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Original Article

Is partial hepatectomy a curable treatment option for hepatocellular carcinoma accompanied by cirrhosis? A meta-analysis and cure model analysis

Byungje Bae, Keera Kang, Sung Kyu Song, Chul-Woon Chung, Yongkeun Park

Department of Surgery, Catholic Kwandong University International St. Mary's Hospital, Incheon, Korea

Backgrounds/Aims: It is challenging to assess the efficacy of partial hepatectomy (PH) as a treatment option for patients with hepatocellular carcinoma (HCC) accompanied by cirrhosis. This study aimed to determine the cure fraction of PH for HCC accompanied by cirrhosis compared to that for HCC without cirrhosis.
Methods: A systematic review was performed on outcomes of previous studies that compared recurrence-free survival (RFS) after PH in patients with HCC with or without cirrhosis. A meta-analysis was conducted to obtain the cumulative hazard ratio for two patient groups: cirrhosis and non-cirrhosis. Cure fractions after PH in both groups were determined using a cure model analysis.
Results: A total of 18 studies were eligible for meta-analysis and 13 studies were selected for the cure model analysis. The cumulative hazard ratio for RFS of the cirrhosis group compared to that of the non-cirrhosis group was 1.66 (95% confidence interval [CI], 1.43–1.93). Survival data of 3,512 patients in both groups were reconstructed from survival curves of original articles for cure model analysis. The probability of being statistically cured after PH for HCC was 14.1% (95% CI, 10.6%–18.1%) in the cirrhosis group lower than that (32.5%) in the non-cirrhosis group (95% CI, 28.6%–36.4%).
Conclusions: The prognosis after PH for HCC accompanied by cirrhosis is inferior to that for HCC without cirrhosis. However, a cure can be expected for one-seventh of patients with HCC accompanied by cirrhosis after PH.

Key Words: Cure fraction; Hepatectomy; Kaplan–Meier estimate; Non-mixture

INTRODUCTION

Primary liver cancer is the 5th most common cancer in the world, with hepatocellular carcinoma (HCC) being the most common (accounting for more than 80%) histologic type of primary liver cancer [1]. Most HCCs are associated with chronic liver disease, which is mainly caused by hepatitis B virus infection, hepatitis C virus infection, alcohol abuse, and non-alcoholic fatty liver disease [1,2]. Recently, the incidence of HCC has been increasing in Europe and America [3,4]. Treatment of patients with HCC remains challenging despite enormous efforts. Less than 25% of patients with HCC receive potentially curative therapy such as liver transplantation (LT), partial hepatectomy (PH), and local ablation [5,6]. The prognosis of these patients is not promising, with an overall five-year survival rate of less than 20% [6]. Management of HCC accompanied by cirrhosis is more challenging because a diminished functional hepatic reservoir limits not only standard curative treatment, but also experimental therapeutic trials.

In cases of HCC accompanied by cirrhosis, LT is the primary treatment as it can treat both the tumor and the underlying liver disease simultaneously [7]. However, LT is not always feasible. In addition, it has a few limitations [8,9]. PH can be an alternative option in some cases, for example, when the functional reservoir of the liver is sufficient for PH to be carried out [10]. Recent studies suggest that the prognosis after PH in patients with HCC accompanied by cirrhosis is comparable

to that after LT [10-12]. On the other hand, there are negative views of PH as a curative treatment for HCC accompanied by cirrhosis due to a relatively higher recurrence rate after PH than that after LT. However, this argument has been only based on clinical studies carried out in the immediate postoperative period [6,7,11]. Clinicians may underestimate the value of PH as a treatment option for patients with HCC accompanied by cirrhosis because there is little information on changes in prognosis over time. Thus, a more meticulous statistical analysis of PH needs to be conducted. The cure model analysis is a stepping-stone for solving this issue.

A cure model analysis is a useful statistical method for analyzing post-treatment survival data of long-term survivors with specific diseases, for example, long-term survivors with cancer. The cure model is a valuable tool that can analyze cure fraction in patients under various settings. The use of the cure model could explain the long-term effect of a specific treatment for the disease. It may provide the prospect of cure [13,14].

In this study, we attempted to examine the possibility of PH curing patients with HCC accompanied by cirrhosis. We also compared PH cure fraction for patients with HCC with that for patients without cirrhosis to estimate the statistical chance of cure after PH for patients with HCC using a non-mixture cure model. Outcomes were also compared between non-cirrhotic and cirrhotic patients [15].

MATERIALS AND METHODS

Literature search

A comprehensive search of Medline, Embase, and KoreaMed databases was performed for articles published between January 1995 and July 2020 reporting recurrence-free survival (RFS) after PH in patients with HCC and comparing RFS according to the presence or absence of cirrhosis. To include as many relevant articles as possible, we selected "carcinoma, hepatocellular" and "liver cirrhosis" or "fibrosis" and "hepatectomy" as Medical Subject Headings (MeSH) terms. Other keywords such as "hepatocellular carcinoma," "cirrhosis," "resect," and "resection" were also used. We examined titles and abstracts of studies in search results to select relevant ones. For additional screening, two researchers (BB and KK) independently inspected all candidate articles employing inclusion and exclusion criteria. We exclusively abstracted hazard ratios (HRs) from observational studies and then combined them in a meta-analysis. This meta-analysis was conducted following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA).

Eligibility criteria

We selected articles that showed RFS after PH in patients with or without cirrhosis. Studies that provided HRs between cirrhosis and non-cirrhosis groups were included. If HRs were not provided, articles with Kaplan–Meier (KM) survival curve that showed RFS were selected. If two or more studies included
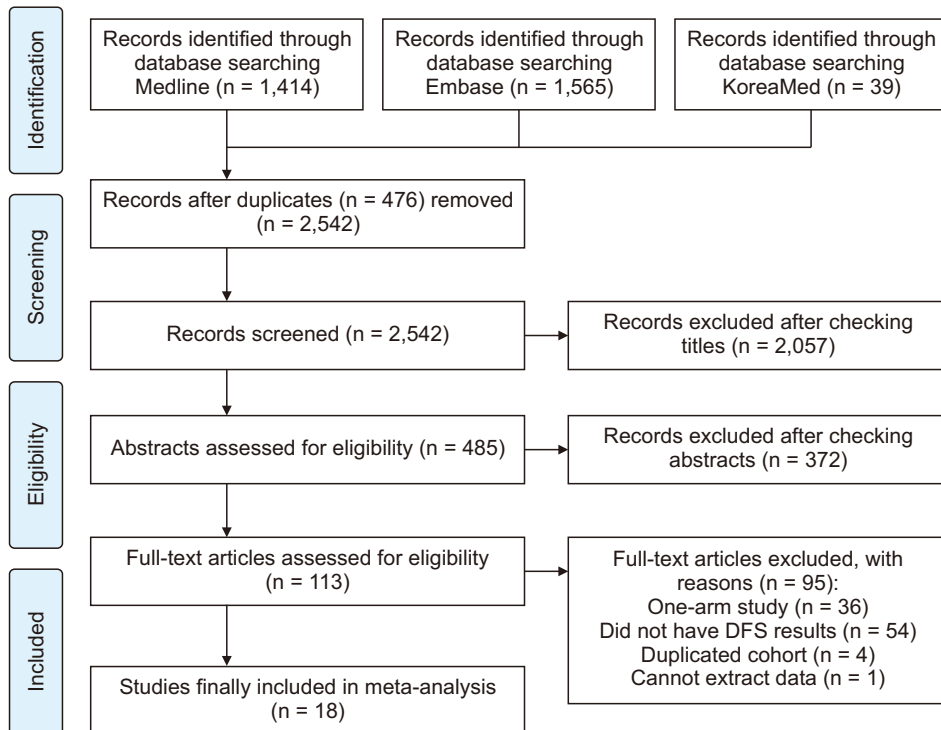

Fig. 1. Flow chart showing study selection. DFS, disease-free survival.

Table 1. Characteristics and baseline demographics of patients in each study included for this research

Study (year)	Study design (country)	Study period	Cirrhosis (No/Yes)	Diagnosis of cirrhosis	Resection type (major/minor)	Male/female (no. of patients)	Age (yr)	CP class (A/B or C)	Etiology (HBV/other)	Stage (AJCC I/II/III/IV)	Vascular invasion (No/Yes)	Alpha-fetoprotein, mean (ng/mL)
Chang et al. (2004) [19]	Cohort (Taiwan)	1991–1998	75/112	Histologically confirmed	16/59 11/101	87%/13%	60	NA	NA	60/71/92 58/94/70	42/181 58/164	13,181 2,716
Yamashita et al. (2007) [20]	Cohort (Japan)	1985–2004	141/180	Histologically confirmed	NA	225/66	60.7	302/19	66/225	NA	NA	415.8
Chua et al. (2010) [21]	Cohort (Australia)	1991–2009	63/34	Histologically confirmed	44/53	75/22	49/48 (<62/≥62)	82/15	33/64	NA	93/4	67/30 (<400/≥400)
Gassmann et al. (2010) [22]	Cohort (Germany)	1997–2007	21/24	Histologically confirmed	NA	17/4 19/5	65.2 69.6	NA 19/5	2/19 5/19	3/11/7 2/18/4 (T1/T2/T3)	6/15 6/18	NA
Fan et al. (2011) [23]	Cohort (China)	1995–2008	97/311	Histologically confirmed	124/284	322/86	314/94 (≤65/>65)	395/13	367/41	NA	292/116	NA
Ho et al. (2012) [24]	Cohort (Taiwan)	2001–2007	408/338	Histologically confirmed	NA	581/165	52.3	NA	494/252	NA	561/185	NA
Mizuguchi et al. (2013) [25]	Cohort (Japan)	2006–2010	79/70	Histologically confirmed	NA	NA	67.8 66.0	NA	34/45 32/38	9/48/13/9 16/25/26/3	NA	NA
Yang et al. (2014) [26]	Cohort (China)	2002–2012	30/128	Histologically confirmed	NA	141/173	49.2 ± 11.5	132/26	143/15	NA	74/84	99/59 (≥20/<20)
Yap et al. (2014) [27]	Cohort (Taiwan)	1992–2002	131/93	Histologically confirmed	141/83	179/45	84/140 (<50/≥50)	192/22	151/73	224/0/0/0	NA	120/58/46 (≤20/20–400/≥400)
Chapman et al. (2015) [28]	Cohort (United States)	1990–2011	151/97	Histologically confirmed	NA	170/78	66 (17–86)	NA	57/191	NA	NA	NA
Kluger et al. (2015) [29]	Cohort (France)	1989–2010	166/147	Histologically confirmed	175/138	250/63	59 ± 14	NA	77/236	NA	155/158	226/87 (≤200/>200)
Huang et al. (2016) [30]	Cohort (China)	2001–2009	44/96	Histologically confirmed	NA	38/6 85/11	45 (28–77) 49 (14–79)	241/15	28/16 90/6	NA	41/3 90/6	39.2 53
Lee et al. (2017) [31]	Cohort (Korea)	1996–2012	262/387	Histologically confirmed	136/126 149/238	208/54 303/84	54.4 ± 10.8 54.9 ± 9.1	NA	162/100 257/130	NA	141/121 208/179	2,185.5 1,560.6
Shehta et al. (2016) [32]	Cohort (Korea)	2004–2013	91/141	Histologically confirmed	20/70 17/124	65/26 100/41	57 (26–79) 57 (31–87)	87/3 125/16	58/33 110/31	53/33/4/1 12/48/36/9 (T1/T2/T3/T4)	59/32 93/48	9.1 15.7
Lee et al. (2017) [33]	Cohort (Korea)	2001–2013	686/314	Histologically confirmed	529/473	807/195	760/242 (<65/≥65)	964/38	747/255	500/374/123/5	571/431	660/70/269 (<200/200–400/≥400)

Table 1. Continued

Study (year)	Study design (country)	Study period	Cirrhosis (No/Yes)	Diagnosis of cirrhosis	Resection type (major/minor)	Male/female (no. of patients)	Age (yr)	CP class (A/B or C)	Etiology (HBV/other)	Stage (AJCC I/II/III/IV)	Vascular invasion (No/Yes)	Alpha-fetoprotein, mean (ng/mL)
Cipriani et al. (2018) [34]	Cohort (Italy, UK, Norway, France, Belgium)	1998–2014	70/333	Histologically confirmed	19/51 31/302	40/30 124/209	70 (7–87) 66 (23–88)	70/0 308/25	NA	NA	NA	NA
Famularo et al. (2018) [35]	Cohort (Italy)	2001–2015	63/291	Histologically confirmed	NA	280/74	66.1	330/24	74/280	NA	234/120	NA
Golse et al. (2018) [36]	Cohort (France)	2012–2016	45/15	Histologically confirmed	18/27 7/8	37/8 10/5	66.6 ± 12 64.1 ± 10	NA	6/39 1/14	NA	24/21 7/8	1,107 1,477

Values are presented as number only, mean (range), or mean ± standard deviation.
CP, Child-Pugh classification; HBV, hepatitis B virus; AJCC, the American Joint Committee on Cancer; NA, not available.

identical cohort data, the one with more accumulated data was used for our study. Papers published in languages other than English were excluded.

Reconstruction of Kaplan–Meier data and obtaining cumulative hazard ratios

Data extracted from each original article included the name of the first author, the year of the publication, study design, patient characteristics including the absence or presence of cirrhosis, and outcomes. If possible, HR and 95% confidential interval (CI) were recorded from the original article. If such information was not available, KM survival data were secondarily restored for each group using printed survival curves to calculate HR. Coordinates of time and survival probability were obtained from printed survival curves applying a DigitizeIt software (www.digitizeit.de). The number of patients at risk with regular time intervals and the total number of events (tumor recurrences) were also recorded from the text if available. Survival data for further analysis were secondarily restored employing a unique algorithm proposed in a previous study [16]. Restored KM data of the two groups were combined to calculate secondarily the corresponding study's HR. Both original and secondarily calculated HRs were used for meta-analysis.

Non-mixture cure model for analyzing long-term survivors

Cure models have been used with the basic premise that a certain portion of patients will never face the event of interest such as disease-specific mortality. They might be particularly appealing to oncologists who believe that a substantial fraction of cancer patients will survive without relapse. This concept can be defined as a cure fraction. What should be noted here is that the estimation of cure is performed at a population level. Practically, when the survival time in a cure model tends to be infinite, it is interpreted as a cure, which can be estimated using a statistical software. In this study, we applied a non-mixture cure model to identify the proportion of patients who could be considered as cured. The non-mixture cure model is a parametric cure model that estimates an asymptote for the survival function at the cure proportion. It was chosen due to its applicability in tumor recurrence modeling [15].

Quality assessment and risk of bias

The quality of included studies was assessed using the modified Newcastle-Ottawa Scale (NOS) that included selection, comparability, and outcome.

Statistical analyses

All statistical analyses were performed using R version 3.6.3 (The R Foundation for Statistical Computing, Vienna, Austria) [17]. "Survminer" and "survival" packages in R were applied for survival analysis, HR calculation, and plotting of survival graph. Meta-analyses were conducted employing the "meta" package. Endpoints in this meta-analysis were evaluated with

HRs and 95% CIs using random-effects model. The significance of the combined HR was estimated applying the Z test ($p < 0.05$). Heterogeneity among enrolled studies was explored using I^2 statistics, which was derived from the Q statistic. It was considered significant if the I^2 statistic was greater than 50% and when the Q statistic had $p < 0.05$ [18]. Another package called "flexsurvcure" in R was also used for the non-mixture cure model analysis.

RESULTS

Characteristics and demographics of included studies

Searching results are shown in Supplementary Table 1. A total of 2,542 studies were checked for eligibility and 2,057 irrelevant ones were excluded based on their titles. Abstracts of the remaining 485 studies were reviewed again and 113 studies were selected for full-text review. Of these studies, 18 were qualified for this study [19-36]. Fig. 1 shows a flow diagram summarizing the study selection process. There was no randomized control trial. Selected studies were all retrospective observational studies. Baseline characteristics of patients enrolled in each selected study are summarized in Table 1. Retrospective studies from 2004 to 2018 were included. The 18 studies qualified for the present study included 11 studies from Asian countries, five from European countries, one from Australia, and one from the United States. A total of 5,734 patients were enrolled in data analysis: 3,111 patients in the cirrhosis group and 2,623 patients in the non-cirrhosis group. Most studies had more male patients than female patients. Those 18 studies included for analysis had NOS scores ranging from 4 to 9, indicating a high quality (14 studies with NOS scores of 7–9 and four studies with NOS scores of 4–6) (Table 2).

Recurrence-free survival after partial hepatectomy for hepatocellular carcinoma according to the presence or absence of cirrhosis in each study

Among 18 enrolled studies, the median RFS ranged from 17.8 to 106.8 months for the non-cirrhosis group and 7.1 to 43 months for the cirrhosis group (Table 3). For the non-cirrhosis group, 1-, 3-, and 5-year RFS rates ranged from 70.3% to 93%, 49.3% to 84%, and 20% to 71%, respectively. For the cirrhosis group, 1-, 3-, and 5-year RFS rates ranged from 39% to 85.5%, 36% to 64.5%, and 4% to 50.8%, respectively.

Cumulative hazard ratios for the two groups from a meta-analysis

To estimate the difference of RFS between the non-cirrhosis and cirrhosis groups, HR was used. It was calculated with the fraction of the risk of tumor recurrence in the cirrhosis group compared to that in the non-cirrhosis group. Original HRs of the RFS could be extracted from ten studies [20,21,26,27,29-31,33,35,36]. However, eight studies did not show their own HRs [19,22-25,28,32,34]. The KM curve for each subject of the non-cirrhotic and cirrhotic groups was obtained separately

Table 2. Quality assessment using the Newcastle-Ottawa Scale

Study (year)	Selection				Comparability	Outcome			Quality score
	1	2	3	4	1	1	2	3	
Chang et al. (2004) [19]	★	★	★	★	★	★	★	★	8
Yamashita et al. (2007) [20]	-	★	★	★	★★	★	★	★	8
Chua et al. (2010) [21]	-	★	★	★	★★	★	-	★	7
Gassmann et al. (2010) [22]	★	-	★	★	★	★	-	★	6
Fan et al. (2011) [23]	-	★	★	★	★★	★	★	★	8
Ho et al. (2012) [24]	-	★	★	★	★	★	★	★	7
Mizuguchi et al. (2013) [25]	★	-	★	★	-	★	-	-	4
Yang et al. (2014) [26]	-	★	★	★	★★	★	★	★	8
Yap et al. (2014) [27]	-	★	★	★	★★	★	★	★	8
Chapman et al. (2015) [28]	-	-	★	★	★	★	★	★	6
Kluger et al. (2015) [29]	-	★	★	★	★	★	-	-	5
Huang et al. (2016) [30]	-	★	★	★	★★	★	★	★	8
Lee et al. (2017) [31]	-	★	★	★	★	★	★	★	7
Shehta et al. (2016) [32]	★	★	★	★	★★	★	★	★	9
Lee et al. (2017) [33]	★	★	★	★	★★	★	★	★	9
Cipriani et al. (2018) [34]	-	-	★	★	★★	★	★	★	7
Famularo et al. (2018) [35]	-	★	★	★	★★	★	-	★	7
Golse et al. (2018) [36]	-	★	★	★	★★	★	-	★	7

Articles were assessed for risk of bias using the Newcastle-Ottawa scale for cohort studies.
★, the study has met the criteria for a domain of the Newcastle-Ottawa scale; -, the criteria were not met.

Table 3. Median recurrence-free survival (months) and 1-, 3-, 5-year recurrence-free survival (%)

Study (year)	Median recurrence free survival (mon)	Recurrence free survival (%)		
		1-year	3-year	5-year
Chang et al. (2004) [19]				
Cirrhosis	34.1	-	-	26.9
Non-cirrhosis	38.2	-	-	36.8
Yamashita et al. (2007) [20]				
Cirrhosis	-	-	-	-
Non-cirrhosis	-	-	-	-
Chua et al. (2010) [21]				
Cirrhosis	8	-	-	-
Non-cirrhosis	24	-	-	-
Gassmann et al. (2010) [22]				
Cirrhosis	7.1	39	-	4
Non-cirrhosis	20.7	76	-	20
Fan et al. (2011) [23]				
Cirrhosis	42.8	-	-	-
Non-cirrhosis	106.8	-	-	-
Ho et al. (2012) [24]				
Cirrhosis	-	-	-	35
Non-cirrhosis	-	-	-	51.8
Mizuguchi et al. (2013) [25]				
Cirrhosis	-	-	-	-
Non-cirrhosis	-	-	-	-
Yang et al. (2014) [26]				
Cirrhosis	-	-	-	-
Non-cirrhosis	-	-	-	-
Yap et al. (2014) [27]				
Cirrhosis	-	81	46.7	34.4
Non-cirrhosis	-	83.4	64.6	54.9
Chapman et al. (2015) [28]				
Cirrhosis	-	-	-	18.4
Non-cirrhosis	-	-	-	30.1
Kluger et al. (2015) [29]	-			
Cirrhosis	20.2	-	-	-
Non-cirrhosis	-	-	-	-
Huang et al. (2016) [30]				
Cirrhosis	-	71	36	25
Non-cirrhosis	-	93	84	71
Lee et al. (2017) [31]				
Cirrhosis	-	80.4	55.6	-
Non-cirrhosis	-	85.1	67.3	-
Shehta et al. (2016) [32]				
Cirrhosis	29.3	-	-	-
Non-cirrhosis	29.1	-	-	-
Lee et al. (2017) [33]				
Cirrhosis	-	74.5	56.8	50.8
Non-cirrhosis	-	70.3	49.3	40.6

Table 3. Continued

Study (year)	Median recurrence free survival (mon)	Recurrence free survival (%)		
		1-year	3-year	5-year
Cipriani et al. (2018) [34]				
Cirrhosis	43	85.5	64.5	37.6
Non-cirrhosis	55	81.4	55.1	45.3
Famularo et al. (2018) [35]				
Cirrhosis	-	-	-	-
Non-cirrhosis	-	-	-	-
Golse et al. (2018) [36]				
Cirrhosis	13.7	-	-	-
Non-cirrhosis	17.8	-	-	-

-, no original raw data.

from eight studies to secondarily calculate HR. Following the proposed algorithm [16], KM survival data were secondarily restored and used to reconstruct pseudo-KM curves and calculate the HR (Fig. 2). The cumulative HR of cirrhosis was 1.66 (95% CI, 1.43–1.93; Fig. 2) in the random-effect model. A high level of heterogeneity existed among the 18 studies ($p < 0.01$; I^2 = 61%). This indicated a large degree of difference among effect sizes of these studies. Publication bias analysis was conducted to compare the endpoint (HR) between non-cirrhosis and cirrhosis groups. Visual evaluation of the overall funnel plot (Fig. 3) revealed an asymmetrical phenomenon. However, the Egger's test showed no apparent publication bias ($p = 0.341$).

Cure fractions after partial hepatectomy in each group

Combined patient survival data of 3,512 patients were reconstructed from KM survival curves of 13 studies: 1,596 patients in the non-cirrhosis group and 1,916 patients in the cirrhotic group [19,21-25,27,29-32,34,36]. Analysis of such data using KM methods demonstrated 1-, 3-, 5-, and 10-year survival rates of 83.3%, 62.1%, 52.2%, and 39.6% in the non-cirrhosis group and 78.8%, 51.3%, 39.7%, and 27.3% in the cirrhosis group, respectively (Fig. 4; $p < 0.001$). The probability of patients being cured by PH for HCC in the non-cirrhosis group was 32.5% (95% CI, 28.6%–36.4%). For patients in the cirrhosis group who underwent PH, the probability of being cured was 14.1% (95% CI, 10.6%–18.1%). From non-mixture cure model results, a larger proportion of patients were cured in the non-cirrhosis group than in the cirrhosis group (HR, 1.43; 95% CI, 1.30–1.57; $p < 0.001$).

DISCUSSION

Although PH is commonly used in the treatment of HCC without cirrhosis, its use in the treatment of HCC with cirrhosis remains controversial. This was attributed to the higher
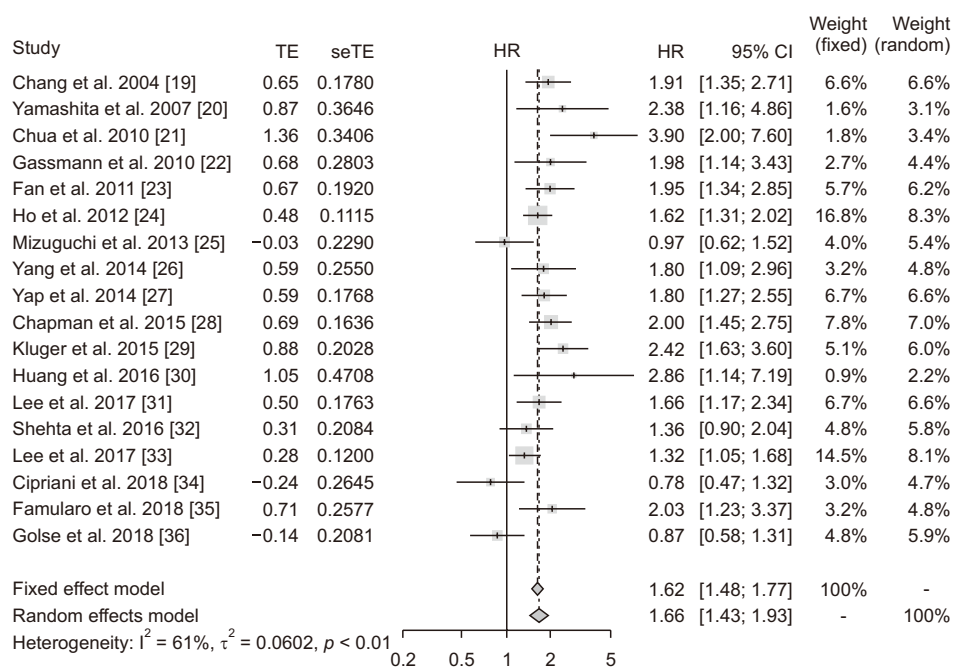
Study	TE	seTE	HR	HR	95% CI	Weight (fixed)	Weight (random)
Chang et al. 2004 [19]	0.65	0.1780		1.91	[1.35; 2.71]	6.6%	6.6%
Yamashita et al. 2007 [20]	0.87	0.3646		2.38	[1.16; 4.86]	1.6%	3.1%
Chua et al. 2010 [21]	1.36	0.3406		3.90	[2.00; 7.60]	1.8%	3.4%
Gassmann et al. 2010 [22]	0.68	0.2803		1.98	[1.14; 3.43]	2.7%	4.4%
Fan et al. 2011 [23]	0.67	0.1920		1.95	[1.34; 2.85]	5.7%	6.2%
Ho et al. 2012 [24]	0.48	0.1115		1.62	[1.31; 2.02]	16.8%	8.3%
Mizuguchi et al. 2013 [25]	−0.03	0.2290		0.97	[0.62; 1.52]	4.0%	5.4%
Yang et al. 2014 [26]	0.59	0.2550		1.80	[1.09; 2.96]	3.2%	4.8%
Yap et al. 2014 [27]	0.59	0.1768		1.80	[1.27; 2.55]	6.7%	6.6%
Chapman et al. 2015 [28]	0.69	0.1636		2.00	[1.45; 2.75]	7.8%	7.0%
Kluger et al. 2015 [29]	0.88	0.2028		2.42	[1.63; 3.60]	5.1%	6.0%
Huang et al. 2016 [30]	1.05	0.4708		2.86	[1.14; 7.19]	0.9%	2.2%
Lee et al. 2017 [31]	0.50	0.1763		1.66	[1.17; 2.34]	6.7%	6.6%
Shehta et al. 2016 [32]	0.31	0.2084		1.36	[0.90; 2.04]	4.8%	5.8%
Lee et al. 2017 [33]	0.28	0.1200		1.32	[1.05; 1.68]	14.5%	8.1%
Cipriani et al. 2018 [34]	−0.24	0.2645		0.78	[0.47; 1.32]	3.0%	4.7%
Famularo et al. 2018 [35]	0.71	0.2577		2.03	[1.23; 3.37]	3.2%	4.8%
Golse et al. 2018 [36]	−0.14	0.2081		0.87	[0.58; 1.31]	4.8%	5.9%
Fixed effect model				1.62	[1.48; 1.77]	100%	-
Random effects model				1.66	[1.43; 1.93]	-	100%

Heterogeneity: $I^2 = 61\%$, $\tau^2 = 0.0602$, $p < 0.01$

0.2 0.5 1 2 5

Fig. 2. Forest plot depicting hazard ratio (HR) of recurrence-free survival after partial hepatectomy in patients with hepatocellular carcinoma (HCC) accompanied by cirrhosis compared to that in patients with HCC without cirrhosis using fixed-effect and random-effect models. TE, estimated treatment effect; seTE, standard error of treatment estimate; CI, confidence interval.

recurrence rate in patients with HCC accompanied by cirrhosis who underwent PH than that in patients who underwent LT [12,37]. In addition, the risk of recurrence after PH was higher in patients with HCC and cirrhosis than in those without cirrhosis [38]. Some reports suggest that PH is a viable option for treating HCC accompanied by cirrhosis by showing acceptable survival rates [38,39]. However, results derived from these studies do not reflect the curability of a certain treatment. The cure model recently discussed and applied in various diseases for its capability to predict the probability of cure is of value. In our study, we used it to examine the probability of PH curing patients with HCC and cirrhosis. We also compared the cure fraction in cirrhotic patients to that in non-cirrhotic patients. In our study, the RFS of patients with HCC accompanied by

cirrhosis after PH was inferior to that of patients with HCC without cirrhosis. Nonetheless, the cure model analysis revealed that patients with HCC accompanied by cirrhosis had a meaningful cure fraction after PH (14.1%; 95% CI, 10.6%–18.1%). To the best of our knowledge, no studies have directly compared cure fractions of patients having HCC with and without cirrhosis after PH.

Recent studies have defined a "cure" as follows: survival curve reaches a plateau at the end, which occurs when the mortality rate of a patient reaches the same level as that in the general population [13,14]. This is generally seen in cancer cases. Currently, the cure model analysis is used in many clinical settings, for instance, to determine the treatment modality and the follow-up term for patients [15]. In the field of oncology, the goal of treatment is to increase a patient's survival time or cure cancer. Application of the cure model in oncology increases with increasing number of long-term survival patients. In our study, the survival curve of patients with HCC after PH showed a plateau at the end. Thus, the cure model was used to analyze data in both patient groups that showed cure fraction. The cure fraction of patients with HCC accompanied by cirrhosis was lower than that of patients with HCC without cirrhosis. However, around 14 percent of patients with HCC accompanied by cirrhosis were cured after PH.

Cirrhosis is a major risk factor of HCC regardless of its etiology [1,40]. Many patients with HCC first suffer from repetitive hepatitis, cirrhosis, and then finally HCC [40]. Chronic liver diseases such as viral hepatitis and alcoholic liver disease can cause damage to hepatocytes, eventually leading to death. In response to liver injury, myofibroblasts are activated, which are derived from hepatic stellate cells or perivascular fibroblasts
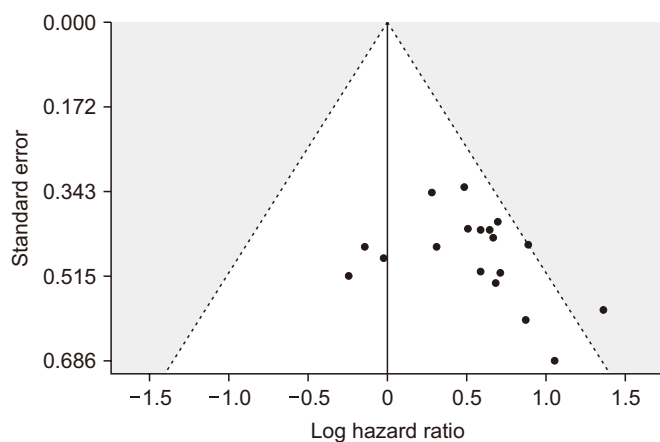
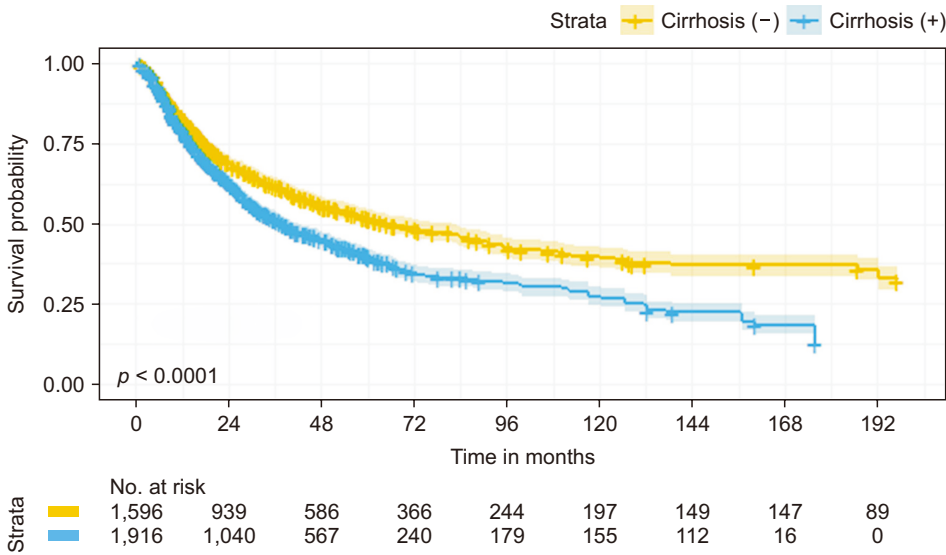**Fig. 3.** Funnel plot of studies included in this meta-analysis.

Fig. 4. Recurrence-free survival based on reconstructed Kaplan–Meier survival data. Survival data of 3,512 patients in both groups were reconstructed from survival curves of original articles and presented.

[41]. Myofibroblasts play an important role in fibrogenesis, which has a protective role in response to liver damage. However, chronic and excessive fibrosis can occur if the underlying disease is not addressed. In addition, the composition of the extracellular matrix (ECM) changes during fibrosis progression. Collagen proteins, predominantly type I collagens, can accumulate in the ECM, causing structural changes and activating growth factors that contribute to malignant changes [40]. A recent study has shown that peritumoral myofibroblasts are associated with a high recurrence rate in patients undergoing PH. These results imply that fibrosis may make the cancer more aggressive [42]. Some reports have demonstrated that the tumor in a cirrhotic liver can progress into a more aggressive form of HCC than a tumor in a non-cirrhotic liver [43,44]. One study has reported the relationship between the expression of geranylgeranyl diphosphate synthase 1 (GGPPS1) and the development of HCC from cirrhosis [43]. The expression of GGPPS1 was higher in tumor tissues than in tumor-free tissues. Moreover, cirrhotic livers showed higher expression levels of GGPPS1 than healthy livers. Interestingly, GGPPS1 also showed a close correlation with prognostic factors such as tumor stage, vessel invasion, and early recurrence [43]. Another study has suggested that 20 hub genes play an important role in HCC progression [44]. These genes were strongly expressed in patients with HCC with cirrhosis. The degree of gene expression was associated with overall survival and disease-free survival in patients with HCC. These studies unanimously demonstrate that a cirrhotic liver could lead to a more aggressive form of HCC, which in turn leads to a poor prognosis.

In patients with HCC accompanied by cirrhosis, LT is considered an ideal treatment option as it can simultaneously treat HCC and the underlying cirrhosis [7]. The overall survival rate and RFS survival rate were higher in patients who underwent LT than in those who underwent PH [11,45]. However, the postoperative mortality at 3 months was higher and hospital stay was longer in patients treated with LT than in those treated with PH [46]. LT has also been criticized for its restrictive selection criteria [8,9]. While efforts have been made to extend selection criteria for LT, only a limited number of patients have received LT. Another problem with LT is the shortage of donor organs. According to one meta-analysis, while waiting for donor organs, some patients underwent loco-regional therapy as a bridging or down-staging therapy. However, these therapeutic approaches did not significantly reduce the risk of waitlist dropout due to HCC progression. Furthermore, there were no differences in post-transplant outcomes between a locoregionally treated group and a group without receiving a loco-regional therapy [47,48]. Therefore, patients with HCC on the waitlist are at risk of disease progression and morbidity or mortality related to cirrhosis. PH can proceed without delay. It can be applied to a wider range of patients with HCC [49]. There are several additional disadvantages related to LT, including the need for immunosuppressants known to have severe side effects such as nephrotoxicity, opportunistic infections, and malignancies [50]. However, the decision on whether to perform PH or LT for HCC accompanied by cirrhosis cannot be made uniformly. It is excessively influenced by tumor characteristics (size, number, and location), presence of portal hypertension, available living donor, and patient's performance status and underlying disease.

Recently, salvage liver transplantation (SLT) has been proposed as an alternative treatment option for HCC recurrence after primary PH. This is being discussed due to donor shortage. According to recent studies, the long-term survival outcome of SLT was comparable to that of primary LT [51,52]. Therefore, PH can be considered as an alternative to primary LT as the primary treatment for patients with HCC accompanied by cirrhosis. Our results corroborated these approaches

because around 14% patients with HCC accompanied by cirrhosis could be cured after PH. Pathological data that affect prognosis such as tumor size, tumor number, and vascular invasion can also be obtained before SLT [53,54]. Consequently, after primary PH, patients who are revealed to be at high risk of recurrence could undergo "prophylactic" liver transplantation for better prognosis [55]. Furthermore, if recurrence occurs, the liver can be transplanted in the future because the majority of recurrences after PH are within the Milan criteria [56]. Thus, if applicable, PH should be initially performed for patients with HCC accompanied by cirrhosis.

The value of the cure model analysis is that the probability of cure can be calculated for patients of interest. In addition, it can provide information that may aid in making decisions in a variety of clinical settings, such as the postoperative surveillance period and decisions on treatment modalities for other combined diseases.

One limitation of this study was that it was a secondary analysis. Factors such as tumor size, alpha-fetoprotein, and vascular invasion affecting HCC recurrence were not fully identified in original articles. In addition, all included studies were retrospective studies, which might have been biased. In this study, we only compared cure fraction according to the presence or absence of cirrhosis. Future studies are needed to conduct additional subgroup cure model analyses for HCC. The impact of the extent of surgery on the prognosis of patients with HCC accompanied by cirrhosis is a matter of debate and another important research topic to be considered. Therefore, further studies about this issue are warranted.

In conclusion, according to results of our study, PH might be able to cure HCC even in patients with cirrhosis. We propose that PH is a reasonable treatment approach for patients with HCC accompanied by cirrhosis in that it could offer a chance for cure.

SUPPLEMENTARY DATA

Supplementary data related to this article can be found at https://doi.org/10.14701/ahbps.21-080.

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No potential conflict of interest relevant to this article was reported.

ORCID

Byungje Bae, https://orcid.org/0000-0001-8192-1693
Keera Kang, https://orcid.org/0000-0002-7276-5980
Sung Kyu Song, https://orcid.org/0000-0003-0170-0802
Chul-Woon Chung, https://orcid.org/0000-0003-0873-567X
Yongkeun Park, https://orcid.org/0000-0001-9481-6542

AUTHOR CONTRIBUTIONS

Conceptualization: All authors. Data curation: BB, KK, YP. Methodology: BB, KK, YP. Visualization: YP. Writing - original draft: BB, SKS, CWC, YP. Writing - review & editing: All authors.

REFERENCES

1. Lafaro KJ, Demirjian AN, Pawlik TM. Epidemiology of hepatocellular carcinoma. Surg Oncol Clin N Am 2015;24:1-17.
2. Fujiwara N, Friedman SL, Goossens N, Hoshida Y. Risk factors and prevention of hepatocellular carcinoma in the era of precision medicine. J Hepatol 2018;68:526-549.
3. Petrick JL, Kelly SP, Altekruse SF, McGlynn KA, Rosenberg PS. Future of hepatocellular carcinoma incidence in the United States forecast through 2030. J Clin Oncol 2016;34:1787-1794.
4. McGlynn KA, Petrick JL, London WT. Global epidemiology of hepatocellular carcinoma: an emphasis on demographic and regional variability. Clin Liver Dis 2015;19:223-238.
5. El-Serag HB, Siegel AB, Davila JA, Shaib YH, Cayton-Woody M, McBride R, et al. Treatment and outcomes of treating of hepatocellular carcinoma among Medicare recipients in the United States: a population-based study. J Hepatol 2006;44:158-166.
6. op den Winkel M, Nagel D, Sappl J, op den Winkel P, Lamerz R, Zech CJ, et al. Prognosis of patients with hepatocellular carcinoma. Validation and ranking of established staging-systems in a large western HCC-cohort. PLoS One 2012;7:e45066.
7. Byam J, Renz J, Millis JM. Liver transplantation for hepatocellular carcinoma. Hepatobiliary Surg Nutr 2013;2:22-30.
8. Halazun KJ, Najjar M, Abdelmessih RM, Samstein B, Griesemer AD, Guarrera JV, et al. Recurrence after liver transplantation for hepatocellular carcinoma: a new MORAL to the story. Ann Surg 2017;265:557-564.
9. Yao FY, Ferrell L, Bass NM, Watson JJ, Bacchetti P, Venook A, et al. Liver transplantation for hepatocellular carcinoma: expansion of the tumor size limits does not adversely impact survival. Hepatology 2001;33:1394-1403.
10. Krenzien F, Schmelzle M, Struecker B, Raschzok N, Benzing C, Jara M, et al. Liver transplantation and liver resection for cirrhotic patients with hepatocellular carcinoma: comparison of long-term survivals. J Gastrointest Surg 2018;22:840-848.
11. Zheng Z, Liang W, Milgrom DP, Zheng Z, Schroder PM, Kong NS, et al. Liver transplantation versus liver resection in the treatment of hepatocellular carcinoma: a meta-analysis of observational studies. Transplantation 2014;97:227-234.
12. Pinna AD, Yang T, Mazzaferro V, De Carlis L, Zhou J, Roayaie S, et al. Liver transplantation and hepatic resection can achieve cure for hepatocellular carcinoma. Ann Surg 2018;268:868-875.

13. Tsilimigras DI, Bagante F, Moris D, Merath K, Paredes AZ, Sahara K, et al. Defining the chance of cure after resection for hepatocellular carcinoma within and beyond the Barcelona Clinic Liver Cancer guidelines: a multi-institutional analysis of 1,010 patients. Surgery 2019;166:967-974.

14. Lambert PC, Thompson JR, Weston CL, Dickman PW. Estimating and modeling the cure fraction in population-based cancer survival analysis. Biostatistics 2007;8:576-594.

15. Othus M, Barlogie B, Leblanc ML, Crowley JJ. Cure models as a useful statistical tool for analyzing survival. Clin Cancer Res 2012;18:3731-3736.

16. Guyot P, Ades AE, Ouwens MJ, Welton NJ. Enhanced secondary analysis of survival data: reconstructing the data from published Kaplan-Meier survival curves. BMC Med Res Methodol 2012;12:9.

17. R Development Core Team. R: a language and environment for statistical computing [Internet]. Vienna: R Foundation for Statistical Computing 2017 [cited 2020 Dec 1]. Available from: https://www.R-project.org/.

18. Higgins JP, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. BMJ 2003;327:557-560.

19. Chang CH, Chau GY, Lui WY, Tsay SH, King KL, Wu CW. Long-term results of hepatic resection for hepatocellular carcinoma originating from the noncirrhotic liver. Arch Surg 2004;139:320-325.

20. Yamashita Y, Taketomi A, Itoh S, Kitagawa D, Kayashima H, Harimoto N, et al. Longterm favorable results of limited hepatic resections for patients with hepatocellular carcinoma: 20 years of experience. J Am Coll Surg 2007;205:19-26.

21. Chua TC, Saxena A, Chu F, Liauw W, Zhao J, Morris DL. Clinicopathological determinants of survival after hepatic resection of hepatocellular carcinoma in 97 patients--experience from an Australian hepatobiliary unit. J Gastrointest Surg 2010;14:1370-1380.

22. Gassmann P, Spieker T, Haier J, Schmidt F, Mardin WA, Senninger N. Prognostic impact of underlying liver fibrosis and cirrhosis after curative resection of hepatocellular carcinoma. World J Surg 2010;34:2442-2451.

23. Fan ST, Poon RT, Yeung C, Lam CM, Lo CM, Yuen WK, et al. Outcome after partial hepatectomy for hepatocellular cancer within the Milan criteria. Br J Surg 2011;98:1292-1300.

24. Ho CM, Lee PH, Chen CL, Ho MC, Wu YM, Hu RH. Long-term outcomes after resection versus transplantation for hepatocellular carcinoma within UCSF criteria. Ann Surg Oncol 2012;19:826-833.

25. Mizuguchi T, Kawamoto M, Meguro M, Nakamura Y, Ota S, Hui TT, et al. Prognosis and predictors of surgical complications in hepatocellular carcinoma patients with or without cirrhosis after hepatectomy. World J Surg 2013;37:1379-1387.

26. Yang LY, Chang RM, Lau WY, Ou DP, Wu W, Zeng ZJ. Mesohepatectomy for centrally located large hepatocellular carcinoma: indications, techniques, and outcomes. Surgery 2014;156:1177-1187.

27. Yap AQ, Millan CA, Wang JH, Wang CC, Lu SN, Wang SH, et al. How to improve the outcome in patients with AJCC stage I hepatocellular carcinoma. Anticancer Res 2014;34:3093-3103.

28. Chapman WC, Klintmalm G, Hemming A, Vachharajani N, Majella Doyle MB, DeMatteo R, et al. Surgical treatment of hepatocellular carcinoma in North America: can hepatic resection still be justified? J Am Coll Surg 2015;220:628-637.

29. Kluger MD, Salceda JA, Laurent A, Tayar C, Duvoux C, Decaens T, et al. Liver resection for hepatocellular carcinoma in 313 Western patients: tumor biology and underlying liver rather than tumor size drive prognosis. J Hepatol 2015;62:1131-1140.

30. Huang ZY, Liang BY, Xiong M, Dong KS, Zhang ZY, Zhang EL, et al. Severity of cirrhosis should determine the operative modality for patients with early hepatocellular carcinoma and compensated liver function. Surgery 2016;159:621-631.

31. Lee HW, Choi GH, Kim DY, Park YN, Kim KS, Choi JS, et al. Less fibrotic burden differently affects the long-term outcomes of hepatocellular carcinoma after curative resection. Oncology 2017;93:224-232.

32. Shehta A, Han HS, Yoon YS, Cho JY, Choi Y. Laparoscopic liver resection for hepatocellular carcinoma in cirrhotic patients: 10-year single-center experience. Surg Endosc 2016;30:638-648.

33. Lee EC, Kim SH, Park H, Lee SD, Lee SA, Park SJ. Survival analysis after liver resection for hepatocellular carcinoma: a consecutive cohort of 1002 patients. J Gastroenterol Hepatol 2017;32:1055-1063.

34. Cipriani F, Fantini C, Ratti F, Lauro R, Tranchart H, Halls M, et al. Laparoscopic liver resections for hepatocellular carcinoma. Can we extend the surgical indication in cirrhotic patients? Surg Endosc 2018;32:617-626.

35. Famularo S, Di Sandro S, Giani A, Lauterio A, Sandini M, De Carlis R, et al. Long-term oncologic results of anatomic vs. parenchyma-sparing resection for hepatocellular carcinoma. A propensity score-matching analysis. Eur J Surg Oncol 2018;44:1580-1587.

36. Golse N, El Bouyousfi A, Marques F, Bancel B, Mohkam K, Ducerf C, et al. Large hepatocellular carcinoma: does fibrosis really impact prognosis after resection? J Visc Surg 2018;155:265-273.

37. Akcam AT, Saritas AG, Ulku A, Rencuzogullari A. Oncological outcomes of hepatic resection vs transplantation for localized hepatocellular carcinoma. Transplant Proc 2019;51:1147-1152.

38. Xu XF, Xing H, Han J, Li ZL, Lau WY, Zhou YH, et al. Risk factors, patterns, and outcomes of late recurrence after liver resection for hepatocellular carcinoma: a multicenter study from China. JAMA Surg 2019;154:209-217.

39. Li ZL, Yu JJ, Guo JW, Sui CJ, Dai BH, Zhang WG, et al. Liver resection is justified for multinodular hepatocellular carcinoma in selected patients with cirrhosis: a multicenter analysis of 1,066 patients. Eur J Surg Oncol 2019;45:800-807.

40. Affo S, Yu LX, Schwabe RF. The role of cancer-associated fibroblasts and fibrosis in liver cancer. Annu Rev Pathol 2017;12:153-186.

41. Fattovich G, Stroffolini T, Zagni I, Donato F. Hepatocellular carcinoma in cirrhosis: incidence and risk factors. Gastroenterology 2004;127(5 Suppl 1):S35-S50.

42. Ju MJ, Qiu SJ, Fan J, Xiao YS, Gao Q, Zhou J, et al. Peritumoral activated hepatic stellate cells predict poor clinical outcome in hepatocellular carcinoma after curative resection. Am J Clin Pathol 2009;131:498-510.

43. Yu DC, Liu J, Chen J, Shao JJ, Shen X, Xia HG, et al. GGPPS1 predicts the biological character of hepatocellular carcinoma in patients with

cirrhosis. BMC Cancer 2014;14:248.

44. Lin Y, Liang R, Ye J, Li Q, Liu Z, Gao X, et al. A twenty gene-based gene set variation score reflects the pathological progression from cirrhosis to hepatocellular carcinoma. Aging (Albany NY) 2019;11:11157-11169.

45. Harimoto N, Yoshizumi T, Fujimoto Y, Motomura T, Mano Y, Toshima T, et al. Surgery for hepatocellular carcinoma in patients with Child-Pugh B cirrhosis: hepatic resection versus living donor liver transplantation. World J Surg 2018;42:2606-2616.

46. Margarit C, Escartín A, Castells L, Vargas V, Allende E, Bilbao I. Resection for hepatocellular carcinoma is a good option in Child-Turcotte-Pugh class A patients with cirrhosis who are eligible for liver transplantation. Liver Transpl 2005;11:1242-1251.

47. Madkhali AA, Fadel ZT, Aljiffry MM, Hassanain MM. Surgical treatment for hepatocellular carcinoma. Saudi J Gastroenterol 2015;21:11-17.

48. Kulik L, Heimbach JK, Zaiem F, Almasri J, Prokop LJ, Wang Z, et al. Therapies for patients with hepatocellular carcinoma awaiting liver transplantation: a systematic review and meta-analysis. Hepatology 2018;67:381-400.

49. Chedid MF, Kruel CRP, Pinto MA, Grezzana-Filho TJM, Leipnitz I, Kruel CDP, et al. Hepatocellular carcinoma: diagnosis and operative management. Arq Bras Cir Dig 2017;30:272-278.

50. Jadlowiec CC, Taner T. Liver transplantation: current status and challenges. World J Gastroenterol 2016;22:4438-4445.

51. Chan DL, Alzahrani NA, Morris DL, Chua TC. Systematic review of efficacy and outcomes of salvage liver transplantation after primary hepatic resection for hepatocellular carcinoma. J Gastroenterol Hepatol 2014;29:31-41.

52. Muaddi H, Al-Adra DP, Beecroft R, Ghanekar A, Moulton CA, Doyle A, et al. Liver transplantation is equally effective as a salvage therapy for patients with hepatocellular carcinoma recurrence following radiofrequency ablation or liver resection with curative intent. Ann Surg Oncol 2018;25:991-999.

53. Qu W, Zhu ZJ, Sun LY, Wei L, Liu Y, Zeng ZG. Salvage liver transplantation for hepatocellular carcinoma recurrence after primary liver resection. Clin Res Hepatol Gastroenterol 2015;39:93-97.

54. Zheng S, Xie Q, Cheng J. Salvage liver transplant for hepatocellular carcinoma: rescues and benefits. Transl Gastroenterol Hepatol 2018;3:65.

55. Lacaze L, Scotté M. Surgical treatment of intra hepatic recurrence of hepatocellular carcinoma. World J Hepatol 2015;7:1755-1760.

56. Chan AC, Chan SC, Chok KS, Cheung TT, Chiu DW, Poon RT, et al. Treatment strategy for recurrent hepatocellular carcinoma: salvage transplantation, repeated resection, or radiofrequency ablation? Liver Transpl 2013;19:411-419.