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ORIGINAL RESEARCH

Extending Surgical Resection for Hepatocellular Carcinoma Beyond Barcelona Clinic for Liver Cancer (BCLC) Stage A: A Novel Application of the Modified BCLC Staging System

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Objective: We aimed to prognosticate survival after surgical resection of HCC stratified by stage with amalgamation of the modified Barcelona Clinic Liver Cancer (BCLC) staging system and location of tumour.

Methods: This single-institutional retrospective cohort study included patients with HCC who underwent surgical resection between 1st January 2000 to 30th June 2016. Participants were divided into 6 different subgroups: A-u) Within MC with Unilobar lesions; A-b) Within MC + Bilobar lesions; B1-u) Out of MC + within Up-To-7 + Unilobar lesions; B1-b) Out of MC + within Up-to-7 + Bilobar lesions; B2-u) Out of MC + Out of Up-To-7 + Unilobar lesions; B2-b) Out of MC + Out of Up-To-7 + Bilobar lesions. A separate survival analysis was conducted for solitary HCC lesions according to three subgroups: A-S (Within MC); B1-S (Out of MC + within Up-To-7); B2-S (Out of MC + out of Up-To-7).

Results: A total of 794 of 1043 patients with surgical resection for HCC were analysed. Groups A-u (64.6%), A-b (58.4%) and B1-u (56.2%) had 5-year cumulative overall survival (OS) rates above 50% after surgical resection and median OS exceeding 60 months (P = 0.0001). The 5-year cumulative recurrence-free survival rates (RFS) were 40.4% (group A-u), 38.2% (group A-b), 36.3% (group B1-u), 24.6% (group B2-u), and 7.3% (group B2-b)(P=0.0001). For solitary lesions, the 5-year OS for the subgroups were A-S (65.1%), B1-S (56.0%) and B2-S (47.1%) (P = 0.0003). Compared to A-S, there was also a significant trend towards relatively poorer OS as the lesion sizes increased in B1-S (HR 1.46, 95% CI 1.03–2.08) and B2-S (HR 1.65, 95% CI 1.25–2.18).

Conclusion: We adopted a novel approach combining the modified BCLC B sub-classification and dispersion of tumour to show that surgical resection in intermediate stage HCC can be robustly prognosticated. We found that size prognosticates resection outcomes in solitary tumours.

Keywords: hepatocellular carcinoma, surgical resection, Barcelona clinic liver cancer

Plain Language Summary

Should indications for surgical resection be extended to intermediate hepatocellular carcinoma?

Typically, surgical resection is offered only to patients with hepatocellular carcinomas of an early stage – called Barcelona Liver Cancer Clinic (BCLC) A. Here we adapted the BCLC classification system, showing that if you take the location of the tumour into account as well, you can cure some patients with more advanced BCLC B disease as well. Surgery can cure some patients with BCLC Sub class B1 cancers, if the cancer is confined to one lobe. It should be considered in these patients.

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Introduction

Globally, hepatocellular carcinoma (HCC) represents the fourth most common cause of cancer-related mortality.[1] Surgical resection remains the main treatment modality in early HCC provided there is adequate liver function and sufficient future liver remnant.[2] A systematic review of 4209 patients with HCC within the Milan Criteria (MC) demonstrated median 5-year overall survival (OS) of 67% after surgical resection, which crosses 5-year OS of 50% thereby making surgical resection conceptually curative in this group of patients,[3] as first proposed by LLovet and Bruix in 1999[4] and in their subsequent update in 2002.[5] Recent evidence has however suggested that surgical resection may be justifiably offered to select individuals with intermediate- or advanced-stage disease.[6,7]

While a number of staging systems have been validated for prognostic evaluation of HCC, there is no universally adopted system. Nevertheless, the Barcelona Clinic Liver Cancer (BCLC) system is frequently used to compare treatment outcomes.[4] The BCLC system is very similar to the European Association for the Study of Liver (EASL)[8] and the American Association for the Study of Liver Disease (AASLD)[9] systems and recommend surgical resection for patients with Stage 0 (very early), Stage A (early) and solitary tumours; but not for Stage B (intermediate) and C (advanced) given poor 5-year overall survival rates.

However, these recommendations do not adequately address the heterogeneity of HCC within each stage, especially in stages B and C.[10] BCLC stage B, for instance, includes patients with Child-Pugh scores ranging from 5 to 9, which is a diverse group in terms of liver function. Moreover, there is variance in terms of tumour numbers – from as low as four to as high as 20+ bilateral tumours; as well as the lack of an upper limit of tumour size.[2] Such wide clinical heterogeneity of the BCLC B stage portends different clinical outcomes for the same therapeutic modality. In view of this Bolondi et al in 2012 refined the BCLC system to include four substages in stage B disease that primarily incorporates a unique joint consideration of the number of tumours, and the maximum tumour diameter based on the "beyond Milan" and "up-to-7" criteria by Mazzaferro et al[11] and the Child-Pugh score. This modified BCLC B classification has robustly stratified patients according to survival in both untreated HCC[12] and patients treated with trans-arterial chemoembolization (TACE).[13] Most recently, the BCLC classification received a 2022 update, which is further refined based on patient characterisation, and with greater emphasis on personalised treatment in the clinical decision-making process, whilst maintaining the current stratification and stages.[14]

Various centres have attempted to extend the indication of surgical resection beyond the early stages, showing that it is comparable or even superior to trans-arterial chemo-embolization (TACE) in terms of overall survival (OS) in intermediate and advanced HCC.[15–17] Nonetheless, because HCC beyond the BCLC Stage A is not a single entity but a wide spectrum of disease, there is still no consensus on which patients in this heterogenous group will benefit from surgical resection. We aimed to investigate OS rates after surgical resection of HCC stratified by stage with amalgamation of the BCLC system and location of tumour (unilobar versus bilobar), across the entire spectrum of HCC in BCLC Stage A (where tumour burden is similar to the Milan criteria) and B (using the Bolondi sub-classification of the BCLC B stage). A secondary aim of this study is to prognosticate survival outcomes after surgical resection of solitary HCC lesions stratified by size. Contrary to the current BCLC staging system that treats solitary HCC larger than 5cm in size as stage A,[8] recent evidence has shown that solitary large HCC portends poorer outcomes as compared to smaller solitary lesions and may be more appropriately classified as BCLC stage B.[18–22] We attempt to address this knowledge gap with a novel approach to stratify all solitary HCC lesions according to size by incorporating both the Milan and Up-To-7 criteria.

It is our belief that such an approach will illustrate the granularities of survival outcomes, which may better aid surgeons and patients on their decisions for resection of HCC.

Methods

Study Population and Definitions

This single-institutional retrospective cohort study investigated OS and recurrence-free survival (RFS) after surgical resection of HCC in BCLC A and B. Data was abstracted from a prospectively maintained electronic medical record system Sunrise Clinical Manager® (Allscript Health Solutions INC, Chicago, IL). Our surgical technique and patient selection for liver resection arising from this database have been reported previously in multiple publications.[23–26] Included were patients with histologically confirmed HCC who underwent surgical resection between 1st January 2000 to 30th June 2016 at the Singapore General Hospital. The collection and analysis of patient data were approved by the Institutional Review Board (CIRB Reg: 2017–2601).

Data lock was 30th June 2018. This was in view of the enactment of the Human Biomedical Research Act by the Singapore Ministry of Health on 1st November 2018, which did not permit analysis of non-anonymised data without patient consent for patients treated beyond 30th October 2018 in this study (Ministry of Health, 2019).

Patients underwent either standardised CT or MRI scans, which were all reviewed by and reported by specialist Radiologists in our Institution. Patients with the following features were excluded: 1) Macro-vascular invasion (Imaging evidence of invasion into medium to large vessels as reported by the Radiologists, eg, hepatic veins/portal veins); 2) Extra-hepatic invasion; 3) Tumour rupture; 4) Palliative resection; 5) Second primary tumour; 6) Missing data. Preoperative demographic and clinical variables collected in a standardised proforma were Milan Criteria status, Up-to-7 status, lobar involvement, age, gender, hepatitis B and C infection, Child-Pugh-Turcotte score, Albumin-bilirubin score (ALBI), Alpha-fetoprotein (AFP), presence of micro-vascular invasion (based on histopathological assessment of tumour and surrounding hepatic tissue as reported by specialist Pathologists), and degree of tumour capsulation (based on imaging).

Outcome Measures

Primary outcome measures include overall survival (OS) and recurrence-free survival (RFS), which were estimated from the time of surgery to death or recurrence, respectively.

Subgroup Classification

The study cohort was divided into 6 different subgroups based on the Milan Criteria (MC), the "Up-to-7" criteria, and location of lesions. The subgroups are as follow: A-u) Within MC with Unilobar lesions; A-b) Within MC + Bilobar lesions; B1-u) Out of MC + within Up-To-7 + Unilobar lesions; B1-b) Out of MC + within Up-to-7 + Bilobar lesions; B2-u) Out of MC + Out of Up-To-7 + Unilobar lesions; B2-b) Out of MC + Out of Up-To-7 + Bilobar lesions.

Groups A-u and A-b fall within BCLC Stage A;[4] groups B1-u and B1-b fall within BCLC Substage B1; groups B2-u and B2-b fall within BCLC Substage B2.[27]

In a separate analysis, solitary HCC lesions were divided into 3 main group subgroups: A-S (Within MC); B1-S (Out of MC + within Up-To-7); B2-S (Out of MC + out of Up-To-7).

Statistical Analyses

The respective primary and secondary time-to-event outcomes were overall survival (OS) and recurrence-free survival (RFS). OS was defined as the elapsed time between surgical resection and either death or the last follow-up, whichever happened first. RFS was defined as the elapsed time between surgical resection and recurrence or last follow-up as confirmed by imaging. The last follow-up date for the whole cohort was 30th June 2018.

Categorical and continuous variables were summarized based on 6 subgroups, respectively, as frequency (proportion) and mean (standard deviation (SD)) and median (minimum and maximum). Categorical variables were compared using Fisher's test whilst continuous variables were compared using ANOVA test and Mann Whitney *U*-test. In case of significant difference between groups, pairwise comparisons were made with Bonferroni correction to account for multiple comparisons.

Difference between the 6 subgroups in terms of OS and RFS was analysed using Kaplan–Meier (KM) analysis with Log rank test. Cox proportional hazard regression (CPHR) model was used to find association between the 6 subgroups and OS or RFS. Quantitative association from CPHR was expressed as hazard ratios (HR) with 95% confidence intervals (95% CI). P value <0.05 was considered as statistically significant unless its stated otherwise and all tests were two sided. Statistical analyses were performed using STATA, version 16.1. (StataCorp. 2019. Stata Statistical Software: Release 16. College Station, TX: StataCorp LLC.)

Results

Baseline Demographic Data

One thousand and forty three (1043) patients with HCC underwent resection during the study period. As shown in the CONSORTdiagram (Figure 1), 794 remained after exclusion of patients based on our criteria, of which 641 had unifocal disease and 153 had multifocal disease. There were 448, 25, 112, 20, 145 and 44 patients in Subgroups A-u, A-b, B1-u,

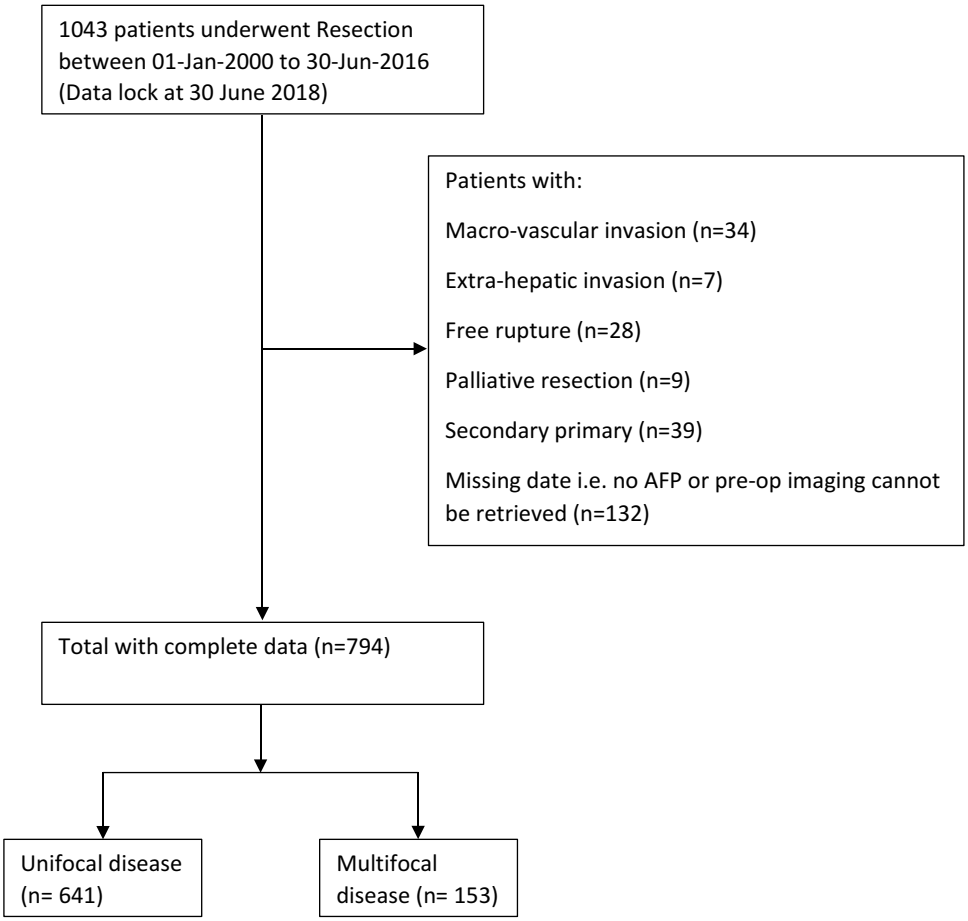

Figure 1 CONSORT diagram.[28]

B1-b, B2-u and B2-b, respectively. Demographic and clinical characteristics are summarised in Tables 1 and 2. Table 1 depicts the baseline demographics based on BCLC status while Table 2 demonstrates the 6 subgroups that are stratified based on uni- vs bilobar disease. Notably, in terms of etiology, there was a significant difference in prevalence of Hepatitis B and Non-B-Non-C patients amongst the 3 BCLC groups, with Hepatitis B being highest in BCLC A and lowest in BCLC B2 ($P < 0.0001$) (Table 1). There were however no significant differences when comparing uni- vs bilobar disease within the various BCLC groups (Table 2). The proportion of non-viral etiology was significantly higher in BCLC B2 as compared to BCLC A ($P < 0.0001$) and BCLC B1 ($P = 0.0006$) (Table 1).

Of note, in terms of mean Alpha-Fetoprotein (AFP) levels, BCLC B2 had a significantly higher AFP level as compared to both A ($P < 0.0001$) and B1 ($P < 0.0001$) (Table 2). In comparing uni- vs bilobar lesions, uni-lobar lesions had a significantly higher number of nodules as compared to bilobar lesions within each BCLC group (Group A-u vs Group A-b: $P < 0.0001$; Group B1-u vs B1-b: $P = 0.0098$; Group B2-u vs B2-b: $P < 00.0001$) (Table 2). There was no significant difference in the maximum size nodules between uni- and Bilobar lesions (Table 2).

Survival Analysis

Overall Survival

Groups A-u (64.6%, 95% CI: 59.5–69.3%), A-b (58.4%, 95% CI: 33.1–77.1%) and B1-u (56.2%, 95% CI: 44.9–66.0%) had 5-year cumulative OS rates above 50%, whilst groups B1-b (45.5%, 95% CI: 20.0–68.0%), B2-u (44.0%, 95% CI: 34.4–53.0%) and B2-b (38.2%, 95% CI: 21.5–54.8%) had 5-year OS below 50%. These findings were statistically significant ($P < 0.001$). Corroborative findings were observed in the analysis of median OS. Median OS above 60 months

Table 1 Baseline Demographics and Clinical Variables Based on BCLC Status

Variable	BCLC Status				OverAll P – value*	Pairwise Comparisons‡		
	A N = 473	B1 N = 132	B2 N = 189	Total N = 794		A vs B1	A vs B2	B1 vs B2
Age (years)								
Mean (SD)£	62.2 (10.0)	63.5 (11.4)	63.7 (14.0)	62.7 (11.3)	0.2030			
Median (Min, Max)€	62.7 (30, 85)	64.2 (25, 88)	66.6 (15, 88)	64.0 (15, 88)	0.0089	0.1965	0.0118	0.5952
Gender, n(%)					0.4533			
Male	359 (75.9)	0102 (77.3)	0152 (80.4)	0613 (77.2)				
Female	114 (24.1)	0030 (22.7)	0037 (19.6)	0181 (22.8)				
Hepatitis B, n (%)	346 (73.2)	78 (59.1)	95 (50.3)	519 (65.4)	<0.0001	<0.0001	<0.0001	<0.0001
Hepatitis C, n (%)	48 (10.1)	23 (17.4)	14 (7.4)	85 (10.7)	0.0183	0.0312	0.3043	0.0074
Non Hepatitis B/C, n (%)	89 (18.8)	033 (25.0)	83 (43.9)	205 (25.8)	<0.0001	0.1404	<0.0001	0.0006
Child-Pugh Score, n (%)					<0.0001	0.2064	<0.0001	0.0496
5	366 (77.4)	96 (72.7)	113 (59.8)	575 (72.4)				
6	88 (18.6)	33 (25.0)	68 (36.0)	189 (23.8)				
7–9	19 (4.0)	3 (2.3)	8 (4.2)	30 (3.8)				
Albumin-bilirubin (ALBI) score								
Mean (SD)£	−2.51 (0.434)	−2.48 (0.40)	−2.37 (0.43)	−2.47 (0.43)	0.0004	1.0000	0.0003	0.0468
Median (Min, Max)€	−2.56 (−3.44, −0.76)	−2.52 (−3.71, −1.24)	−2.37 (−3.35, −1.16)	−2.52 (−3.71, −0.76)	<0.0001	0.4369	<0.0001	0.0573
Alpha-Fetoprotein (AFP) (ng/mL)								
Mean (SD)£	402.2 (1919)	1725.3 (7536.3)	8825.0 (21,889.6)	2627.1 (11,722)	<0.0001	0.6917	<0.0001	<0.0001
Median (Min, Max)€	10.9 (1, 29,483)	13.1 (1, 70,700)	77.4 (1, 175,000)	13.15 (1, 175,000)	<0.0001	0.1240	<0.0001	0.0337
Tumour Capsule, n (%)					0.4600			
Not encapsulated	147 (35.8)	36 (31.6)	47 (28.7)	230 (33.4)				
Completely encapsulated	119 (29.0)	32 (28.1)	48 (29.3)	199 (28.9)				
Partially encapsulated	145 (35.3)	46 (40.4)	69 (42.1)	260 (37.7)				
Micro Vascular Invasion, n (%)	95 (21.1)	39 (31.0)	105 (56.8)	239 (31.4)	<0.0001	0.0234	<0.0001	<0.0001
Number of nodules, n(%)					<0.0001	<0.0001	<0.0001	0.0002
1	438 (92.6)	73 (55.3)	130 (68.8)	641 (80.7)				
2	31 (6.6)	43 (32.6)	28 (14.8)	102 (12.8)				
3–5	4 (0.8)	16 (12.1)	23 (12.2)	43 (5.4)				
> 5	0	0	8 (4.2)	8 (1.0)				
Maximum size nodules, n (%)					<0.0001	<0.0001	<0.0001	<0.0001
<3 cm	288 (60.9)	1 (0.8)	1 (0.5)	290 (36.5)				
3–5 cm	185 (39.1)	52 (39.4)	4 (2.1)	241 (30.4)				
>5 cm	0	79 (59.8)	184 (97.4)	263 (33.1)				

Notes: ‡After adjusting for Bonferroni correction p-value <0.0167 is considered as statistical significance. *P-value <0.05 is considered as statistical significance. P-values for categorical and continuous data were based on Fisher's exact test and ANOVA £Or Mann–Whitney *U*-test €Whichever appropriate, respectively.

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Table 2 Baseline Demographics and Clinical Variables Based on Milan Criteria, Up-to-7 Criteria and Dispersion of Tumour

Variable	Milan Unilobar N = 448 (Grp 1)	Milan Bilobar N = 25 Grp 2	B1 - Out of Milan Within Upto 7 Unilobar N = 112 (Grp 3)	B1 - Out of Milan Within Upto 7 Bilobar N = 20 (Grp 4)	B2 - Out of Milan Out of Upto7 Unilobar N = 145 (Grp 5)	B2 - Out of Milan Out of Upto 7 Bilobar N = 44 (Grp 6)	Overall P - value*	P – value to Compare ‡		
								Grp 1 vs Grp 2	Grp 3 vs Grp 4	Grp 5 vs Grp 6
Age (years)										
Mean (SD)£	62.0 (9.95)	64.9 (10.62)	63.5 (11.54)	63.2 (11.19)	63.7 (13.24)	63.7 (16.25)	0.2030			
Median (Range)€	65.43 (30, 85)	62.61 (39, 82)	64.3 (25, 88)	64.12 (41, 84)	68.08 (15, 85)	66.53 (15, 88)	0.0416	0.1427	0.8094	0.7305
Gender, n (%)							0.4533			
Male	345 (77.0)	14 (56.0)	86 (76.8)	16 (80.0)	118 (81.4)	34 (77.3)				
Female	103 (23.0)	11 (44.0)	26 (23.2)	4 (20.0)	27 (18.6)	10 (22.7)				
Hepatitis B, n (%)	329 (73.4)	17 (68.0)	69 (61.6)	9 (45.0)	74 (51.0)	21 (47.7)	<0.0001	0.6427	0.2175	0.7332
Hepatitis C, n (%)	45 (10.0)	3 (12.0)	20 (17.9)	3 (15.0)	10 (6.9)	4 (9.1)	0.0183	0.7315	1.0000	0.7422
Non Hepatitis B/C, n (%)	84 (18.8)	5 (20.0)	25 (22.3)	8 (40.0)	63 (43.4)	20 (45.5)	0.0006	0.7968	0.1010	0.8632
Child-Pugh Score, n (%)							<0.0001	0.3992	0.2894	0.4373
5	348 (77.7)	18 (72.0)	80 (71.4)	16 (80.0)	83 (57.2)	30 (68.2)				
6	81 (18.1)	7 (28.0)	30 (26.8)	3 (15.0)	55 (37.9)	13 (29.5)				
7–9	19 (4.2)	0	2 (1.8)	1 (5.0)	7 (4.8)	1 (2.3)				
Albumin-bilirubin (ALBI) score										
Mean (SD)£	−2.51 (0.44)	−2.50 (0.40)	−2.46 (0.39)	−2.59 (0.44)	−2.36 (0.45)	−2.40 (0.377)	0.0004	0.8982	0.2446	0.5561
Median (Range)€	−2.59 (−3.44, −0.76)	−2.56 (−3.32, −1.72)	−2.73 (−3.71, −1.24)	−2.5 (−3.29, −1.56)	−2.35 (−3.35, −1.16)	−2.39 (−3.08, −1.16)	0.0006	0.7346	0.1042	0.5281
Alpha-Fetoprotein (AFP) (ng/mL)										
Mean (SD)£	395.2 (1929.0)	527.8 (1758.6)	1948.5 (8149.6)	474.9 (1279)	7572.6 (20,778.8)	12,952.2 (25,026.1)	<0.0001	0.7180	0.0752	0.1995
Median (Range)€	010.5 (1, 29,483)	31.2 (2, 8739)	13.1 (1, 70,700)	16.1 (3, 4306)	77.4 (1, 175,000)	58.4 (1, 70,700)	<0.0001	0.0332	0.9975	0.5616
Tumour Capsule, n (%)							0.4600			
Not encapsulated	139 (35.5)	008 (40.0)	0031 (32.0)	005 (29.4)	0031 (25.0)	00016 (40.0)				
Completely encapsulated	115 (29.4)	004 (20.0)	0028 (28.9)	004 (23.5)	0039 (31.5)	00009 (22.5)				
Partially encapsulated	137 (35.0)	008 (40.0)	0038 (39.2)	008 (47.1)	0054 (43.5)	00015 (37.5)				
Micro Vascular Invasion, n (%)	090 (21.0)	005 (22.7)	0032 (30.2)	007 (35.0)	0083 (58.9)	00022 (50.0)	<0.0001	0.7921	0.7925	0.3837
Number of nodules, n(%)							<0.0001	<0.0001	0.0098	<0.0001
1	425 (94.9)	13 (52.0)	68 (60.7)	5 (25.0)	113 (77.9)	17 (38.6)				
2	21 (4.7)	10 (40.0)	32 (28.6)	11 (55.0)	16 (11.0)	12 (27.3)				
3–5	2 (0.4)	2 (8.0)	12 (10.7)	4 (20.0)	12 (8.3)	11 (25.0)				
>5	0	0	0	0	4 (2.8)	4 (9.1)				
Maximum size nodules, n (%)							<0.0001	0.8351	0.1359	0.0835
<3 cm	272 (60.7)	16 (64.0)	1 (0.9)	0	00	1 (2.3)				
3–5 cm	176 (39.3)	9 (36.0)	40 (35.7)	12 (60.0)	2 (1.4)	2 (4.5)				
>5 cm	0	0	71 (63.4)	8 (40.0)	143 (98.6)	41 (93.2)				

Notes: ‡ After adjusting for Bonferroni correction p-value <0.025 is considered as statistical significance. *P-value <0.05 is considered as statistical significance. P-values for categorical and continuous data were based on Fisher's exact test and ANOVA £Or Mann–Whitney *U*-test, €Whichever appropriate, respectively.

Table 3 Summary of Overall Survival Analysis results

Group	HCC Stage, Location	BCLC Stage	5 Years Survival Rate (%) (95% CI)	Median Survival Time (Months) (95% CI)	P value (Log Rank)
A-u	Milan Unilobar	BCLC A	64.6 (59.5, 69.3)	100.43 (89.33, 132.73)	<0.0001
A-b	Milan Bilobar	BCLCA	58.4 (33.1, 77.1)	64.59 (23.72, 101.39)	
B1-u	Out of Milan Within Upto7 Unilobar	BCLC B1	56.2 (44.9, 66.0)	74.84 (48.26, 98.46)	
B1-b	Out of Milan Within Upto7 Bilobar	BCLC B1	45.5 (20.0, 68.0)	51.35 (18.83, 95.01)	
B2-u	Out of Milan Out of Upto7 Unilobar	BCLC B2	44.0 (34.4, 53.0)	51.78 (35.94, 67.91)	
B2-b	Out of Milan Out of Upto7 Bilobar	BCLC B2	38.2 (21.5, 54.8)	40.18 (21.19, NE)	

Abbreviations: NE, Not estimable; CI, confidence interval; HCC, hepatocellular carcinoma; BCLC, Barcelona clinic liver cancer staging system.

was noted in groups A-u (100.4 months), A-b (64.6 months) and B1-u (74.8 months). Median OS in groups B1-b, B2-u and B2-b were 51.4, 51.8 and 40.2 months, respectively. A summary of these findings can be found in Table 3.

Relative to group A-u, group A-b (HR 2.02, 95% CI 1.19–3.42, P = 0.009), B1-u (HR 1.49, 95% CI 1.10–2.01, P = 0.009), B1-b (HR 2.30, 95% CI 1.28–4.14, P = 0.005), B2-u (HR 1.92, 95% CI 1.48–2.49, P < 0.001) and B2-b (HR 2.34, 95% CI 1.50–3.65, P < 0.001) demonstrated significantly poorer OS. However, visual evaluation of the KM graph revealed that the survival curves of groups A-b, B1-u, B1-b, B2-u and B2-b inter-crossed at various time points, which limits appropriate interpretation and comparison of HRs amongst these groups since it violates the proportional hazards assumption (Figure 2).

Recurrence-Free Survival

The 5-year cumulative RFS were 40.4% (group A-u), 38.2% (group A-b), 36.3% (group B1-u), 24.6% (group B2-u), and 7.3% (group B2-b), with a sharp decline noted as the disease severity progressed from group B1-u to B2-b (36.3% to 24.6% respectively). These differences were statistically significant (Log rank test P < 0.0001). There were no patients in

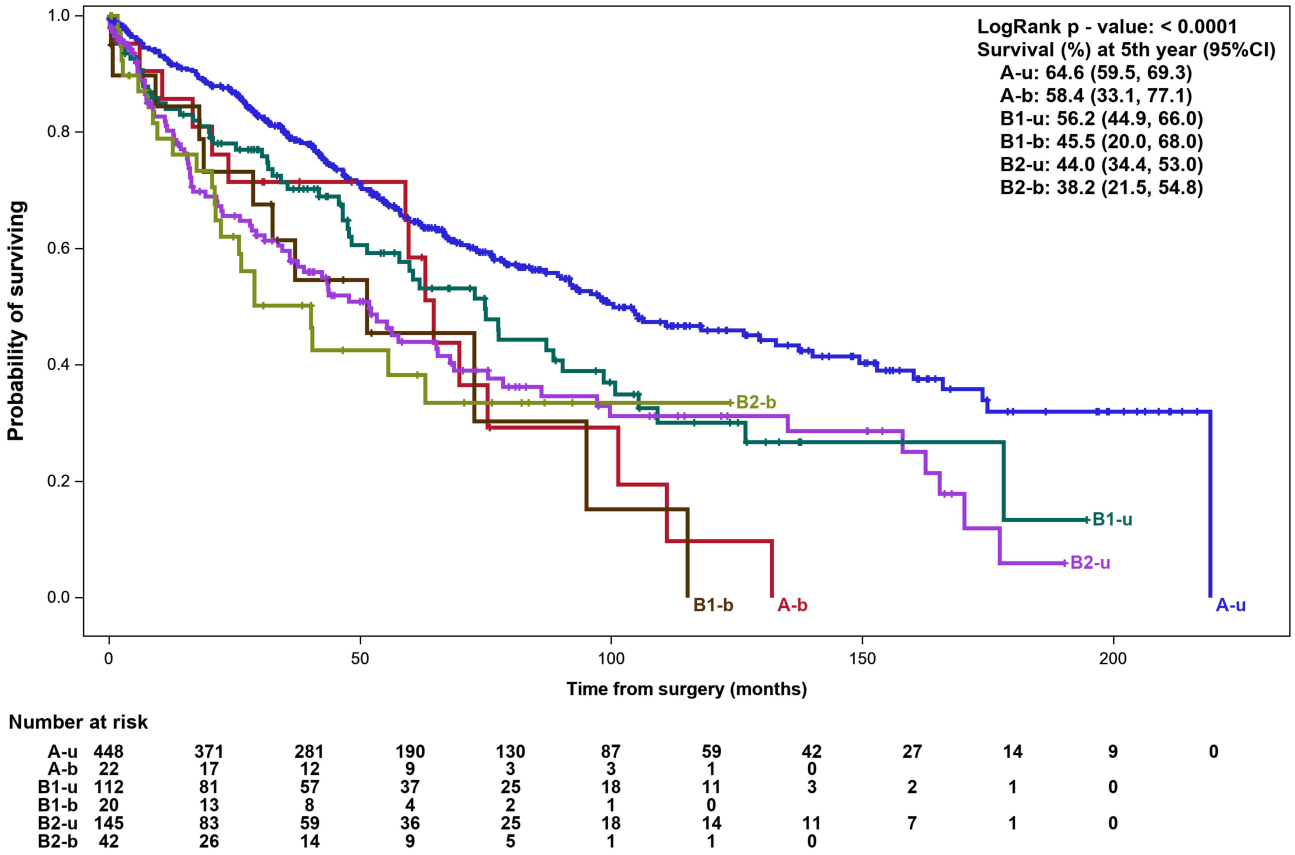

Figure 2 Kaplan Meier curves depicting overall survival analysis of 6 subgroups.

group B1-b who had RFS beyond 5 years. The median RFS were 42.8, 40.7, 22.0, 15.6, 13.4 and 9.0 months, respectively, for groups A-u to B2-b, demonstrating a consistent decline in median RFS as the severity of HCC disease progressed. A summary of these findings can be found in Supplementary Table 1.

Using CPHR, there were no statistically significant differences in RFS between groups A-u and A-b (HR 1.15, 95% CI 0.64–2.0, P = 0.647), and between A-u and B1-u (HR 1.27, 95% CI 0.97–1.66, P = 0.089). In contrast, groups B1-b (HR 2.20, 95% CI 1.28–3.78, P = 0.004), B2-u (HR 1.75, 95% CI 1.38–2.21, P < 0.001), and B2-b (HR 2.54, 95% CI 1.74–3.72, P < 0.001) exhibited significantly poorer RFS as compared to group A-u. Similarly, visual evaluation of the KM graph revealed crossing of the KM survival curves in groups A-b to B2-b at various time points, thus violating the proportional hazards assumption (Supplementary Figure 1).

Survival Outcomes of Solitary Lesions Stratified by Size

Survival analyses were conducted for solitary HCC lesions stratified by the Milan Criteria and up-to-7 criteria according to the three subgroups described above: A-S (within MC; n = 436), B1-S (Out of MC+ within Up-To-7; n = 73), B2-S (Out of MC + out of Up-To-7; n = 130).

The 5-year cumulative OS for subgroups A-S (65.1%) and B1-S (56.0%) were above 50%, while subgroup B2-S was below 50% (47.1%) (Log rank test P < 0.0003). Furthermore, a consistent decline in median OS was noted across subgroups A-S (100.4 months), B1-S (75.0 months) and B2-S (53.3 months) (Table 4). There was a significant trend towards relatively poorer overall survival as the lesion sizes increased in B1-S (HR 1.46, 95% CI 1.03–2.08, P = 0.035) and B2-S (HR 1.70, 95% CI 1.29–2.24, P < 0.001) in comparison to A-S (Figure 3).

The 5-year cumulative RFS were comparable between subgroups A-S (45.1%) and B1-S (38.7%), but notably lower for subgroup B2-S (25.9%) (P < 0.0005). There was however a consistent decline in median RFS across subgroups A-S (45.7 months), B1-S (20.3 months) and B2-S (15.6 months) (Supplementary Table 2). Statistically significant RFS was observed in B2-S as compared to A-S (HR 1.62, 95% CI 1.26–2.07, P < 0.0001); but not between B1-S and A-S (HR 1.27, 95% CI 0.91–1.76, P = 0.156) (Supplementary Figure 2).

Discussion

There has been a paradigm shift in therapeutic aims for HCC beyond BCLC A. In the BCLC staging system, the earlier premise for surgical resection of HCC revolved around BCLC A,[4] where there was possibility of cure for surgically resected HCC.[29] Surgical resections for lesions that fell outside of BCLC A were purposed to downstage disease or to improve and prolong quality of life and were not recommended. Surgical resection for solitary HCC of all sizes was subsequently proposed in the 2012 EASL guidelines.[8]

Whilst the BCLC system has attempted to allow for a more comprehensive prognostic assessment, it does not adequately address the granularities arising from the heterogeneous presentation of HCC especially in BCLC B stage. In a move to rectify this Bolondi et al in 2012 refined the BCLC system to include four substages in stage B disease that primarily incorporated a unique joint consideration of the number of tumours, and the maximum tumour diameter based on the "beyond Milan" and "up-to-7" criteria by Mazzaferro et al[11,27] Although this does not alter treatment options as TACE is still recommended across all substages, what it does offer is prognostication across different substages after TACE.[27] This was further supported by the Italian Liver Cancer Group (ITA LI CA), which showed that subclassification of intermediate HCC better predicts prognosis of untreated disease, allowing different therapeutic interventions to be better assessed across the various substages.[12]

Table 4 Summary of Survival Outcomes of Solitary Lesions Stratified by Size

Group	Solitary Lesions Stratified by Size	5 Years Survival Rate (%) (95% CI)	Median Survival Time (Months) (95% CI)	P value (Log Rank)
A-S	Within Milan	65.1 (59.9, 69.8)	100.44 (89.33, 129.48)	0.0003
B1-S	Out of Milan Within Upto7	56.0 (42.2, 67.7)	74.97 (46.52, 109.18)	
B2-S	Out of Milan Out of Upto7	47.1 (37.0, 56.5)	53.29 (38.77, 86.05)	

Abbreviation: CI, confidence interval.

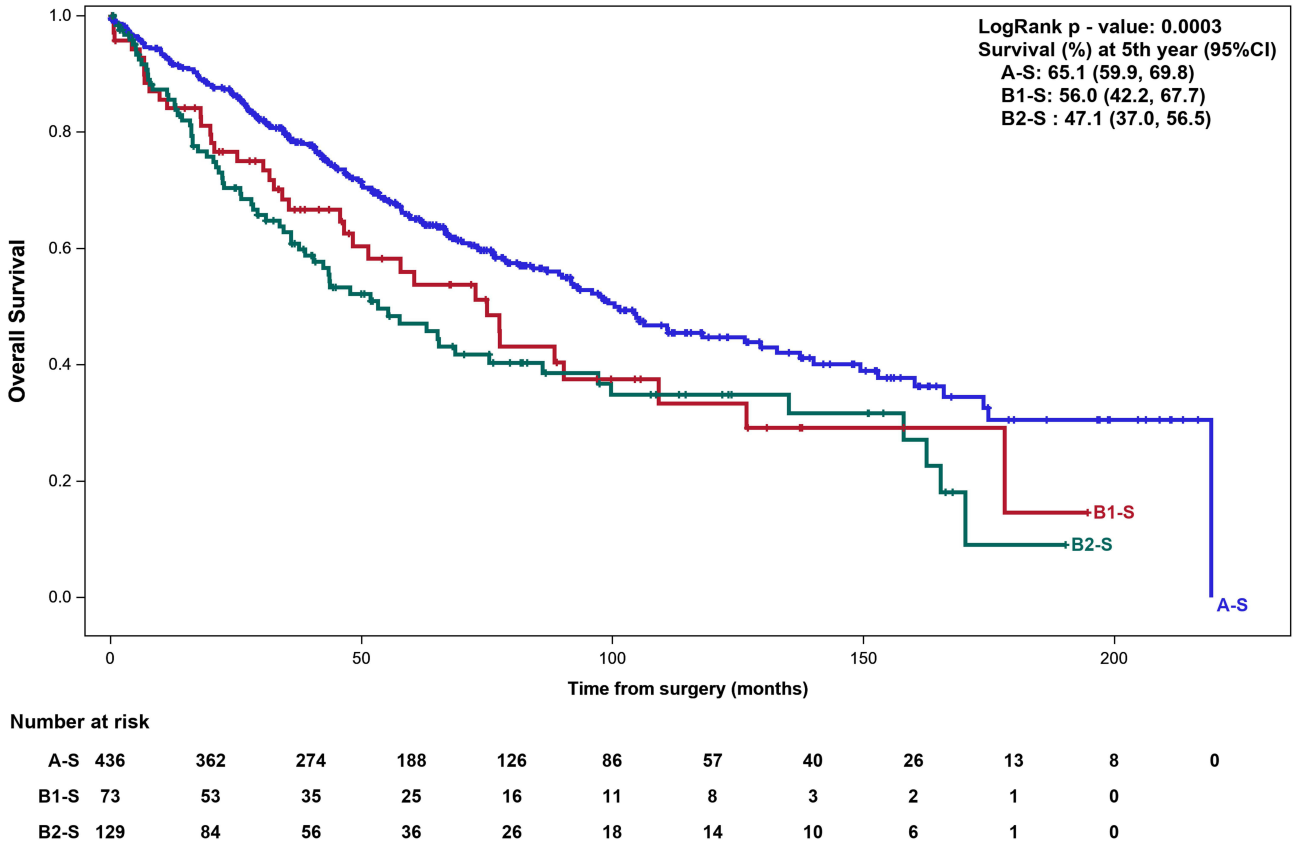

Figure 3 Kaplan Meier curves depicting overall survival analysis of solitary HCC lesions.

Since then, several other groups have emerged with their own classification systems albeit also limited to TACE as a treatment option for intermediate stage disease.[30,31] Notably, the Kinki Criteria by Kudo et al showed comparable survival curves between substage B1 and BCLC stage A after TACE, suggesting that TACE can be performed for a selective subgroup of intermediate HCC disease.[31,32] Scaffaro et al published corroborative findings, showing that survival rates stratified according to the BCLC B substaging differed significantly among subgroups after TACE. In particular, although comparison of mean survival rates between BCLC A and B groups was dismal (38.1 vs 29.0 months), subgroup B1 actually showed comparable mean survival rates to BCLC A patients (33.5 months vs 38.1 months).[13] Similar subclassifications have also been employed to prognosticate other treatment options such as selective internal radiation therapy (SIRT) with Yttrium-90 (Y(). Mathew et al, for instance, showed that the use of Bolondi et al's subclassification system enhanced prognostication after SIRT by reducing clinical heterogeneity. Specifically, the median OS of HCC in substage B1 (48.2 months) was almost twice of that in substage B2 (28.7), demonstrating significant disparity and heterogeneity within BCLC B HCC disease.[33]

Although highlights of recent research have revolved around TACE and SIRT as evident above, there is mounting evidence supporting surgical resections beyond BCLC Stage A.[15,17,29] However, there are no studies to our knowledge that have attempted to incorporate the refined BCLC system as proposed by Bolondi et al[27] to specifically prognosticate various substages within BCLB Stage B after surgical resection.

We believe our study to be the first to have performed survival analysis after surgical resection of HCC stratified by an amalgamation of both the refined BCLC system and location of disease. Importantly, we have shown that unilobar lesions staged BCLC B1 that fall within the "Up-To-7" criteria can be potentially cured with surgical resection, as evidenced by a 5-year OS of greater than 50%, which is comparable to groups A-u and A-b in our study, ie, HCC within the Milan Criteria that underwent resection. Our findings further lend support to a recent RCT by Lei Yin et al, which showed superior 1-, 2-, and 3-year OS after partial hepatectomy (PH) as compared to TACE for HCC outside of Milan

Criteria. Whilst not formally categorised like we have done for our study, it appears on examination of the publication that that the majority of HCC in their study were also within the "up-to-7" criteria.[29] Our findings – based on a much more granular approach – thus serve as an important basis for surgeons to offer surgical resection for patients with BCLC B HCC; and as a basis for future studies to re-evaluate surgical outcomes based on different subgroups of intermediate HCC disease.

In addition, our survival analysis on surgical resections of solitary HCC lesions stratified by size adds to the emerging pool of evidence proposing that larger lesions to be staged as intermediate disease.[20–22] Hitherto, the BCLC stage for solitary HCC remains ambiguous. The original BCLC staging system published in 1999 classified large solitary HCC as Stage A;[4] but the cut-off size of 5cm was later introduced in the revised versions, which then recommended large solitary HCC to be classified either as Stage A or B.[5,34] EASL guidelines classify large solitary HCC lesions as BCLC Stage A and recommend surgical resection for these lesions on the premise that a single tumour regardless of size exhibits a more benign biology, the major caveat being that there must be preserved liver function.[8,35] This is consistent with the revised stance of the BCLC Spanish group recommending for an unresectable single large HCC (poor liver function, unsuitable location) to be classified as Stage B.[5,9,34,36] However, other studies have now shown that larger lesions regardless of liver function correlate to more aggressive tumour with higher incidence of poor differentiation and microvascular invasion.[37,38] This may also be confounded by the epidemiology of hepatitis B (HBV) and C (HCV) infection in Asian and Western countries, where chronic HBV infection is the bigger risk factor for HCC in the former while the latter sees a higher rate of chronic HCV infection in their patients with HCC.[39] Related to this is the observation that patients with HBV infection are more likely to develop larger HCC tumours as compared to those with HCV infection.[40] Therefore, tumour biology is likely to be different between HCC tumours in Asian and Western countries, regardless of whether they are solitary. Hitherto, the recommended treatment for solitary large HCC lesions remain unclear. Although we demonstrated poorer survival outcomes after resecting solitary lesions that are beyond both the Milan and Up-To-7 criteria, Wan et al showed that surgical resections of solitary HCC beyond 5cm conferred superior OS compared to TACE.[21] Nonetheless, we recommend further studies to confirm these findings.

We recognised that HCC is a heterogeneous disease with features unique to different population groups and demographic which has given rise to different consensus guidelines in different parts of the world.[21,41] We recently published real-world data on clinical outcomes adopting an approach of multidisciplinary management combined with decisions made by consensus and with patients exercising considerable autonomy. This single-centre local experience highlights the importance of integrating personalised medicine and multidisciplinary management to optimise outcomes for a heterogenous disease like HCC.[42] Thus, international guidelines should be contextualised to the local context and to the individual patient.

The main limitations of our study are the known biases arising from a retrospective study design. Secondly, a few potential confounders remained unaddressed. In particular, increasing AFP levels relates to more aggressive tumour biology and is known to be an independent predictor of pathological grade, tumour size and prognosis.[43,44] Although a formal multivariate regression analysis was consciously not performed, this has been clearly reflected in Table 1. A regression analysis against Child-Pugh score was also not undertaken since the subgroups were already pre-designed with this variable in mind, taking reference from Bolondi et al's subclassification.[27] Ultimately, while we recognise that there could be residual disease factors that may affect prognosis including extent of tumour differentiation, microvascular invasion and degree of cirrhosis, these are post-resection findings which do not influence the decision for surgical resection. The key focus of this study is to prognosticate survival based on pre-operative variables.

Conclusion

Our study suggests that surgery may be curative in a select subgroup of patients with intermediate HCC that fall outside BCLC Stage A, specifically those with unilobar lesions and are within the "up-to-7" criteria. Furthermore, solitary HCC lesions exhibit different survival outcomes after surgical resection depending on its size, with larger lesions displaying poorer outcomes. Therefore, indications for surgery in selected intermediate HCC should be reconsidered. Ultimately, this also signals a need for more well-conducted randomized trials to better guide treatment options.

Data Sharing Statement

The data that support the findings of this study are not publicly available due to information that could compromise the privacy of research participants but are available from corresponding author upon reasonable request.

Statement of Ethics

This study was approved by the Institutional Review Board (CIRB Ref: 2017-2601) and was conducted ethically in accordance with the World Medical Association Declaration of Helsinki. Exemption from patient consent was granted by IRB as the study only analysed anonymized data collected in the course of clinical service.

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Author Contributions

Pierce K.H. Chow was responsible for the design of the study and for the analysis of data and the writing of the paper. Ian J.Y. Wee prepared the manuscript and conducted the literature searches and literature selection. Fiona N.N. Moe carried out the primary data analysis, Rehena Sultana contributed to the critical reviewing of statistical outcome. Reiko W.T. Ang, Pearly P. S. Quek, Jacelyn S.S. Chua, Ashley W.Y. Ng, Jade S.Q. Goh, Fiona N.N. Moe performed the data acquisiton. All authors contributed to data analysis, drafting or revising the article, have agreed on the journal to which the article will be submitted, gave final approval of the version to be published, and agree to be accountable for all aspects of the work.

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Disclosure

Pierce K.H. Chow declares the following conflicts of interest: Consulting or Advisory Role: Sirtex Medical, Bayer, Roche, New B Innovation, MSD, BTG PLC, Eisai, Abbott, IQVIA, Genentech, L.E.K Consulting, AstraZeneca, Guerbet, Ipsen, OncoSil, Eisai, Worrell, COR2ED and Bristol-Myers Squibb; Speakers' Bureau: Sirtex Medical; Leadership Role and Stock Ownership: AVATAMED (Chief Medical Officer); and Research Funding: Roche, Sirtex Medical, New B Innovation, IQVIA, Genentech, Perspectum, AMiLi, MiRXES and Engine Biosciences. The authors report no other conflicts of interest in this work.

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