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Original Article

Selection of patients with solitary hepatocellular carcinoma for hepatic resection: reassessment of a 5-cm tumor size cut-off

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Abstract: This study compared the efficacy of hepatic resection in patients with solitary hepatocellular carcinoma (HCC) with a tumor diameter > 5 cm or ≤ 5 cm. A consecutive sample of 386 patients with solitary HCC who were treated by initial resection was divided into those with tumor diameter > 5 cm (n = 203) and those with tumor diameter ≤ 5 cm (n = 183). A comprehensive literature search of relevant databases was also conducted to assess available evidence on 5 cm as a cut-off point for staging single HCC. Hospital mortality was similar between patients with solitary HCC > 5 cm and those with ≤ 5 cm, but patients with solitary HCC > 5 cm showed significantly higher morbidity and lower overall survival (both $P < 0.05$). Meta-analysis of the results of our cohort study with results of 9 studies in the literature (corresponding to 6,008 patients) showed that patients with solitary HCC > 5 cm had significantly worse overall survival than those with ≤ 5 cm. Therefore, our cohort analysis and literature review suggest that 5 cm is a reliable cut-off point for staging solitary HCC and selecting patients for resection.

Keywords: Cut-off point, hepatocellular carcinoma, hepatic resection, overall survival

Introduction

Hepatocellular carcinoma (HCC) is one of the most common malignancies worldwide [1, 2]. Its high recurrence rate means that even after curative hepatic resection (HR), which remains the first-line therapy for HCC, patient prognosis is far from satisfactory [3-5]. Various studies, each involving more than 2,000 patients, have shown that the 5-year disease-free survival rate after HR is only 37% for patients with early-stage HCC [6], 27% for those with intermediate-stage disease [7], and 18% [7] for those with advanced disease.

The potentially large differences in patient prognosis after HR depending on disease stage highlight the importance of proper preoperative staging. Until recently, the Barcelona Clinic Liver Cancer (BCLC) system [8-10], perhaps the most widely accepted HCC staging system and treatment algorithm in Western countries [11, 12], suggested a tumor diameter of 5 cm as a cut-off for defining solitary HCC as early- or intermediate-stage disease [8-10]. A range of specialists at large hepatobiliary treatment centers in the US, Europe and China have also advocated using5 cm as the cut-off [7, 13-17]. Now the BCLC system recommends that all single nodules be classified as early-stage disease, regardless of tumor size [18-20]. Thus, the cut-off value of 5 cm remains controversial [21-25], and validating it (or not) can strongly affect treatment decisions. Previous BCLC system recommended offering only palliative therapies to patients with solitary HCC > 5 cm [8-10]. The new position in the BCLC system is that HR should be the first-line therapy for such patients [18-20].

To help resolve the controversy about how to stage solitary HCC and what treatments to recommend, we retrospectively analyzed a large patient cohort who underwent HR at our two institutions, and we reviewed available evidence in PubMed.

Patients and methods

Patients

Medical records were retrospectively analyzed for patients with newly diagnosed solitary HCC who had preserved liver function and who underwent HR as their initial therapy at The Second People's Hospital of Jingmen and the Affiliated Tumor Hospital of Guangxi Medical University between January 1996 and December 2003. Patients were excluded if they had concomitant or isolated tumor thrombi in the portal vein, hepatic vein, vena cava, or bile duct; if they had tumor metastasis to the lymph nodes or distant organs; or if they had undergone neoadjuvant transarterial chemoembolization.

HCC diagnosis was confirmed in all patients based on histopathological examination of surgical samples taken after HR. During initial hospitalization, baseline information on patient demographics, tumor size, serum biochemistry, liver cirrhosis, type of hepatectomy, and blood loss was recorded.

This study protocol was approved by the research ethics committees of both medical centers, and it complied with current ethical guidelines. All patients signed written informed consent before any HCC-specific treatments were given.

Treatment and follow-up

HR was performed using standard procedures as described [13, 26]. Liver function was analyzed using a conventional liver function test and classified based on the Child-Pugh scheme. Starting immediately after HR, monthly follow-up was conducted for all patients involving regular clinical examinations, liver function tests, assays of serum levels of alpha-fetoprotein (AFP), chest X-ray, and abdominal ultrasound. Moreover, computed tomography scanning and/or magnetic resonance imaging was performed every 2-3 months to monitor for recurrence. Recurrence was defined as the appearance of a new lesion after surgery with radiological features characteristic of HCC. The two participating medical centers conducted follow-up independently. Follow-up for all participants started from the date of surgery and continued until March 2015.

Statistical analysis

Categorical data were reported as frequencies and percentages, and differences were assessed for significance using Pearson's chi-squared test or Fisher's exact test as appropriate (2-tailed). Continuous variables were summarized as median and range, and compared using Student's t test or the Mann-Whitney test. Kaplan-Meier survival curves were used to examine overall survival (OS) and were compared using the log-rank test. All analyses were carried out in SPSS 19.0 for Windows (IBM, Armonk, NY). A two-tailed $P < 0.05$ was defined as the threshold of significance.

Literature review

Randomized trials, cohort studies, and case-control studies published up to June 30, 2016 and indexed in databases of PubMed, Wiley Online Library, Cochrane Central Register of Controlled Trials, Science Direct, Web of Science, CNKI, Chong Qing VIP, Wan Fang, and China Biology Medicine disc were identified using the following search strings: (*hepatocellular carcinoma* OR *liver tumor* OR *liver cancer* OR *liver carcinoma*) AND (*resection* OR *hepatectomy* OR *surgery*) AND (*single* OR *solitary* OR *tumor size*). Reference lists in retrieved papers and review articles were searched manually to identify additional articles. Studies were included in the literature review only if they were available as full text, if they were written in English, and if they compared the efficacy of HR for primary solitary HCC > 5 cm *vs* ≤ 5 cm. Studies evaluating HR to treat multinodular or recurrent HCC were excluded. If multiple studies involved the same patient population based on recruiting center and enrollment period, only the study with the largest number of participants was included in the review.

Data from included studies were analyzed using Review Manager 5.3 (Cochrane Collaboration). Given the likelihood of high mortality, the Mantel-Haenszel method was used to

Table 1. Demographic characteristics, baseline clinicopathological data and outcomes of patients with single hepatocellular carcinoma after initial hepatic resection

Parameter	Tumor size		*P*
	≤ 5 cm (n = 183)	> 5 cm (n = 203)	
Age, yr	48.4 ± 9.7	47.8 ± 10.2	0.351
Male/Female	154/29 (84/16)	173/30 (85/15)	0.779
Positive for hepatitis B surface antigen	163 (89)	179 (88)	0.873
Platelet count, × 10^9/L	162 (32-442)	182 (52-517)	0.002
Prothrombin time, sec	13.1 (8.9-22.1)	12.7 (9.1-21.0)	0.092
Albumin, g/L	40.1 ± 5.2	40.4 ± 4.7	0.081
Alanine aminotransferase, U/L	36.1 (2.1-394.0)	36.0 (2.0-401.0)	0.712
Total bilirubin, μmol/L	14.1 ± 7.4	13.7 ± 8.1	0.435
α-fetoprotein			
≥ 400 ng/mL	57 (31)	81 (40)	0.089
< 400 ng/mL	126 (69)	122 (60)	
Child-Pugh class			
A	156 (85)	185 (91)	0.081
B	27 (15)	18 (9)	
Cirrhosis			
Present	126 (69)	138 (68)	0.913
Absent	57 (31)	65 (32)	
Esophagogastric varices	18 (10)	24 (12)	0.624
Diabetes mellitus	37 (20)	43 (21)	0.900
Tumor capsule			
Complete	112 (61)	106 (52)	0.081
Incomplete/absent	71 (39)	97 (48)	
Microvascular invasion	49 (27)	63 (31)	0.371
Tumor differentiation			
Well	42 (23)	43 (21)	0.517
Moderate	82 (45)	83 (41)	
Poor	59 (32)	77 (38)	
Tumor size, cm	3.61 ± 1.3	8.24 ± 4.25	< 0.001
Major hepatectomy	5 (3)	37 (18)	< 0.001
Blood loss, mL	200 (50-1400)	300 (80-4100)	< 0.001
30-day mortality	0 (0)	2 (1.0)	0.500
90-day mortality	0 (0)	5 (2.5)	0.063
Complications	33 (18.3)	70 (34.5)	< 0.001
Survival time, mos.	75 (4-118)	63 (1-119)	0.004

Values shown are mean ± SD, median (range), or n (%).

meta-analyze data. A random-effects meta-analysis model was used if the studies were found to contain significant heterogeneity, defined as $I^2 > 50\%$; otherwise, a fixed-effects meta-analysis model was used. If the two models gave different results, both sets of results were reported. Point estimates of risk ratios were considered significant when $P < 0.05$. Sensitivity analysis was performed to determine the impact of excluding certain studies, such as those associated with significant heterogeneity in the corresponding meta-analysis or those involving specific patient subpopulations.

Results

Characteristics of the cohort population

From January 1996 to December 2003, 386 patients with solitary HCC at our two medical

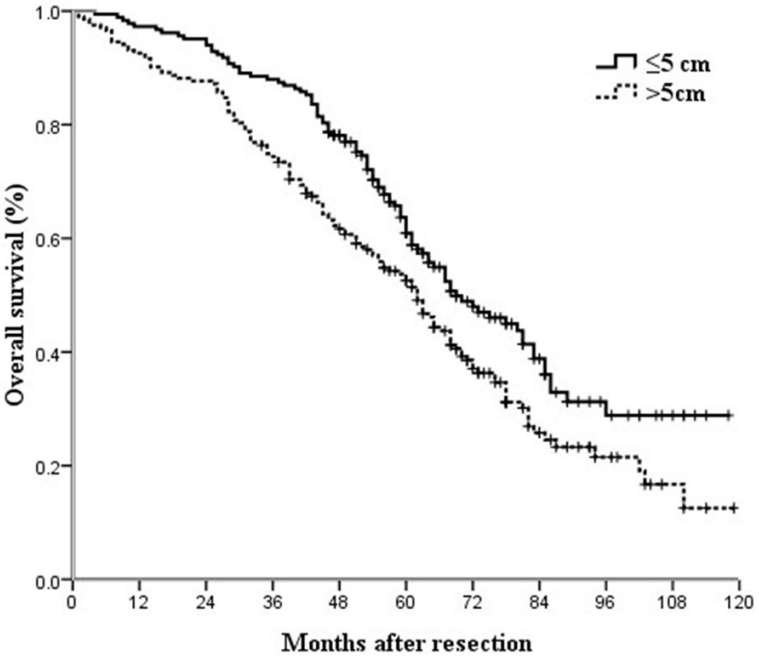

Figure 1. Kaplan-Meier survival curves for patients with solitary hepatocellular carcinoma following hepatic resection.

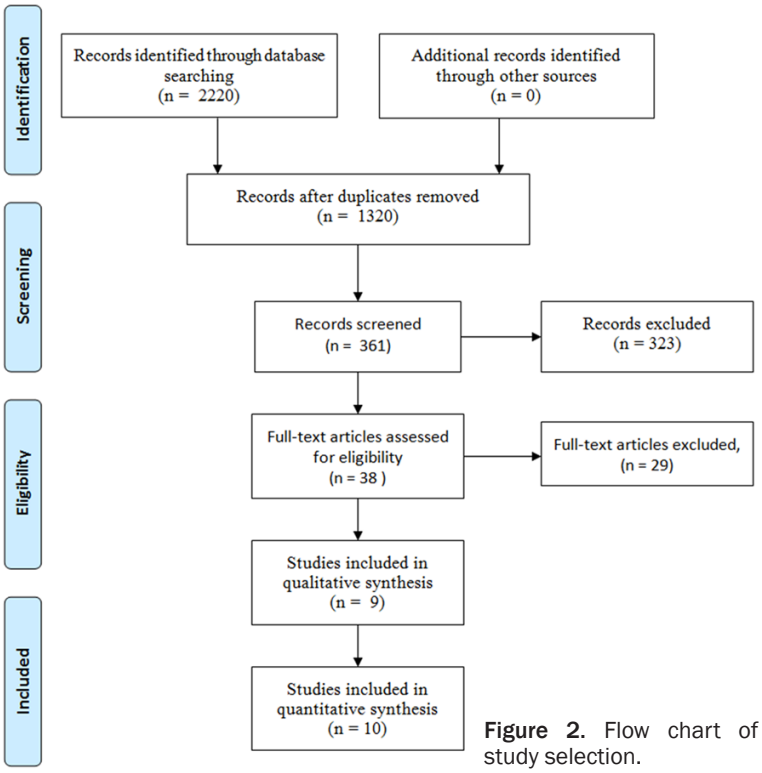

Figure 2. Flow chart of study selection.

centers were found to fit the inclusion and exclusion criteria and were enrolled in this retrospective study. Of this total, 183 (47.4%) had tumors with diameters ≤ 5 cm, while 203 (52.6%) had tumors with diameters > 5 cm. Baseline demographic and clinicopathological data for all 386 patients are presented in **Table 1**.

The two groups did not differ significantly in age; gender; Child-Pugh classification; levels of prothrombin time, albumin, alanine aminotransferase, total bilirubin, or AFP; presence of hepatitis B surface antigen, cirrhosis, esophagogastric varices, diabetes mellitus, tumor capsule, microvascular invasion; or poor tumor differentiation (all $P > 0.05$). However, patients in the > 5 cm group showed significantly higher platelet count, tumor diameter, and blood loss, as well as a higher rate of major hepatectomy (all $P < 0.05$).

Morbidity and mortality of the cohort population

Perioperative morbidity was assessed using the Clavien-Dindo classification [27]. Patients in the ≤ 5 cm group showed a significantly lower rate of morbidity than those in the > 5 cm group ($P < 0.001$). However, no significant differences were observed between the two groups in 30-day mortality ($P = 0.500$) or 90-day mortality ($P = 0.063$) (**Table 1**).

OS of the cohort population

During follow-up, 97 patients (53.0%) died in the ≤ 5 cm group and 137 (67.5%) died in the > 5 cm group. Median survival time was 75 months in the ≤ 5 cm group and 63 months in the > 5 cm group. The ≤ 5 cm group showed significantly better OS than the > 5 cm group ($P = 0.004$;

Table 2. Post-hepatic resection overall survival of patients with single small (≤ 5 cm) and large (> 5 cm) tumors in the present work and in studies in PubMed

Study	Country	Enrollment period	Sample size*	Overall survival (%)			*P*
				1-yr	3-yr	5-yr	
Cho et al, 2007 [29]	South Korea	1998-2001	169/61	88/85	70/59	59/53	0.385
Ho et al, 2014 [30]	Taiwan	2001-2007	134/121	91/80	78/59	72/56	0.010†
Hwang et al, 2015 [31]	South Korea	2000-2012	1702/448	97/93	89/81	81/69	< 0.001
Jung et al, 2016 [32]	South Korea	2004-2009	134/41‡	97/93	82/80	77/76	> 0.05†
Liu et al, 2016 [33]	China (Southern)	2004-2013	426/431	97/92	81/64	63/45	< 0.001
Yang et al, 2009 [35]	China (Central)	1992-2002	135/260	93/87	68/56	48/38	0.129
Yang et al, 2014 [34]	China (Western)	2006-2012	303/515§	88/71	80/50	71/36	< 0.001
Zhang et al, 2014 [36]	China (Eastern)	2002-2010	380/229	97/95	83/75	72/66	0.044
Zhou et al, 2011 [37]	China (Northern)	1995-2002	48/85	96/94	74/56	69/47	0.041
This study	China (Southern)	1996-2003	183/203	97/93	88/75	64/54	0.004

*Single tumor ≤ 5 cm *vs* single tumor > 5 cm. †Overall survival was derived from reported survival curves. ‡Single tumor > 2 cm and ≤ 5 cm or 2-3 nodules ≤ 3 cm *vs* single tumor > 5 cm. §Single tumor < 5 cm *vs* single tumor ≥ 5 and < 10 cm.

Figure 1): OS in the ≤ 5 cm group was 97% at 1 year, 88% at 3 years, and 64% at 5 years; the corresponding rates in the > 5 cm group were 93%, 75%, and 54%.

Literature review

Databases search yielded 2,220 titles, of which 1,320 were short listed for title and abstract review. After excluding studies based on title and abstract review, 38 were read in full. No additional relevant titles were identified based on manual searches of reference lists in review articles. One study [28] was excluded because the sample size of patients with tumors ≤ 5 cm or > 5 cm was not reported. In the end, 9 retrospective case series [29-37] were included in the literature review (**Figure 2**). These studies, combined with the present cohort analysis, involved a total of 6,008 patients (**Table 2**). Patient populations showed some heterogeneity across studies. For example, in the study by Jung and co-workers [32], patients in the ≤ 5 cm group comprised those with single tumors > 2 cm and ≤ 5 cm or with 2-3 nodules ≤ 3 cm; in the study by Yang and colleagues [34], patients in the > 5 cm group comprised those with tumors ≥ 5 and < 10 cm. Three studies [35-37] contained patients with macrovascular invasion; these studies were included because the proportion of such patients was small.

Meta-analysis of available data

Patients in the ≤ 5 cm group showed significantly better 1-year OS, with a pooled risk ratio of 1.06 [95% confidence interval (CI) 1.03 to 1.10, $P < 0.001$] based on random-effects meta-analysis ($I^2 = 74\%$, $P < 0.001$) (**Figure 3**). The ≤ 5 cm group also showed significantly better OS at 3 and 5 years (**Figure 3**). Similar results were obtained after excluding the studies by Jung and co-workers [32] and Yang and colleagues [34], which eliminated significant heterogeneity from the meta-analysis (**Figure 4**). Similar results were obtained after excluding these two studies [32, 34] as well as three studies containing patients with macrovascular invasion [35-37] (**Figure 5**). Fixed- and random-effects models gave similar results for the meta-analyses. However, funnel plots of the 10 studies in the meta-analysis showed a symmetrical shape, suggesting minimal risk of publication bias.

Discussion

The latest recommendations of the BCLC group are to consider patients with preserved liver function, a solitary tumor of any size and nomacrovascular invasion as having early HCC [18-20]. The 6th and 7th versions of the American Joint Committee on Cancer (AJCC) Tumor-Node-Metastasis (TNM) staging system classify solitary HCC of any size with or without microvascular invasion as T1 or T2. This tumor size-independent approach is supported by one of the large studies included in the present review that reported OS after HR to be independent of tumor size in patients with solitary HCC without microvascular invasion [36]. However, the results of another included study [33] suggest-

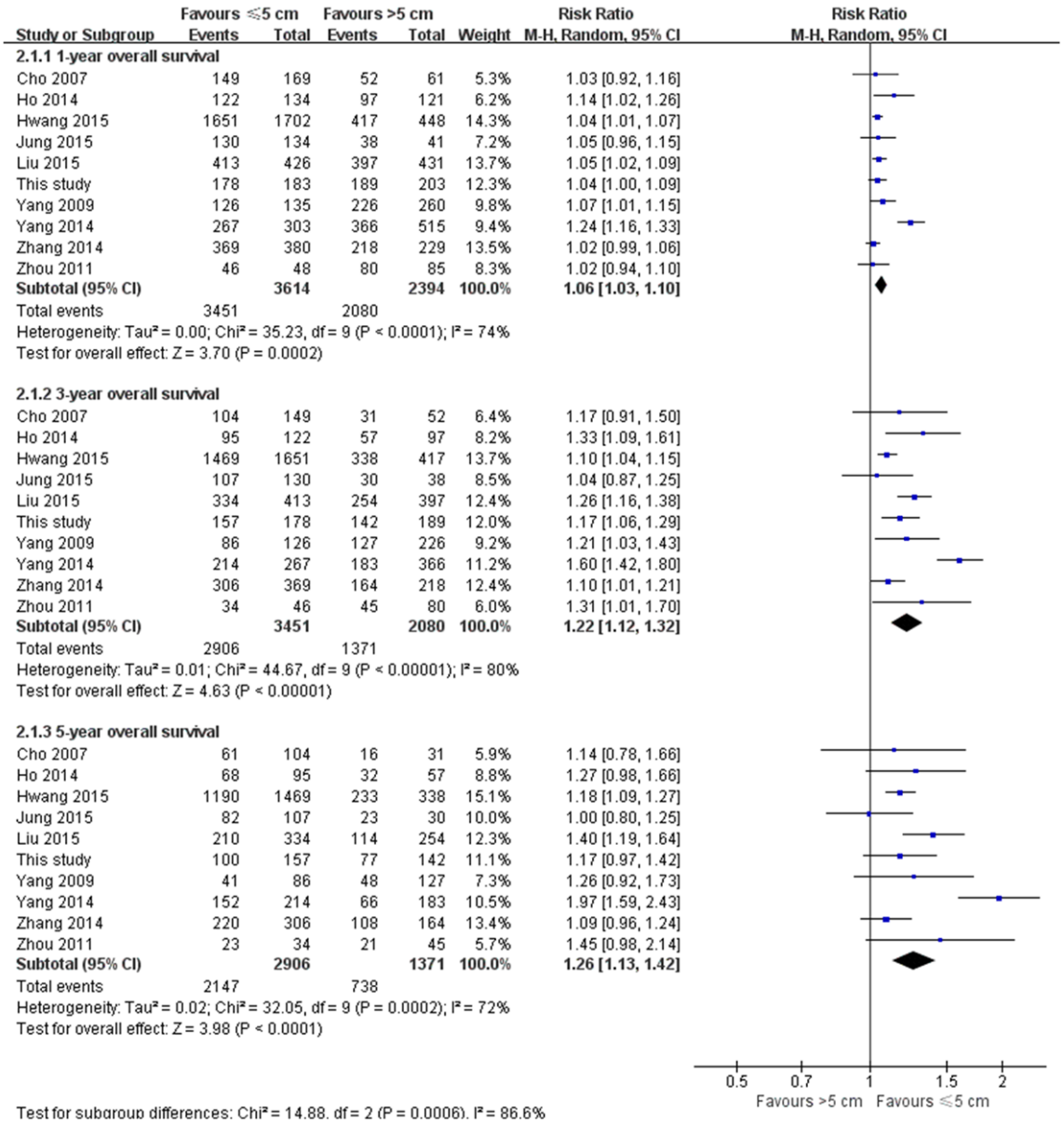

Figure 3. Total sample size analysis.

ed a need to revise the BCLC staging system, while the results of one excluded study [28] and two included studies [30, 31] suggested that the current version of the AJCC staging system underestimates the prognostic impact of tumor size. Reflecting this controversy, other large studies and even official guidelines have considered the possibility of using 5 cm as the tumor size cut-off for defining solitary HCC as early- or intermediate-stage [21-24].

The present cohort of 386 patients with solitary HCC treated by HR at two medical centers showed that patients with a tumor size > 5 cm or ≤ 5 cm showed similar 30- and 90-day mortality, but those in the > 5 cm group showed a significantly higher rate of morbidity and lower OS. These results were supported by meta-analysis of data pooled from the present cohort and another 9 studies, involving a total of 6,008 patients. Our findings support 5 cm as an appropriate cut-off for defining solitary HCC as different stages and therefore for selecting patients for whom HR is associated with lower risk of morbidity and/or mortality.

Our findings are consistent with previous work from our group and others identifying tumor

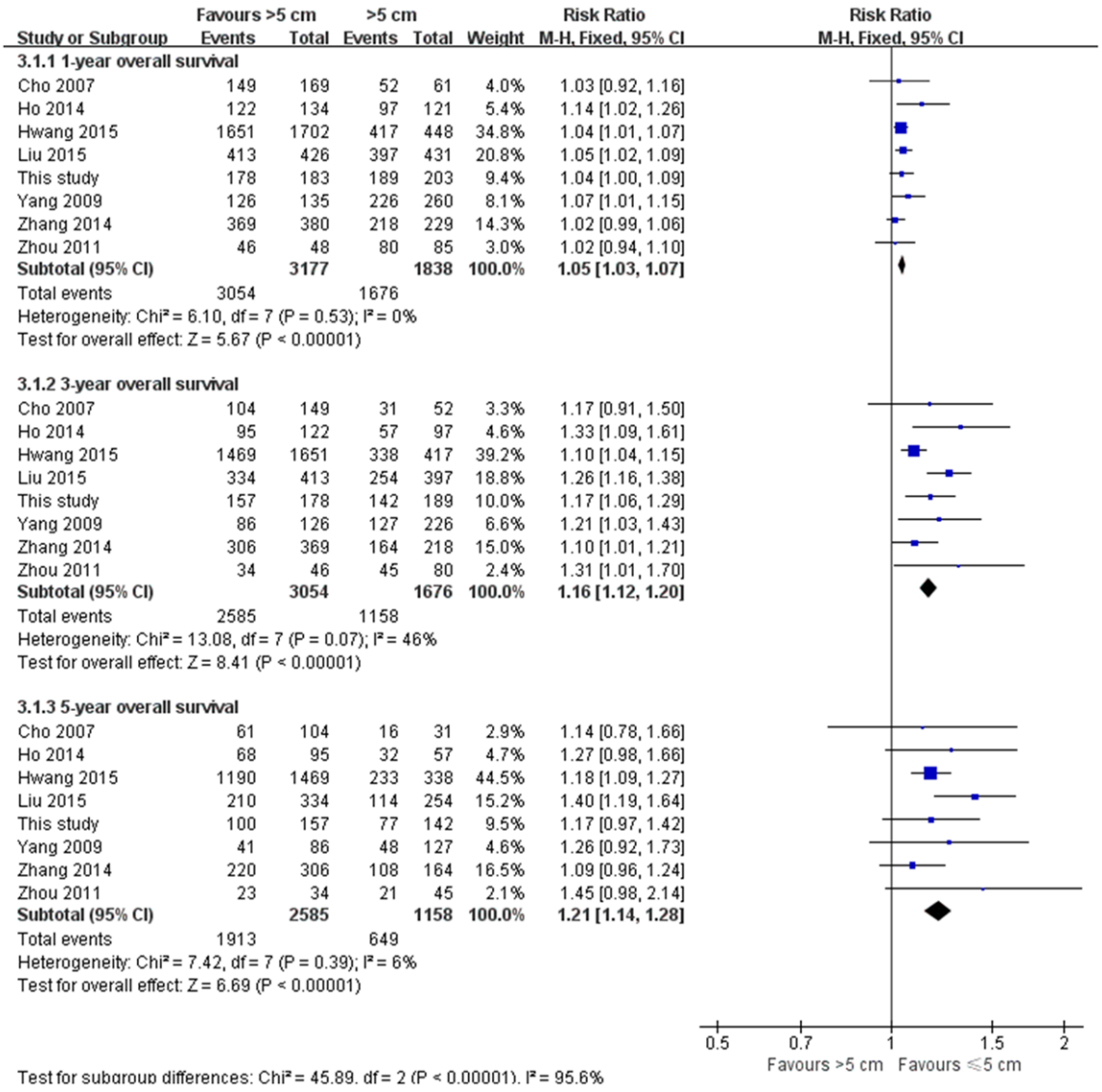

Figure 4. Sensitivity analysis after excluding two studies [32, 34] involving patients with multiple tumors or with single tumors > 10 cm.

size as one of the most important preoperative factors for the prognosis of HCC patients, with larger tumors associated with less favorable patient outcomes. Our group previously conducted post-HR OS analysis of a different cohort of patients with solitary HCC [33]. Classifying patients according to tumor size in 2-cm increments showed that as tumor diameter increased, OS decreased and tumor recurrence increased. Combining adjacent tumor size categories with similar OS led to three groups: ≤ 5 cm, > 5 and ≤ 8 cm, and > 8 cm. Patients in the ≤ 5 cm group showed significantly higher OS than those in the > 5 and ≤ 8 cm group, who in turn showed significantly higher OS than those in the > 8 cm group [33]. These results suggest that tumor size is a significant predictor of OS and tumor recurrence. These previous findings, together with the present cohort study and literature review, strongly suggest that current BCLC and AJCC TNM staging systems need to be revised.

In the present study, our cohort included only patients with single HCC after initial HR without macrovascular invasion or tumor metastasis to lymph nodes or distant organs. However, our full meta-analysis of available evidence from

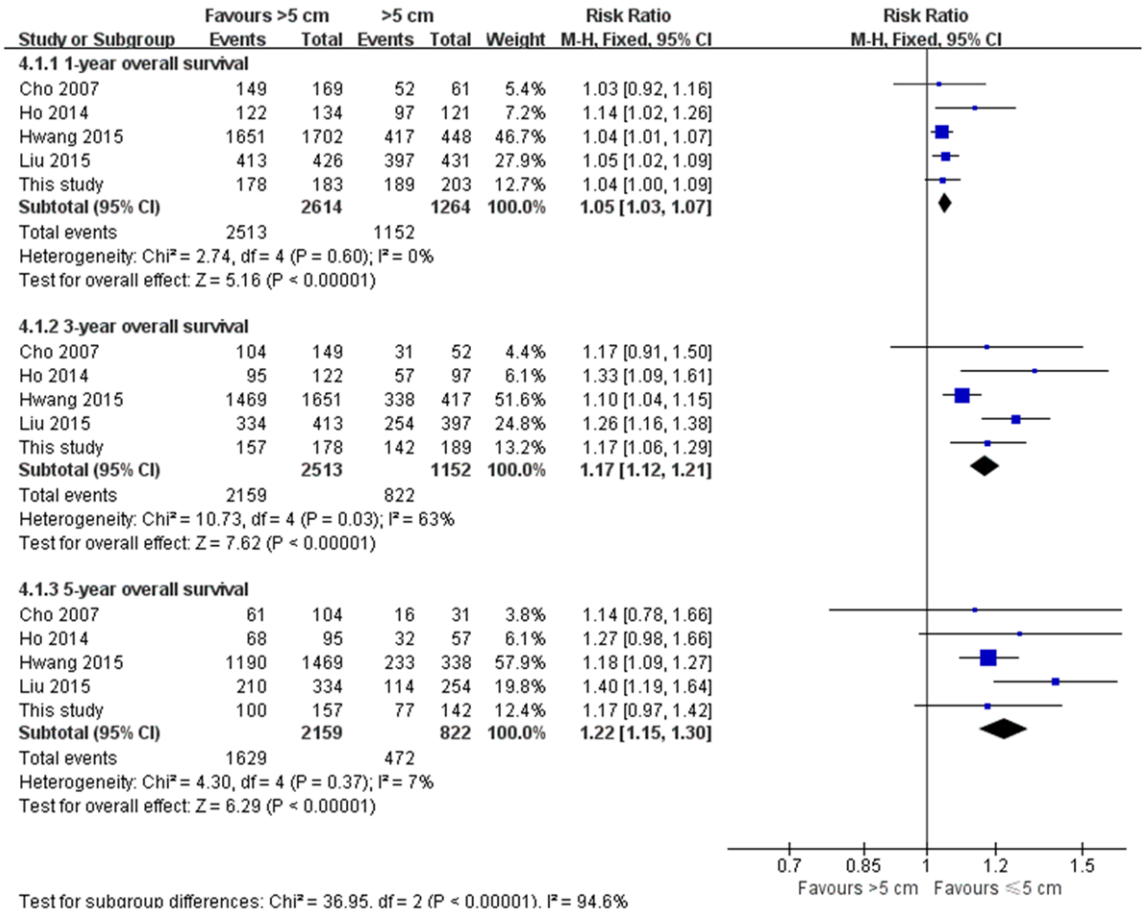

Figure 5. Sensitivity analysis after excluding five studies [32, 34-37] associated with clinical heterogeneity in the meta-analysis.

PubMed included approximately 10% of patients with multiple tumors or vascular invasion. Both microvascular invasion and poor histology grade have been associated with poor outcomes of HCC patients after HR [12], but the rates of these two factors were similar between our cohort groups with > 5 cm or ≤ 5 cm. In addition, our meta-analysis gave similar results regardless of whether we excluded such patients. We conclude that tumor size is an independent predictor of OS after HR.

Although we combined an original study with a review of literature in PubMed to gain a comprehensive understanding of post-HR outcomes for patients with solitary HCC, our work has several limitations. First, most patients in the meta-analysis had chronic hepatitis B virus infection, and all were from Asian countries. Therefore our results may not be generalizable to other ethnic groups. Second, our cohort was selected to be highly homogeneous, which may not reflect clinical reality. This drawback is mitigated by the fact that we pooled our data with work from several studies and obtained meta-analysis results that were robust to sensitivity analysis. Further large studies, particularly in Western countries, are needed to corroborate our findings.

In conclusion, our analysis suggests that tumor size need not be considered a contraindication of HR for patients with solitary HCC, but that 5 cm is a valid cut-off value for tumor size when staging solitary HCC.

Acknowledgements

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Disclosure of conflict of interest

None.

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