] Uchino K, Obi S, Tateishi R, *et al*. Systemic combination therapy of intravenous continuous 5-fluorouracil and subcutaneous pegylated interferon alfa-2a for advanced hepatocellular carcinoma. J Gastroenterol 2012; 47: 1152-1159. http://dx.doi.org/10.1007/s00535-012-0574-3

[22] Cao H, Phan H, Yang LX. Improved chemotherapy for hepatocellular carcinoma. Anticancer Res 2012; 32: 1379-1386.

[23] Ono T, Yamanoi A, Nazmy El Assal O, *et al*. Adjuvant chemotherapy after resection of hepatocellular carcinoma causes deterioration of long-term prognosis in cirrhotic patients: metaanalysis of three randomized controlled trials. Cancer 2001; 91: 2378-2385. http://dx.doi.org/10.1002/1097-0142(20010615)91:12<2378::AID-CNCR1271>3.0.CO;2-2

[24] Yan F, Wang XM, Liu ZC, *et al*. JNK1, JNK2, and JNK3 are involved in P-glycoprotein-mediated multidrug resistance of hepatocellular carcinoma cells. Hepatobiliary Pancreat Dis Int 2010; 9: 287-295.

[25] Matsushima-Nishiwaki R, Kumada T, Nagasawa T, *et al*. Direct Association of Heat Shock Protein 20 (HSPB6) with Phosphoinositide 3-kinase (PI3K) in Human Hepatocellular Carcinoma: Regulation of the PI3K Activity. PLoS One 2013; 8: e78440. http://dx.doi.org/10.1371/journal.pone.0078440

[26] Davis AJ, Tannock JF. Repopulation of tumour cells between cycles of chemotherapy: a neglected factor. Lancet Oncol 2000; 1: 86-93. http://dx.doi.org/10.1016/S1470-2045(00)00019-X

[27] Lai EC, Lo CM, Fan ST, *et al*. Postoperative adjuvant chemotherapy after curative resection of hepatocellular carcinoma: a randomized controlled trial. Arch Surg 1998; 133: 183-188. http://dx.doi.org/10.1001/archsurg.133.2.183

[28] Abou-Alfa GK, Johnson P, Knox JJ, *et al*. Doxorubicin plus sorafenib vs doxorubicin alone in patients with advanced hepatocellular carcinoma: a randomized trial. JAMA 2010; 304: 2154-2160. http://dx.doi.org/10.1001/jama.2010.1672

[29] Llovet JM, Ricci S, Mazzaferro V, *et al*. Sorafenib in advanced hepatocellular carcinoma. N Engl J Med 2008; 359: 378-390. http://dx.doi.org/10.1056/NEJMoa0708857

[30] Cheng AL, Kang YK, Chen Z, *et al*. Efficacy and safety of sorafenib in patients in the Asia-Pacific region with advanced hepatocellular carcinoma: a phase III randomised, double-blind, placebo-controlled trial. Lancet Oncol 2009; 10: 25-34. http://dx.doi.org/10.1016/S1470-2045(08)70285-7

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