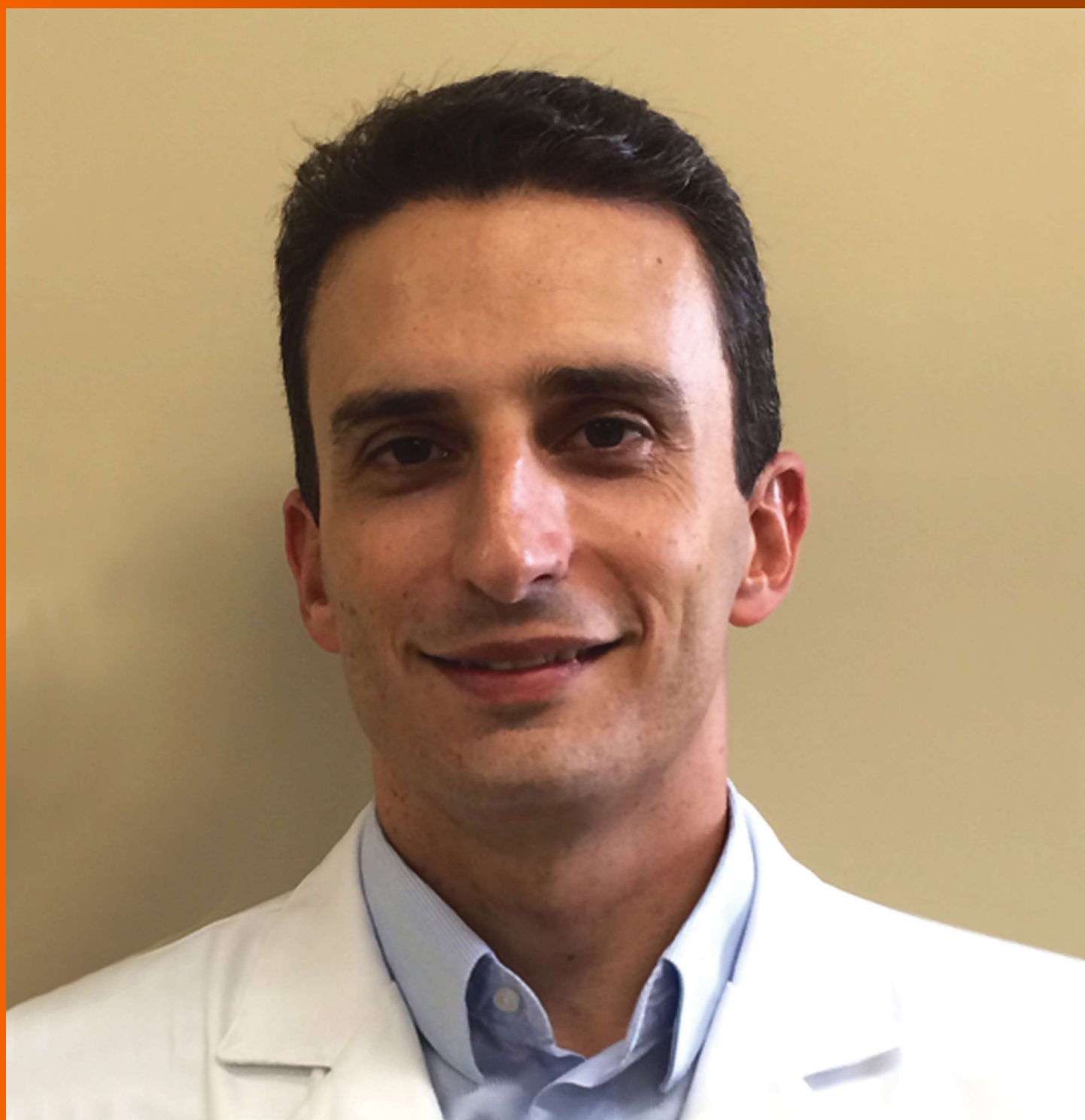


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WJH covers topics concerning liver biology/pathology, cirrhosis and its complications, liver fibrosis, liver failure, portal hypertension, hepatitis B and C and inflammatory disorders, steatohepatitis and metabolic liver disease, hepatocellular carcinoma, biliary tract disease, autoimmune disease, cholestatic and biliary disease, transplantation, genetics, epidemiology, microbiology, molecular and cell biology, nutrition, geriatric and pediatric hepatology, diagnosis and screening, endoscopy, imaging, and advanced technology. Priority publication will be given to articles concerning diagnosis and treatment of hepatology diseases. The following aspects are covered: Clinical diagnosis, laboratory diagnosis, differential diagnosis, imaging tests, pathological diagnosis, molecular biological diagnosis, immunological diagnosis, genetic diagnosis, functional diagnostics, and physical diagnosis; and comprehensive therapy, drug therapy, surgical therapy, interventional treatment, minimally invasive therapy, and robot-assisted therapy.

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Systematic review of the outcomes of surgical resection for intermediate and advanced Barcelona Clinic Liver Cancer stage hepatocellular carcinoma: A critical appraisal of the evidence

Ye Xin Koh, Hwee Leong Tan, Weng Kit Lye, Juinn Huar Kam, Adrian Kah Heng Chiow, Siong San Tan, Su Pin Choo, Alexander Yaw Fui Chung, Brian Kim Poh Goh

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Abstract

AIM

To perform a systematic review to determine the survival outcomes after curative resection of intermediate and advanced hepatocellular carcinomas (HCC).

METHODS

A systematic review of the published literature was performed using the PubMed database from 1st January 1999 to 31st Dec 2014 to identify studies that reported outcomes of liver resection as the primary curative treatment for Barcelona Clinic Liver Cancer (BCLC) stage B or C HCC. The primary end point was to determine the overall survival (OS) and disease free survival (DFS) of liver resection of HCC in BCLC stage B or C in patients with adequate liver reserve (*i.e.*, Child's A or B status). The secondary end points were to assess the morbidity and mortality of liver resection in large HCC (defined as lesions larger than 10 cm in diameter) and to compare the OS and DFS after surgical resection of solitary *vs* multifocal HCC.

RESULTS

We identified 74 articles which met the inclusion criteria and were analyzed in this systematic review. Analysis of the resection outcomes of the included studies were grouped according to (1) BCLC stage B or C HCC, (2) Size of HCC and (3) multifocal tumors. The median 5-year OS of BCLC stage B was 38.7% (range 10.0-57.0); while the median 5-year OS of BCLC stage C was 20.0% (range 0.0-42.0). The collective median 5-year OS of both stages was 27.9% (0.0-57.0). In examining the morbidity and mortality following liver resection in large HCC, the pooled RR for morbidity [RR (95%CI) = 1.00 (0.76-1.31)] and mortality [RR (95%CI) = 1.15 (0.73-1.80)] were not significant. Within the spectrum of BCLC B and C lesions, tumors greater than 10 cm were reported to have median 5-year OS of 33.0% and multifocal lesions 54.0%.

CONCLUSION

Indication for surgical resection should be extended to BCLC stage B lesions in selected patients. Further studies are needed to stratify stage C lesions for resection.

Key words: Barcelona Clinic Liver Cancer; Hepatocellular carcinoma; Hepatectomy; Milan criteria

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Core tip: This is a systematic review of the current literature reporting the surgical outcomes of liver resection for Barcelona Clinic Liver Cancer (BCLC) Stage B and C hepatocellular carcinomas (HCC). Based on this review, there is robust evidence that indications for primary surgical resection of HCC should be extended to include BCLC stage B lesions in selected patients. There is a need for further studies that stratify BCLC stage C lesions and potentially extend surgical indications for resectable lesions.

Koh YX, Tan HL, Lye WK, Kam JH, Chiow AKH, Tan SS, Choo SP, Chung AYE, Goh BKP. Systematic review of the outcomes of surgical resection for intermediate and advanced Barcelona Clinic

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INTRODUCTION

Hepatocellular carcinoma (HCC) remains a significant disease burden worldwide today^[1]. Appropriate treatment for HCC is complex because radical oncological clearance and preservation of adequate liver function need to be carefully balanced. Several staging systems have been developed to guide management of HCC^[2-7].

Surgical resection for HCC within the "Milan Criteria" or Barcelona Clinic Liver Cancer (BCLC) stage A is the widely accepted standard of care^[8]. However, surgical treatment for BCLC stage B (intermediate) or C (advanced) lesions remains controversial^[4-7]. Presently, the European Association for the Study of Liver Disease (EASL) and the American Association for the Study of Liver Disease (AASLD) guidelines do not recommend surgical resection for these patients^[4,7,9].

However, despite the recommendations from these two large reputable organizations, many international high-volume tertiary centers, especially centers in Asia, still routinely perform surgical resection for large solitary lesions, multifocal lesions and lesions with macrovascular invasion^[10-16]. Critical appraisal of both Western and Asian literature is needed to resolve the controversies.

The aim of this study was to perform a systematic review and summarize the current literature to determine the long-term survival outcomes after curative resection of intermediate and advanced HCCs.

MATERIALS AND METHODS

A systematic review of the published literature was performed using the PubMed database from 1st January 1999 to 31st Dec 2014 to identify studies that reported outcomes of liver resection as the primary curative treatment for BCLC stage B or C HCC.

The primary end point was to determine the overall survival (OS) and disease free survival (DFS) of liver resection of HCC in BCLC stage B or C in patients with adequate liver reserve (*i.e.*, Child's A or B status) and in good general status (PS 0-2). The secondary end points were to assess the morbidity and mortality of liver resection in large HCC (defined as lesions larger than 10 cm in diameter) and to compare the OS and DFS after surgical resection of solitary *vs* multifocal HCC.

The Medical Subject Heading (MeSH) major topic was "hepatocellular carcinoma". The keywords used were "liver tumor", "hepatoma", "liver neoplasm", "liver cancer", "Barcelona Clinic Liver Cancer", "multifocal" and "vascular invasion". The keywords used for surgical resection were "hepatectomy", "liver resection", "liver

surgery", "partial hepatectomy", "hemi-hepatectomy", "sectionectomy", "segmentectomy", "non-anatomical resection", "anatomical resection", "curative surgery" and "surgical procedures". The keywords used for liver reserve were "Child A/B", "Child Pugh A/B", "early liver disease" and "early liver cirrhosis". Key references of the short-listed studies were also searched manually.

Two authors conducted the search independently, with the search results obtained by both authors discussed with the senior author Goh BK. The final list of studies to be short-listed was decided by consensus between all three authors. This study was conducted in accordance to the PRISMA guidelines^[17].

Data extraction

All short-listed studies were assessed independently according to a modified Newcastle-Ottawa scale. The three main factors assessed were: (1) selection of the patients; (2) comparability of the study groups; and (3) outcome assessment. The scoring scale ranged from 0-9 and studies of score 6 or greater were considered high quality and included in this study. The following data was extracted from the included studies: first author, year of data collection, year of publication, country of origin, characteristics of study population, number of patients, clinico-pathological characteristics, OS and DFS.

Inclusion criteria

The inclusion criteria were: (1) studies reporting surgical resection of lesions fulfilling the criteria of BCLC stage B (intermediate) or BCLC stage C (advanced) HCC, studies reporting surgical resection for large HCC, multifocal HCC and HCC with vascular invasion; (2) evaluation of at least one of the clinico-pathological or survival characteristics mentioned in the "parameters and outcomes of interest" section below; and (3) for studies reported by the same institution (and/or) authors with overlapping cohorts, only the study with the larger sample size or the one with higher quality was included. Major resection was defined as resection of 3 segments or more whereas minor resection involved 2 segments or less^[18].

Studies which described adjunctive treatments such as radiofrequency ablation (RFA), selective internal radiation therapy (SIRT), trans-arterial chemoembolization (TACE) and infusional chemotherapy were also included.

Exclusion criteria

All studies that did not meet the inclusion criteria were excluded. In addition, the following exclusion criteria were used: (1) studies that did not report the survival outcomes of surgically resected HCC; (2) studies that focused on transplant, RFA, TACE and SIRT; (3) studies that focused on DNA, biochemical and proteomic analysis of HCC; (4) studies that focused on radiological imaging techniques; (5) studies reporting patients with Child-Pugh grade C or unknown status; (6) studies reporting tumor rupture, extra-hepatic metastases and/or lymph node metastases; (7) studies which included palliative

(R2) resections; and (8) studies written in languages other than English.

Definitions, parameters and outcomes of interest

The most updated BCLC staging criteria was used as the reference staging system^[4,7,9]. Adequate liver function was defined as Child-Pugh grade A or B. The main outcomes of interest were the OS and DFS. Clinico-pathological characteristics including age, gender, Child-Pugh status, hepatitis status, tumor size, number of nodules, extent of macrovascular invasion, extent of liver resection, post-operative morbidity, mortality and recurrent disease were recorded.

Statistical methods

If the data on the OS or DFS was not provided explicitly in a study, the information was derived from the survival graphs if present, or calculated from the primary data using a measurement method as described by Lim *et al.*^[8]. The 1, 3 and 5 year OS and DFS were summarized graphically using bubble plots, with the sample size of each cohort relative to the size of the bubble.

The inverse variance (IV) method was used to pool the RR across studies. A fixed 0.5 zero-cell correction was used when the number of events for one of the groups was zero. Pairwise comparisons of subtypes were done. If there were no events in an outcome of interest for both groups that were compared, the study was excluded from the meta-analysis for the specific outcome.

Heterogeneity between the studies was evaluated using the chi-squared test of heterogeneity. A random effects model was used. Sensitivity analyses were performed by excluding each study individually from the pool of studies combined for each outcome. Pooled results from these subgroups were computed and compared with the pooled results from the set of studies without these exclusion criteria. All statistical analyses were conducted using SAS 9.3 (SAS Institute, Cary, NC, United States) and Review Manager 5 (Nordic Cochrane, Copenhagen, Denmark).

RESULTS

The systematic review identified 1908 articles, from which 130 articles were selected for full text review. Seventy-four articles met the inclusion criteria and were analyzed in this systematic review^[10-14,19-87]. Fifty-six articles were excluded for the following reasons^[88-143]: Three because they were not published in the English language^[88-90], 11 because other treatment modalities were used as primary treatment^[91-101], 19 because of overlapping cohorts^[102-120], nine due to incomplete data^[121-129], two due to inclusion of palliative liver resection^[130-131], and 12 because the study populations included patients with other types of hepatic malignancies^[132-143] (Supplementary Figure 1). Analysis of the resection outcomes of the included studies were

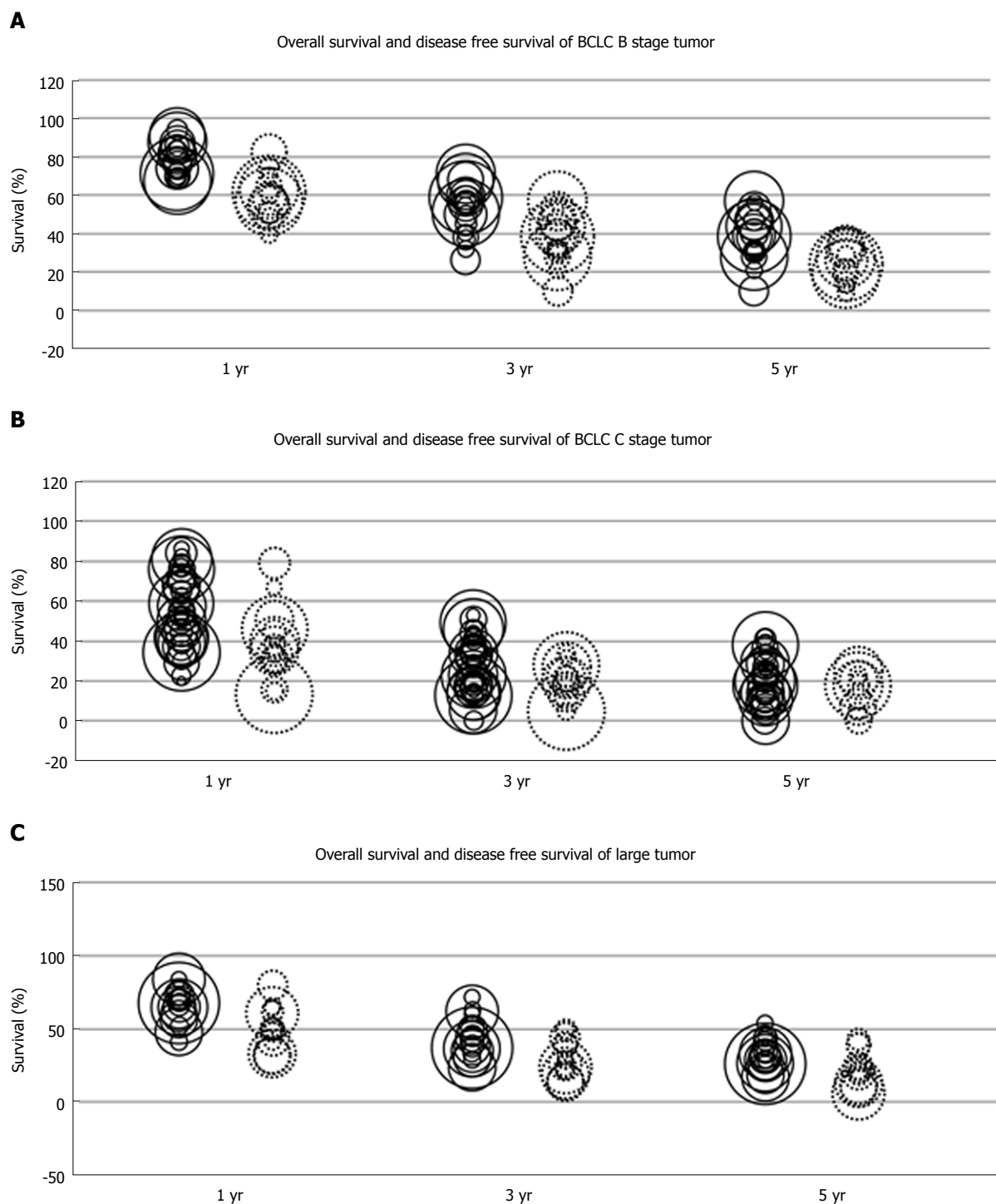


Figure 1 Bubble plot of overall survival and disease-free survival of BCLC B, C and large tumors.

grouped according to (1) BCLC stage B or C HCC; (2) Size of HCC; and (3) multifocal tumors.

BCLC Stage B or C HCC

Studies which classified HCC according to BCLC Staging System^[4-7] utilized the following common definitions: Stage B - single tumor more than 5 cm in diameter; 2 to 3 tumors of which at least one is more than 3 cm in diameter; or more than 3 tumors of any diameter; Stage C - any tumor with radiologically evident and

histologically proven macrovascular invasion, N1 disease or M1 disease.

The baseline characteristics of the patients are presented in Table 1. There are 6103 BCLC stage B cases in 19 studies and 3449 BCLC stage C cases in 32 studies. The clinical outcomes are summarized in Table 2. The study recruitment periods extended from 1982 to 2011. Figure 1 are bubble plots showing OS and DFS, with bubble size indicating relative sample size. The median 5-year OS of BCLC stage B was

38.7% (range 10.0-57.0); while the median 5-year OS of BCLC stage C was 20.0% (range 0.0-42.0). The collective median 5-year OS of both stages was 27.9% (0.0-57.0).

Size of HCC

HCC analyzed according to size criterion were categorized as: Large HCC - greater than or equal to 10 cm in diameter; and Small HCC - less than 10 cm in diameter.

The baseline characteristics are presented in Table 3. There are 2437 cases of large HCC in 21 studies and 5436 cases of small HCC in 14 studies. The clinical outcomes are summarized in Table 4. The study recruitment periods extended from 1964 to 2011. Supplementary Figure 2A and B are forest plots showing the morbidity and mortality respectively of the included studies. The pooled RR for morbidity [RR (95%CI): 1.00 (0.76-1.31)] and mortality [RR (95%CI): 1.15 (0.73-1.80)] were not significant. The median 5-year OS of large HCC was 33.0 % (range: 16.7-79.0) and the median 5-year OS of small HCC was 52.3% (range 21.0-89.2).

Multifocal HCC

The baseline characteristics are presented in Supplementary Table 1. There are 1095 cases in 9 studies. The clinical outcomes are summarized in Supplementary Table 2. The study recruitment periods extended from 1992 to 2011. Supplementary Figure 3 displays the bubble plot showing overall and disease free survival rate of the included studies, with bubble size indicating relative sample size. The median 5-year OS was 54.0% (29.9-75.5). Supplementary Figure 4 was plotted to show 5 year OS for those studies with sample size greater or equal to 100 against the midpoint of recruitment period. The trend line was fitted using weighted least squares regression with sample size as weight. An uptrend with weighted slope 0.38 was seen in the plot.

DISCUSSION

BCLC stage B or C HCC

Presently, a major controversy in the management of HCC is the role of surgical resection for intermediate (BCLC stage B) and advanced (BCLC stage C) stage HCC. According to EASL and the AASLD guidelines, surgical resection is not offered for BCLC stages B and C HCC because of the poor 5-year overall survival rates^[7,9].

However, the results of this systematic review demonstrate that the median 5 year OS after surgical resection for BCLC B is 38.9% (range: 10.0%-57.0%). These outcomes are clearly not attainable by other modalities such as TACE which only confers a 40% two year survival and median survival of 20 mo for similar lesions^[144].

This systematic review demonstrates that for BCLC C lesions, surgical resection results in uniformly poor results with a median 5-year OS of 20% (range:

0%-42.0%). However, proponents of resection argue that the tumor thrombus has the potential to cause portal vein obstruction, intractable ascites, esophageal variceal bleeding and liver failure^[66-68]. This frequently leads to an even more rapid demise of these patients.

In general, the prognosis for tumor thrombus located within the main trunk has been reported to be poorer as compared to more distal lesions^[58,62,68]. Some authors have advocated for portal vein resection for 1st order portal vein tumor thrombus with minimal bifurcation involvement, citing results of 5-year OS over 20% which was superior to thrombectomy alone^[53,75]. However, statistical analysis could not be performed due lack of stratification based on the extent of PV invasion, heterogeneous surgical procedures and different extents of hepatic vein and inferior vena cava involvement.

Size of HCC

The median 5 year OS in these large lesions was 33% (range: 16.7%-79.0%). The 10 cm arbitrary cut-off used by many studies represents the more advanced cases in the spectrum of BCLC B HCC^[32-43]. In addition, BCLC C lesions that were > 10 cm, usually with worse prognosis, were not excluded from the analysis in these studies, confounding the results. Despite this, the relatively favorable survival still indicates that surgical resection is beneficial for selected lesions within the combined spectrum of large HCCs^[32-43].

Multifocal HCC

The EASL guidelines do not recommend surgical resection as first line therapy for all multifocal lesions^[4,7,9]. On the other end of the spectrum, the APASL guidelines support resection of all lesions regardless of multifocality^[2]. The APASL guidelines are supported by the fact that that over 65% OS has been reported after surgical resection for multifocal HCC within the "Milan criteria"^[8]. In addition, studies from large specialized liver centers have showed favorable 5-year OS of over 50% after surgical resection for multifocal HCC^[13,77,82]. This was further improved to between 55%-75% 5-year OS when performed in combination with RFA for bilobar lesions^[76,78,80]. In this review, the median 5-year OS for all surgically resected multifocal HCC analyzed in this systematic review is 54.0% (range: 29.9%-75.5%), supporting surgical resection as the primary management of multifocal HCC.

It is important to highlight that surgical series of the aforementioned groups represent the entire spectrum of tumors beyond the "Milan criteria", and the wide range of survival reported for these lesions can be attributed to the heterogeneity of tumors encompassing large solitary and multifocal lesions of various sizes. Differentiation of the outcomes of purely single or multifocal HCC within this heterogeneous selection and is often not pursued in many studies and making interpretation of the data difficult.

Based on this review, it is evident that arbitrary classifications by the current guidelines do not adequately

Table 1 Characteristics of patients classified as BCLC stage B or C hepatocellular carcinoma

Ref.	Year	n	Male (%)	Cirrhosis (%)	HBV (%)	HCV (%)	Median tumor diameter (cm)
BCLC stage B							
Régimbeau <i>et al</i> ^[25]	1999	94	75 (79.8)	37 (39.4)	35 (37.2)	10 (10.6)	12.0
Hanazaki <i>et al</i> ^[19]	2001	133	105 (78.9)	NS	NS	NS	8.6
Ng <i>et al</i> ^[10]	2005	380	278 (73.2)	380 (100.0)	281 (73.9)	20 (5.3)	NS
Chen <i>et al</i> ^[26] (TP1)	2006	959	816 (85.1)	717 (74.8)	776 (80.9)	NS	14.9
Chen <i>et al</i> ^[26] (TP2)	2006	1143	968 (84.7)	897 (78.5)	940 (82.2)	NS	11.1
Cho <i>et al</i> ^[26]	2007	230	46 (20.0)	35 (15.2)	40 (17.4)	5 (2.2)	7.1
Vitale <i>et al</i> ^[31]	2009	124	NS	NS	NS	NS	NS
Yang <i>et al</i> ^[11]	2009	260	228 (87.7)	198 (76.2)	239 (91.9)	NS	9.6
Zhou <i>et al</i> ^[29] (SX)	2009	56	49 (87.5)	50 (89.3)	55 (98.2)	0 (0.0)	9.5
Zhou <i>et al</i> ^[29] (TCSX)	2009	52	48 (92.3)	49 (94.2)	51 (98.1)	0 (0.0)	9.0
Delis <i>et al</i> ^[27]	2010	66	45 (68.2)	NS	36 (54.5)	15 (22.7)	8.4
Lin <i>et al</i> ^[30]	2010	93	75 (80.6)	NS	60 (64.5)	22 (23.7)	8.0
Ramacciato <i>et al</i> ^[28]	2010	51	37 (72.5)	44 (86.3)	NS	NS	8.2
Xu <i>et al</i> ^[21]	2010	165	NS	NS	NS	NS	NS
Wei <i>et al</i> ^[22]	2011	51	NS	NS	NS	NS	NS
Zhou <i>et al</i> ^[20]	2011	85	74 (87.1)	65 (76.5)	68 (80.0)	6 (7.1)	NS
Chang <i>et al</i> ^[32]	2012	318	263 (82.7)	97 (30.5)	201 (63.2)	57 (17.9)	7.4
Hsu <i>et al</i> ^[34]	2012	268	213 (79.5)	NS	176 (65.7)	48 (17.9)	NS
Ma <i>et al</i> ^[23]	2012	178	158 (88.8)	79 (44.4)	140 (78.7)	41 (23.0)	NS
Torzilli <i>et al</i> ^[12]	2013	737	586 (79.5)	360 (48.8)	158 (21.4)	208 (28.2)	6.0
Zhong <i>et al</i> ^[120]	2013	660	NS	NS	NS	NS	NS
BCLC Stage C							
Ohkubo <i>et al</i> ^[79]	2000	47	41 (87.2)	NS	20 (42.6)	11 (23.4)	NS
Wu <i>et al</i> ^[57] (SX 1 st bifurcation)	2000	15	13 (86.7)	NS	14 (93.3)	2 (13.3)	10.8
Wu <i>et al</i> ^[57] (SX 1 st)	2000	97	83 (85.6)	NS	67 (69.1)	25 (25.8)	8.8
Minagawa <i>et al</i> ^[58]	2001	18	NS	NS	NS	NS	5.3
Poon <i>et al</i> ^[59]	2003	20	18 (90.0)	NS	17 (85.0)	NS	8.6
Fan <i>et al</i> ^[60] (SX, CHT)	2005	84	76 (90.5)	NS	NS	NS	10.5
Fan <i>et al</i> ^[60] (SX)	2005	24	20 (83.3)	NS	NS	NS	NS
Pawlik <i>et al</i> ^[10]	2005	102	87 (85.3)	NS	NS	NS	10
Chen <i>et al</i> ^[62] (SX 1 st)	2006	286	248 (86.7)	NS	172 (60.1)	NS	7.7
Chen <i>et al</i> ^[62] (SX Main)	2006	152	135 (88.8)	NS	95 (62.5)	NS	8.1
Ikai <i>et al</i> ^[64]	2006	78	57 (73.1)	NS	24 (30.8)	36 (46.2)	NS
Le Treut <i>et al</i> ^[63]	2006	26	22 (84.6)	NS	NS	NS	9
Kamiyama <i>et al</i> ^[66] (RTSX)	2007	15	13 (86.7)	NS	NS	NS	6.47
Kamiyama <i>et al</i> ^[66] (SX)	2007	28	25 (89.3)	NS	NS	NS	11
Takizawa <i>et al</i> ^[65]	2007	12	8 (66.7)	NS	NS	NS	8.24
Ban <i>et al</i> ^[69]	2009	45	NS	NS	NS	NS	NS
Inoue <i>et al</i> ^[70] (TB)	2009	20	19 (95.0)	NS	6 (30.0)	12 (60.0)	NS
Inoue <i>et al</i> ^[70] (EN)	2009	29	26 (89.7)	NS	10 (34.5)	15 (51.7)	NS
Kondo <i>et al</i> ^[68] (SX, Main)	2009	5	NS	NS	NS	NS	NS
Kondo <i>et al</i> ^[68] (SX, 1 st -3 rd)	2009	43	NS	NS	NS	NS	NS
Peng <i>et al</i> ^[67] (TC)	2009	51	46 (90.2)	NS	31 (60.8)	5 (9.8)	9.04
Peng <i>et al</i> ^[67] (SX)	2009	53	50 (94.3)	NS	40 (75.5)	3 (5.7)	8.39
Vitale <i>et al</i> ^[31]	2009	48	NS	NS	NS	NS	NS
Shi <i>et al</i> ^[71]	2010	406	361 (88.9)	NS	354 (87.2)	3 (0.7)	NS
Xu <i>et al</i> ^[21]	2010	95	NS	NS	NS	NS	NS
Lin <i>et al</i> ^[72] (TP1)	2011	21	NS	NS	NS	NS	NS
Lin <i>et al</i> ^[72] (TP2)	2011	47	NS	NS	NS	NS	NS
Peng <i>et al</i> ^[14]	2011	201	187 (93.0)	NS	172 (85.6)	4 (2.0)	NS
Wei <i>et al</i> ^[22]	2011	17	NS	NS	NS	NS	NS
Chang <i>et al</i> ^[32]	2012	160	140 (87.5)	60 (37.5)	112 (70.0)	20 (12.5)	7.5
Huang <i>et al</i> ^[56] (SX)	2012	54	40 (74.1)	NS	41 (75.9)	2 (3.7)	21.4
Huang <i>et al</i> ^[56] (SXTCT)	2012	62	42 (67.7)	NS	50 (80.6)	0 (0.0)	20.5
Liu <i>et al</i> ^[74]	2012	65	54 (83.1)	NS	NS	NS	NS
Ma <i>et al</i> ^[23]	2012	46	41 (89.1)	25 (54.3)	41 (89.1)	0 (0.0)	NS
Li <i>et al</i> ^[75]	2013	13	11 (84.6)	NS	NS	NS	10.2
Nitta <i>et al</i> ^[77]	2013	35	28 (80.0)	NS	7 (20.0)	21 (60.0)	7
Roayaie <i>et al</i> ^[78]	2013	164	132 (80.5)	NS	61 (37.2)	70 (42.7)	90
Tang <i>et al</i> ^[76]	2013	186	166 (89.2)	NS	159 (85.5)	23 (12.4)	9.53
Torzilli <i>et al</i> ^[12]	2013	297	228 (76.8)	169 (56.9)	61 (20.5)	100 (33.7)	6.0
Zhong <i>et al</i> ^[120]	2013	248	NS	NS	NS	NS	NS

TP: Time period; SX: Surgery; TC: Trans-arterial chemoembolization; CHT: Chemotherapy; TB: Thrombectomy; EN: *En.bloc*; RT: Radiotherapy.

Table 2 Clinical outcomes of liver resection in BCLC stage B or C hepatocellular carcinoma

Ref.	Recruitment period	n	Overall survival (%)			Median OS (mo)	Disease free survival (%)			Median DFS (mo)
			1-yr	3-yr	5-yr		1-yr	3-yr	5-yr	
BCLC stage B										
Régimbeau <i>et al</i> ^[25]	1984-1996	94	69.0	45.0	31.0	NS	51.0	35.0	21.0	NS
Hanazaki <i>et al</i> ^[19]	1983-1997	133	70.0	38.0	28.0	NS	65.0	26.0	20.0	NS
Ng <i>et al</i> ^[10]	1982-2001	380	74.0	50.0	39.0	36.9	54.0	38.0	26.0	15.6
Chen <i>et al</i> ^[26] (TP1)	1990-2003	959	67.8	50.7	27.9	16.0	56.5	34.7	18.9	10.0
Chen <i>et al</i> ^[26] (TP2)	1990-2003	1143	71.2	58.8	38.7	19.0	61.5	38.6	23.8	17.0
Cho <i>et al</i> ^[26]	1998-2001	230	85.0	59.3	52.9	NS	58.3	40.0	31.7	NS
Vitale <i>et al</i> ^[31]	2000-2007	124	85.0	56.0	NS	NS	NS	NS	NS	NS
Yang <i>et al</i> ^[11]	1992-2002	260	87.0	55.5	38.2	45.5	82.4	51.0	35.0	36.7
Zhou <i>et al</i> ^[29] (SX)	2001-2003	56	69.6	32.1	21.1	NS	39.2	21.4	8.9	NS
Zhou <i>et al</i> ^[29] (TCSX)	2001-2003	52	73.1	40.4	30.7	NS	48.9	25.5	12.8	NS
Delis <i>et al</i> ^[27]	2002-2008	66	69.0	37.0	32.0	36.0	60.0	33.0	29.0	29.0
Lin <i>et al</i> ^[30]	2001-2007	93	83.0	49.0	30.0	27.6	NS	NS	NS	NS
Ramacciato <i>et al</i> ^[28]	2000-2006	51	NS	NS	56.1	68.0	NS	NS	41.3	NS
Xu <i>et al</i> ^[21]	1991-2004	165	75.6	57.4	40.2	NS	NS	NS	NS	NS
Wei <i>et al</i> ^[22]	2003-2007	51	84.3	54.9	NS	NS	70.2	45.4	NS	NS
Zhou <i>et al</i> ^[20]	1995-2002	85	93.8	56.2	47.0	56.0	74.3	34.4	14.8	36.0
Chang <i>et al</i> ^[32]	1991-2006	318	81.2	59.4	46.5	NS	55.8	39.4	31.9	6.0
Hsu <i>et al</i> ^[34]	2002-2010	268	82.0	68.0	46.0	NS	NS	NS	NS	NS
Ma <i>et al</i> ^[23]	1998-2011	178	77.0	26.0	10.0	27.9	49.0	18.0	NS	16.8
Torzilli <i>et al</i> ^[12]	1990-2009	737	88.0	71.0	57.0	NS	63.0	38.0	27.0	NS
Zhong <i>et al</i> ^[120]	2000-2007	660	91.0	67.0	44.0	NS	NS	NS	NS	NS
BCLC stage C										
Ohkubo <i>et al</i> ^[79]	1985-1997	47	53.9	33.2	23.9	NS	31.2	17.9	NS	NS
Wu <i>et al</i> ^[57] (SX 1 st bifurcation)	1990-1998	15	80.0	44.0	26.4	NS	67.0	32.0	21.1	NS
Wu <i>et al</i> ^[57] (SX 1 st)	1990-1998	97	68.0	34.0	28.5	NS	51.0	22.0	20.4	NS
Minagawa <i>et al</i> ^[58]	1989-1998	18	82.0	42.0	42.0	40.8	NS	NS	NS	7.8
Poon <i>et al</i> ^[59]	1989-2000	20	30.0	13.3	13.3	6.0	15.0	5.0	5.0	2.9
Fan <i>et al</i> ^[60] (SX, CHT)	1997-2002	84	29.3	15.6	NS	15.1	NS	NS	NS	NS
Fan <i>et al</i> ^[60] (SX)	1997-2002	24	22.7	0.0	NS	10.1	NS	NS	NS	NS
Pawlik <i>et al</i> ^[10]	1984-1999	102	45.0	17.0	10.0	11.0	NS	NS	NS	NS
Chen <i>et al</i> ^[62] (SX 1 st)	1990-2003	286	58.7	22.7	18.1	18.8	NS	NS	NS	NS
Chen <i>et al</i> ^[62] (SX Main)	1990-2003	152	39.5	5.7	0.0	10.1	NS	NS	NS	NS
Ikai <i>et al</i> ^[64]	1990-2002	78	45.7	21.7	10.9	8.9	NS	NS	NS	NS
Le Treut <i>et al</i> ^[63]	1988-2004	26	38.5	20.0	13.0	9.0	NS	NS	NS	NS
Kamiyama <i>et al</i> ^[66] (RTSX)	1990-2006	15	86.2	43.5	34.8	19.6	NS	NS	NS	NS
Kamiyama <i>et al</i> ^[66] (SX)	1990-2006	28	39.0	13.1	13.1	9.1	NS	NS	NS	NS
Takizawa <i>et al</i> ^[65]	1992-2003	12	63.6	53.0	26.0	26.0	NS	NS	NS	NS
Ban <i>et al</i> ^[69]	1992-2008	45	69.6	37.4	22.4	20.0	30.4	21.2	0.0	NS
Inoue <i>et al</i> ^[70] (TB)	1995-2006	20	58.0	46.0	39.0	NS	34.0	34.0	23.0	NS
Inoue <i>et al</i> ^[70] (EN)	1995-2006	29	65.0	41.0	41.0	NS	38.0	22.0	18.0	NS
Kondo <i>et al</i> ^[68] (SX, Main)	1996-2004	5	20.0	NS	NS	NS	NS	NS	NS	NS
Kondo <i>et al</i> ^[68] (SX, 1 st -3 rd)	1996-2004	43	54.0	33.0	27.0	NS	NS	NS	NS	NS
Peng <i>et al</i> ^[67] (TC)	1996-2004	51	50.9	33.8	21.6	13.0	NS	NS	NS	NS
Peng <i>et al</i> ^[67] (SX)	1996-2004	53	33.3	17.0	8.5	9.0	NS	NS	NS	NS
Vitale <i>et al</i> ^[31]	2000-2007	48	55.0	44.0	0.0	NS	NS	NS	NS	NS
Shi <i>et al</i> ^[71]	2001-2003	406	34.4	13.0	NS	NS	13.3	4.7	NS	NS
Xu <i>et al</i> ^[21]	1991-2004	95	37.5	18.2	14.2	NS	NS	NS	NS	NS
Lin <i>et al</i> ^[72] (TP1)	1996-2006	21	77.0	19.0	5.0	21.0	NS	NS	NS	NS
Lin <i>et al</i> ^[72] (TP2)	1996-2006	47	76.0	51.0	36.0	36.0	NS	NS	NS	NS
Peng <i>et al</i> ^[14]	2002-2007	201	42.0	14.1	11.1	20.0	NS	NS	NS	NS
Wei <i>et al</i> ^[22]	2003-2007	17	52.9	29.4	NS	NS	35.2	17.6	NS	NS
Chang <i>et al</i> ^[32]	1990-2009	34	45.0	20.0	20.0	NS	NS	NS	NS	NS
Huang <i>et al</i> ^[56] (SX)	1991-2006	160	57.6	33.8	29.1	NS	35.3	27.2	25.0	NS
Huang <i>et al</i> ^[56] (SXTC)	1998-2008	54	71.0	35.0	11.0	NS	NS	NS	NS	NS
Liu <i>et al</i> ^[74]	1998-2008	62	71.0	24.0	6.0	NS	NS	NS	NS	NS
Ma <i>et al</i> ^[23]	2000-2009	65	84.0	NS	NS	17	79.0	NS	NS	14.0
Li <i>et al</i> ^[75]	1998-2011	46	37.0	16.0	NS	16.9	16.0	NS	NS	7.7
Nitta <i>et al</i> ^[77]	1997-2009	13	53.8	15.4	NS	NS	NS	NS	NS	NS
Roayaie <i>et al</i> ^[78]	2006-2008	35	78.0	37.4	32.7	NS	45.0	11.8	11.8	NS
Tang <i>et al</i> ^[76]	1992-2010	164	50.0	23.0	14	13.1	40.0	20.0	18.0	8.1
Torzilli <i>et al</i> ^[12]	2006-2008	186	40.1	13.6	NS	10.0	NS	NS	NS	NS
Zhong <i>et al</i> ^[120]	1990-2009	297	76.0	49.0	38.0	NS	46.0	28.0	18.0	NS
Ohkubo <i>et al</i> ^[79]	2000-2007	248	81.0	46.0	20.0	NS	NS	NS	NS	NS

TP: Time period; SX: Surgery; TC: Trans-arterial chemoembolization; CHT: Chemotherapy; TB: Thrombectomy; EN: *En bloc*; RT: Radiotherapy.

Table 3 Characteristics of patients classified as large or small hepatocellular carcinoma

Ref.	Year	n	Male (%)	Cirrhosis (%)	HBV (%)	HCV (%)	Median tumor diameter (cm)
Large HCC							
Poon <i>et al</i> ^[36]	2002	120	99 (82.5)	32 (26.7)	103 (85.8)	NS	13.8
Yeh <i>et al</i> ^[38]	2003	211	164 (77.7)	63 (29.9)	163 (77.3)	16 (7.6)	13.9
Zhou <i>et al</i> ^[37]	2003	621	NS	NS	NS	NS	NS
Liau <i>et al</i> ^[41]	2005	82	48 (58.5)	8 (9.8)	NS	NS	14.7
Nagano <i>et al</i> ^[40]	2005	26	19 (73.1)	5 (19.2)	14 (53.8)	3 (11.5)	14.8
Pawlik <i>et al</i> ^[10]	2005	300	222 (74.0)	NS	188 (62.7)	NS	NS
Lee <i>et al</i> ^[43]	2007	100	77 (77.0)	NS	NS	NS	12.5
Pandey <i>et al</i> ^[44]	2007	166	143 (86.1)	80 (48.2)	130 (78.3)	2 (1.2)	13.0
Shah <i>et al</i> ^[42]	2007	24	NS	NS	9 (37.5)	1 (4.2)	13.1
Young <i>et al</i> ^[45]	2007	42	29 (69.0)	2 (4.8)	NS	NS	14.0
Shimada <i>et al</i> ^[46]	2008	85	72 (84.7)	NS	27 (31.8)	19 (22.4)	12.0
Taniai <i>et al</i> ^[47]	2008	29	26 (89.7)	12 (41.4)	6 (20.7)	17 (58.6)	13.5
Choi <i>et al</i> ^[50]	2009	50	34 (68.0)	13 (26.0)	33 (66.0)	1 (2.0)	NS
Miyoshi <i>et al</i> ^[49]	2009	22	19 (86.4)	5 (22.7)	NS	NS	12.0
Ng <i>et al</i> ^[48]	2009	44	33 (75.0)	NS	15 (34.1)	3 (6.8)	12.4
Yamashita <i>et al</i> ^[51]	2011	53	48 (90.6)	NS	18 (34.0)	22 (41.5)	13.2
Truant <i>et al</i> ^[35]	2012	52	38 (73.1)	23 (44.2)	6 (11.5)	NS	14.0
Allemann <i>et al</i> ^[55]	2013	22	NS	9 (40.9)	4 (18.2)	2 (9.1)	13.5
Ariizumi <i>et al</i> ^[54]	2013	107	NS	NS	NS	NS	NS
Shrager <i>et al</i> ^[52]	2013	130	98 (75.4)	NS	56 (43.1)	23 (17.7)	14.2
Yang <i>et al</i> ^[53]	2013	258	212 (82.2)	171 (66.3)	195 (75.6)	NS	13.2
Small HCC							
Miyoshi <i>et al</i> ^[49]	2009	230	160 (69.6)	114 (49.6)	NS	NS	3.4
Allemann <i>et al</i> ^[55]	2013	79	NS	61 (77.2)	10 (12.7)	13 (16.5)	4.9
Poon <i>et al</i> ^[36]	2002	368	295 (80.2)	203 (55.2)	311 (84.5)	NS	5.4
Yeh <i>et al</i> ^[38]	2003	778	776 (99.7)	591 (76.0)	616 (79.2)	305 (39.2)	4.5
Zhou <i>et al</i> ^[37]	2003	2039	NS	NS	NS	NS	NS
Liau <i>et al</i> ^[41]	2005	111	80 (72.1)	40 (36.0)	NS	NS	6.1
Nagano <i>et al</i> ^[40]	2005	143	112 (78.3)	81 (56.6)	17 (11.9)	87 (60.8)	3.3
Shah <i>et al</i> ^[42]	2007	165	NS	NS	73 (44.2)	36 (21.8)	4.7
Young <i>et al</i> ^[45]	2007	43	30 (69.8)	10 (23.3)	NS	NS	5.0
Taniai <i>et al</i> ^[47]	2008	291	225 (77.3)	156 (53.6)	135 (46.4)	78 (26.8)	3.7
Choi <i>et al</i> ^[50]	2009	447	344 (77.0)	244 (54.6)	331 (74.0)	26 (5.8)	NS
Yamashita <i>et al</i> ^[51]	2011	412	328 (79.6)	NS	60 (14.6)	311 (75.5)	3.8
Truant <i>et al</i> ^[35]	2012	37	28 (75.7)	26 (70.3)	1 (2.7)	NS	4.7
Yang <i>et al</i> ^[53]	2013	293	236 (80.5)	201 (68.6)	216 (73.7)	NS	6.7

HCC: Hepatocellular carcinoma.

measure the extent of tumor burden, or prognosticate the continuum of outcomes after resection in the wide spectrum of tumors beyond the "Milan criteria". The "up-to-seven" criteria described by Mazzaferro *et al*^[145] which is a better surrogate measure of tumor burden, could be useful for selection of patients with appropriately sized large solitary HCC or multifocal HCC with an acceptable number of lesions to undergo surgery^[145,146].

As evidenced by the results of this systematic review, long-term survival results after surgical resection are acceptable and represent the best possible therapeutic option for selected BCLC stage B HCC. This review showed that resection beyond criteria advised by the AASLD and EASL guidelines, has achieved survival exceeding that accorded by non-curative methods such as TACE and sorafenib which typically confers a median OS between 8-12 mo^[147-152].

There are several limitations of this systematic review. Firstly, the studies in this review comprise a group of highly selected patients who underwent surgical resection. They do not represent the entire spectrum

of patients with BCLC stage B or C HCC and will be biased towards patients who are more suitable surgical candidates. Secondly, there exists a myriad of neo-adjuvant and adjuvant treatment protocols included in these studies. However, the evidence does not show definitive benefit in terms of survival and thus the effect is not likely to be significant^[153-155].

In conclusion, the results of the current systematic review provides evidence that indications for surgical resection of HCC should be extended to include selected BCLC stage B lesions and further studies should seek to identify the optimal criteria for the consideration of the criteria for liver resection.

ARTICLE HIGHLIGHTS

Research background

Hepatocellular carcinoma (HCC) remains a significant disease burden worldwide today. Appropriate treatment for HCC is complex because radical oncological clearance and preservation of adequate liver function need to be carefully balanced. Several staging systems have been developed to guide

Table 4 Clinical outcomes of liver resection in large or small hepatocellular carcinoma

Ref.	Recruitment period	n	Overall survival (%)			Median OS (mo)	Disease free survival (%)			Median DFS (mo)
			1-yr	3-yr	5-yr		1-yr	3-yr	5-yr	
Large HCC										
Poon <i>et al</i> ^[36]	1991-2000	120	60.6	37.8	27.5	18.8	32.0	14.1	9.5	5.5
Yeh <i>et al</i> ^[38]	1982-2001	211	48.1	24.0	16.7	NS	32.9	18.8	12.7	NS
Zhou <i>et al</i> ^[37]	1964-1999	621	68.0	37.3	26.2	NS	NS	NS	NS	NS
Liau <i>et al</i> ^[41]	1985-2002	82	73.0	49.0	33.0	32.0	80.0	44.0	24.0	22.0
Nagano <i>et al</i> ^[40]	1985-2001	26	41.0	29.3	29.3	10.1	65.4	49.0	NS	29.0
Pawlik <i>et al</i> ^[10]	1981-2000	300	64.9	36.7	26.9	20.3	NS	NS	NS	NS
Lee <i>et al</i> ^[43]	1997-2003	100	66.0	44.0	31.0	NS	43.0	26.0	20.0	NS
Pandey <i>et al</i> ^[44]	1995-2006	166	65.0	35.0	28.6	20.0	NS	NS	NS	NS
Shah <i>et al</i> ^[42]	1993-2004	24	69.0	63.0	54.0	NS	41.0	23.0	NS	8.4
Young <i>et al</i> ^[45]	1994-2006	42	70.0	45.0	45.0	NS	62.0	49.0	43.0	NS
Shimada <i>et al</i> ^[46]	1988-2004	85	NS	NS	31.5	NS	NS	NS	NS	NS
Taniai <i>et al</i> ^[47]	1987-2006	29	51.9	33.6	33.6	NS	48.4	21.5	21.5	NS
Choi <i>et al</i> ^[50]	1996-2006	50	70.0	50.2	40.2	NS	49.0	38.6	38.6	9.0
Miyoshi <i>et al</i> ^[49]	1987-2004	22	71.8	60.3	45.2	20.5	53.3	29.1	18.2	12.0
Ng <i>et al</i> ^[48]	1990-2008	44	66.4	38.1	27.8	21.5	49.6	23.9	19.1	10.7
Yamashita <i>et al</i> ^[51]	1995-2007	53	74.0	43.0	35.0	NS	50.0	40.0	24.0	NS
Truant <i>et al</i> ^[35]	2000-2010	52	NS	NS	43.3	NS	NS	NS	39.3	NS
Allemann <i>et al</i> ^[55]	1997-2009	22	84.0	72.0	45.0	27.0	64.0	28.0	27.0	10.0
Ariizumi <i>et al</i> ^[54] (S)	1990-2008	NS	81.0	60.0	47.0	14.3	41.0	18.0	12.0	NS
Ariizumi <i>et al</i> ^[54] (M)	1990-2008	NS	88.0	83.0	79.0	38.5	76.0	54.0	48.0	NS
Shrager <i>et al</i> ^[52]	1992-2010	130	56.9	30.2	18.8	17.0	31.8	13.4	11.5	6.7
Yang <i>et al</i> ^[53]	2002-2011	258	84.0	62.0	33.0	NS	61.0	24.0	6.0	NS
Small HCC										
Miyoshi <i>et al</i> ^[49]	1987-2004	230	89.3	74.6	60.4	48.2	68.0	43.7	26.7	20.0
Allemann <i>et al</i> ^[55]	1997-2009	79	75.0	42.0	21.0	24.0	50.0	18.0	14.0	15.0
Poon <i>et al</i> ^[36]	1991-2000	368	83.3	64.2	51.6	62.8	64.6	41.8	28.2	25.4
Yeh <i>et al</i> ^[38]	1982-2001	778	81.4	57.3	39.5	NS	61.2	40.7	32.1	NS
Zhou <i>et al</i> ^[37]	1964-1999	2039	85.0	65.1	54.3	NS	NS	NS	NS	NS
Liau <i>et al</i> ^[41]	1985-2002	111	80.0	58.0	39.0	40.0	70.0	49.0	31.0	28.0
Nagano <i>et al</i> ^[40]	1985-2001	143	93.1	74.5	44.7	53.4	80.0	46.5	31.0	33.9
Shah <i>et al</i> ^[42]	1993-2004	165	88.0	70.0	53.0	NS	76.0	53.0	43.0	38.0
Young <i>et al</i> ^[45]	1994-2006	43	82.0	63.0	57.0	NS	71.0	54.0	48.0	NS
Taniai <i>et al</i> ^[47]	1987-2006	291	81.0	61.4	45.0	NS	74.6	37.1	25.4	NS
Choi <i>et al</i> ^[50]	1996-2006	447	91.3	77.2	65.9	NS	72.7	53.1	45.4	35.0
Yamashita <i>et al</i> ^[51]	1995-2007	412	89.0	67.0	54.0	NS	72.0	45.0	37.0	NS
Truant <i>et al</i> ^[35]	2000-2010	37	NS	NS	89.2	NS	NS	NS	60.7	NS
Yang <i>et al</i> ^[53]	2002-2011	293	83.0	66.0	39.0	NS	56.0	26.0	9.0	NS

HCC: Hepatocellular carcinoma; M: Multi nodules; S: Single nodule.

management of HCC.

Research motivation

Surgical resection for HCC within the "Milan Criteria" or Barcelona Clinic Liver Cancer (BCLC) stage A is the widely accepted standard of care. However, surgical treatment for BCLC stage B (intermediate) or C (advanced) lesions remains controversial. Presently, the European Association for the Study of Liver Disease (EASL) and the American Association for the Study of Liver Disease (AASLD) guidelines do not recommend surgical resection for these patients. However, despite the recommendations from these two large reputable organizations, many international high-volume tertiary centers, especially centers in Asia, still routinely perform surgical resection for large solitary lesions, multifocal lesions and lesions with macrovascular invasion. Critical appraisal of both Western and Asian literature is needed to resolve the controversies.

Research objectives

The aim of this study was to perform a systematic review and summarize the current literature to determine the long-term survival outcomes after curative resection of intermediate and advanced HCCs.

Research methods

We conducted a systematic review of the published literature using the PubMed database from 1st January 1999 to 31st Dec 2014 to identify studies

that reported outcomes of liver resection as the primary curative treatment for BCLC stage B or C HCC. The primary end point was to determine the overall survival (OS) and disease free survival (DFS) of liver resection of HCC in BCLC stage B or C in patients with adequate liver reserve (*i.e.*, Child's A or B status) and in good general status (PS 0-2). The secondary end points were to assess the morbidity and mortality of liver resection in large HCC (defined as lesions larger than 10 cm in diameter) and to compare the OS and DFS after surgical resection of solitary vs multifocal HCC.

Research results

We included a total of 74 articles in this systematic review. Analysis of the resection outcomes of the included studies were grouped according to: (1) BCLC stage B or C HCC; (2) Size of HCC; and (3) multifocal tumors. The median 5-year OS of BCLC stage B was 38.7% (range 10.0-57.0); while the median 5-year OS of BCLC stage C was 20.0% (range 0.0-42.0). The collective median 5-year OS of both stages was 27.9% (0.0-57.0). In examining the morbidity and mortality following liver resection in large HCC, the pooled RR for morbidity [RR (95%CI): 1.00 (0.76-1.31)] and mortality [RR (95%CI): 1.15 (0.73-1.80)] were not significant. Within the spectrum of BCLC B and C lesions, tumors greater than 10 cm were reported to have median 5-year OS of 33.0% and multifocal lesions 54.0%.

Research conclusions

In conclusion, the results of the current systematic review provides evidence

that indications for surgical resection of HCC should be extended to include selected BCLC stage B lesions and further studies should seek to identify the optimal criteria for the consideration of the criteria for liver resection.

Research perspectives

As evidenced by the results of this systematic review, long-term survival results after surgical resection are acceptable and represent the best possible therapeutic option for selected BCLC stage B HCC. This review showed that resection beyond criteria advised by the AASLD and EASL guidelines, has achieved survival exceeding that accorded by non-curative methods such as TACE and sorafenib which typically confers a median OS between 8-12 mo. Further studies should seek to identify the optimal criteria for the consideration of the criteria for liver resection.

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