Updates in Surgery (2019) 71:285–293
https://doi.org/10.1007/s13304-019-00649-w

ORIGINAL ARTICLE

Surgical and oncological outcomes of hepatic resection for BCLC-B hepatocellular carcinoma: a retrospective multicenter analysis among 474 consecutive cases

Stefano Di Sandro[1] · Leonardo Centonze[1] · Enrico Pinotti[2] · Andrea Lauterio[1] · Riccardo De Carlis[1,3] · Fabrizio Romano[2] · Luca Gianotti[2] · Luciano De Carlis[1,2] · The NTF Research Group

Received: 7 January 2019 / Accepted: 25 March 2019 / Published online: 2 April 2019

Abstract

The Barcelona clinic liver cancer (BCLC) algorithm is the most widely accepted staging system form hepatocellular carcinoma (HCC). Liver resection is traditionally proposed to early stage HCC (BCLC-0/A), even if recent reports have shown that surgical resection could provide a safe and effective treatment also for intermediate-stage HCC (BCLC-B). In this study, we focused on surgical and oncological outcomes of hepatic resection in BLCB-B patients. Patients who received hepatic resection for early- (BCLC-0/A) or intermediate-stage (BCLC-B) HCC in two tertiary hepatobiliary centers between January 2003 and December 2016 were included in study. Four-hundred and twenty-nine patients were included in the analysis. At the time of resection, 298 patients were classified as BCLC-A/0 and 131 as BCLC-B. Despite a higher complication rate in BCLC-B group (49.6% vs 32.9%; $p=0.001$), the incidence of clinically relevant complications did not differ significantly between the two groups (16.0% vs 10.1%; $p=0.079$); moreover, postoperative mortality (4.6% vs 2.7%; $p=0.309$) and relapse-free survival (RFS) were similar between BCLC-0/A and BCLC-B group (1-, 3-, and 5-year RFS: 74, 43, and 31% vs 59, 38, and 34%; $p=0.180$). Overall survival was slightly worse in BCLC-B group (1-, 3-, and 5-year overall survival of 89, 70, and 52% vs. 77, 51, and 44%; $p=0.004$). Focusing on BCLC-B group, a Child–Pugh score B (HR 2.47; $p=0.003$), growing number of nodules (HR 3.04; $p=0.003$), and R1 resection (HR 2.43; $p=0.005$) beard a higher risk of tumor recurrence, while overall survival was negatively affected by the presence of more than two nodules (HR 3.66; $p=0.0001$) and R1 resection (HR 3.06; $p=0.0001$); patients presenting single-large HCC experienced a better overall survival (HR 0.53; $p=0.014$) and lower recurrence-rate (HR 0.60; $p=0.046$). Hepatic resection for intermediate-stage HCC shows acceptable results in terms of perioperative morbidity and mortality, with better oncological outcomes in patients with lower number of lesions despite of their size.

Keywords Hepatocellular carcinoma · BCLC · Liver resection · Liver surgery

NTF (Niguarda Transplant Foundation) Research Group has contributed to the study by data management and statistical analysis.

The members of the NTF Research Group are listed in acknowledgements.

✉ Stefano Di Sandro
stefano.disandro@ospedaleniguarda.it

[1] Department of General Surgery and Transplantation, Niguarda Ca' Granda Hospital, Piazza Ospedale Maggiore 3, 20162 Milan, Italy

[2] School of Medicine and Surgery, University of Milano-Bicocca, Milan, Italy

[3] Department of Surgical Sciences, University of Pavia, Pavia, Italy

Abbreviations

BCLC	Barcelona clinic liver cancer
HCC	Hepatocellular carcinoma
TACE	Transarterial chemoembolization
LT	Liver transplantation
HR	Hepatic resection
RFA	Radiofrequency ablation
CT	Computed tomography
MRI	Magnetic resonance imaging
OR	Odds ratio
HRs	Hazard ratio

Introduction

Hepatocellular carcinoma (HCC) represents the third cause of cancer-related death worldwide, it accounts for 85–90% of primary liver tumors, and it is associated with liver cirrhosis in more than 80% of patients [1, 2].

The Barcelona clinic liver cancer (BCLC) algorithm is the most widely accepted staging system form hepatocellular carcinoma (HCC) [3].

Liver transplantation (LT), radiofrequency ablation (RFA), and hepatic resection (HR) represent potential radical treatments for HCC: RFA feasibility and effectiveness depends on HCC localization and size [4, 5], and LT availability is limited by organ/donor shortage [6, 7]. For these reasons, HR is often the only available option for radical treatment in HCC patients.

Despite HR should be exclusively offered to early stage (BCLC-0/A) HCC according to BCLC algorithm, recent studies have proven its efficacy and safety even for BCLC-B patients [8–10] and other reports have also demonstrated its superiority in comparison with trans-arterial chemoembolization (TACE) [11–13].

In the present study, we retrospectively analyzed surgical and oncological outcomes of HR for BCLC-B patients, considering patients with an early stage (BCLC-0/A) HCC as a control group.

Materials and methods

Study overview

All data were retrieved from two university-affiliated hepato-pancreato-biliary teaching center prospective database, and anonymized prior to analysis.

The study protocol followed the ethical guidelines of the 1975 Declaration of Helsinki (as revised in Brazil 2013).

Local Ethical Committees review of the protocol deemed that formal approval was not required owing to the retrospective, observational, and anonymous nature of this study.

Results are reported according to Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines [14].

Study aim

The primary outcome was to evaluate the surgical and oncological outcomes of HR for BCLC-B patients, considering BCLC-0/A as a control group.

The secondary outcome was to analyze the risk factors for HCC recurrence or death in BLBC-B group.

Study population and definitions

All adult patients (age ≥ 18 years) who consecutively underwent hepatic resection for HCC between January 2003 and December 2016 were evaluated for this study.

As extracted from prospective databases, all tumors were classified according to the 2003 BCLC classification [15], that was followed during data entry until the publishing of the 2018 update [3].

Major hepatectomy was defined as the removal of three or more Couinaud segments.

All postoperative complications were graded according to the Dindo–Clavien classification [16]; clinically relevant complications were defined as Dindo–Clavien grade ≥ 3a.

Overall survival and relapse-free survival were defined as the time between the date of surgery and the date of death or tumor recurrence.

Postoperative mortality was defined as death within 90 days after surgery or before discharge.

BCLC-C tumors, patients with an R2 resection, and patients presenting macrovascular invasion on pathological examination were excluded from the analysis, as well as patients who have received combined hepatectomy and intraoperative ablation.

Pre- and postoperative management

HCC diagnosis was made by computed tomography (CT) or magnetic resonance imaging (MRI) according to EASL guidelines [17], and confirmed by histopathological examination of surgical samples for all patients.

Preoperative liver function was assessed according to the Child–Pugh and MELD scores.

Surgical indication was always discussed in a multidisciplinary team board including hepatologists, oncologists, radiologists, and surgeons.

HR was performed beyond EASL/AASLD recommendations only in patients in whom surgical tumor removal was possible with and estimated risk/benefit ratio in favor of surgery when compared with other available options.

Liver transplantation was excluded in case of HCC extension beyond the up-to-seven criteria [18], advanced age (> 70 years old), or presence of macrovascular invasion.

Postoperative follow-up was carried out according to ESMO/ESDO clinical guidelines [19].

Each recurrence was discussed in a multidisciplinary board to choose the best treatment option, including salvage liver transplantation in selected cases [20, 21].

Table 1 Patient and tumor characteristics

	BCLC-A/0 *N*. 298		BCLC-B *N*. 131		All patients *N*. 429		*p* value
	N	%	*N*	%	*N*	%	
Age > 65	175	58.7	71	54.2	246	57.3	0.383
Male	198	66.4	94	71.8	292	68.1	0.277
Etiology							
HBV	35	11.7	23	17.6	58	13.5	< 0.0001
HCV	158	53.0	44	33.6	202	47.1	
Alcohol	29	9.7	13	9.9	42	9.8	
Alcohol/virus	27	9.1	6	4.6	33	7.7	
Other	49	16.4	45	34.3	94	21.9	
Portal hypertension	77	25.8	37	28.2	114	26.6	0.603
R1	25	8.4	19	14.5	44	10.3	0.054
Splenomegaly	68	22.8	28	21.4	96	22.4	0.741
Child–Pugh A	267	89.9	110	84.0	377	88.1	0.081
MELD ≤ 9	232	77.8	97	74.0	329	76.7	0.390
Platelet count $< 100 \times 10^3/mm^2$	83	28.8	26	20.2	109	26.1	0.063
α-fetoprotein, units/ml [median, (IQR)]	9	4–48	17	5–316	10	5–60	0.057
Bilobar disease	14	4.7	26	19.8	40	9.3	< 0.0001
Major hepatectomy	12	4.0	36	27.5	48	11.2	< 0.0001
Laparoscopic resection	60	20.1	5	3.8	65	15.1	< 0.0001
Pringle maneuver	81	27.2	48	36.6	129	30.1	0.049
CT Scan: number of nodules							
1	262	87.9	75	57.2	337	78.5	< 0.0001
2	29	9.7	42	32.1	71	16.6	
3	7	2.3	6	4.6	13	3.0	
> 3	–	–	8	6.1	8	1.9	
CT scan: size of biggest nodule (cm)							
≤ 2	88	29.5	2	1.5	90	21.0	< 0.0001
> 2–≤ 5	210	70.5	31	23.7	241	56.2	
> 5	–	–	98	74.8	98	22.8	
pT							
1	188	63.1	49	37.4	237	55.2	< 0.0001
2	99	33.2	52	39.7	151	35.2	
3	11	3.7	30	22.9	41	9.6	
Grading							
G1	27	9.2	4	3.1	31	7.3	0.057
G2	162	55.3	71	54.6	233	55.1	
G3	104	35.5	55	42.3	159	37.6	
Presence of microvascular invasion	77	25.8	57	43.5	134	31.2	0.0003

Surgical procedure

All patients received low-molecular weight heparin the day before surgery and 2 g of cefazolin 30 min before skin incision. Surgical procedures were performed both in open and laparoscopic approach, as described elsewhere [22]. In open surgery, the first step to achieve liver isolation was hepatic pedicle suspension on an umbilical cotton tape, while, in laparoscopic surgery, this step was performed only if necessary. Intraoperative ultrasound was systematically performed both in open and laparoscopic surgery to define the limit of parenchymal transection and to assess the vascular anatomy of the liver. After hepatic mobilization, anatomical or non-anatomical

Table 2 Postoperative complications in patients with BCLC A/0 and B HCC

	BCLC-A/0 *N*. 298		BCLC-B *N*. 131		All patients *N*. 429		
	N	%	*N*	%	*N*	%	*p* value
Overall complication	98	32.9	65	49.6	163	38.0	0.001
Clinically relevant complications	30	10.1	21	16.0	51	11.9	0.079
Postoperative mortality	8	2.7	6	4.6	14	3.3	0.309
Complication severity (Clavien–Dindo classification)							
No complications	200	67.1	66	50.4	266	62.0	0.026
Grade 1	21	7.0	11	8.4	32	7.5	
Grade 2	47	15.8	33	25.2	80	18.7	
Grade 3	14	4.7	12	9.2	26	6.1	
Grade 4	8	2.7	3	2.3	11	2.6	
Grade 5	8	2.7	6	4.6	14	3.3	
Operative time (min)							
≤ 180	175	58.9	59	45.0	234	54.7	0.008
> 180	122	41.1	72	55.0	194	45.3	
Length of stay (days)							
≤ 8	167	56.8	46	35.7	213	50.4	< 0.0001
> 8	127	43.2	83	64.3	210	49.6	

resections were performed using Cavitron Ultrasound Surgical Aspiration-irrigation devices (CUSA) and Ligasure sealing devices; hemostasis and cauterization of the raw hepatic surface performed by bipolar forceps and/or prolene 4–5/0 stitches. Intermittent hepatic pedicle clamping (15 min of clamp with 5 min of releases) was used in several cases according to surgeon preference and hepatectomy extension.

Statistical analysis

Differences in the distribution of patients and tumor characteristics according to BCLC classification (A/0 vs B) were evaluated using the Chi-square test.

The relapse-free survival and overall survival functions were estimated using the Kaplan–Meier method.

The log-rank test was used to assess differences between groups.

The hazard ratios (HRs) were estimated using Cox proportional hazards model.

All the analyses were carried out using the SAS software (SAS Institute, Cary, NC).

p values < 0.05 were deemed statistically significant; all reported p values were two-sided.

Results

Study group characteristics

Four-hundred and seventy-four patients underwent hepatic resection for HCC in the two centers between January 2003 and December 2016.

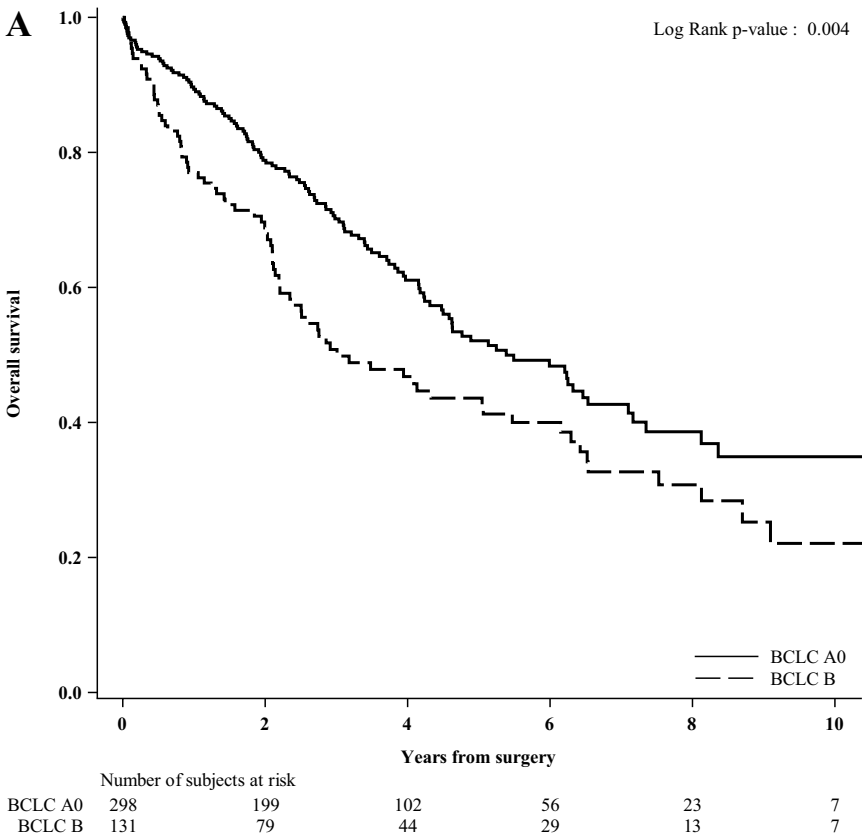
Twenty-five patients were excluded from analysis, because they were classified as BCLC-C, 5 patients were excluded for the presence of macroscopic infiltration of the resection margins (R2), and 15 patients were excluded for detection of macrovascular invasion on resected specimen; 429 patients were finally included in the analysis.

Two-hundred and ninety-eight patients were classified as BCLC-A/0 and 131 as BCLC-B and included in the analysis.

The two groups showed no statistically significant differences in terms of age, gender, preoperative liver function, and a-FP levels, while the number and size of lesions was greater in BCLC-B group ($p < 0.0001$).

Major resections were more frequent in BCLC-B group ($p < 0.0001$), as well as pedicle clamping ($p = 0.049$), while laparoscopic approach was less frequently used ($p < 0.0001$).

At histologic examination, there was no difference in terms of tumor grading, while microvascular invasion was more frequent in BCLC-B group ($p = 0.0003$) (Table 1).



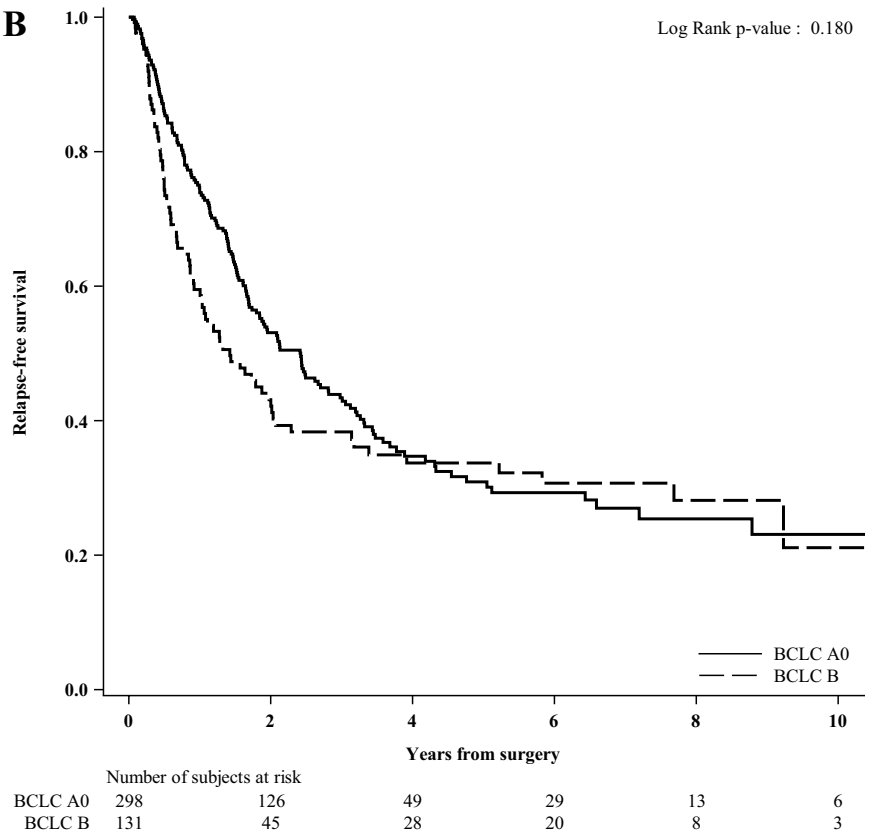


Fig. 1 Relapse-free survival (**a**) and overall survival (**b**) for BCLC-A/0 and BCLC-B patients after liver resection for HCC

Table 3 Cox's regression model for relapse-free and overall survival of BCLC-B patients included in the study

Variable	Levels	*N.*	Overall survival			Relapse-free survival		
			N. deaths	HR (95% CI)	*p* value	*N.* relapses	HR (95% CI)	*p* value
All patients	–	131	79	–	–	79		
Age	≤ 65	60	35	Ref.		38	Ref.	
	> 65	71	44	0.95 (0.61–1.49)	0.834	41	0.79 (0.51–1.23)	0.304
Gender	Female	37	22	Ref.		24	Ref.	
	Male	94	57	0.95 (0.58–1.56)	0.853	55	0.78 (0.49–1.27)	0.332
Child–Pugh	A	110	64	Ref.		65	Ref.	
	B	21	15	3.04 (1.68–5.53)	0.0002	14	2.47 (1.35–4.52)	0.003
MELD score	≤ 9	97	54	Ref.		59	Ref.	
	> 9	34	25	2.26 (1.38–3.70)	0.001	20	1.35 (0.81–2.26)	0.254
α-Fetoprotein	≤ 20	38	21	Ref.		23	Ref.	
	20–400	17	11	1.42 (0.69–2.97)	0.899	13	1.44 (0.71–2.91)	0.314
	> 400	16	11	1.39 (0.67–2.89)	0.771	10	0.97 (0.46–2.03)	0.924
Number of nodules	1	75	42	Ref.		42	Ref.	
	2	42	25	1.43 (0.87–2.36)	0.159	28	1.74 (1.07–2.82)	0.026
	> 2	14	12	3.66 (1.87–7.15)	0.0001	9	3.04 (1.45–6.35)	0.003
Bilobar disease	No	105	61	Ref.		60	Ref.	
	Yes	26	18	1.53 (0.90–2.60)	0.113	19	1.93 (1.14–3.25)	0.014
Size of the biggest nodule	≤ 5 cm	33	22	Ref.		21	Ref.	
	> 5 cm	98	57	0.53 (0.32–0.88)	0.014	58	0.60 (0.36–0.99)	0.046
Resection margins	R0	112	62	Ref.		67	Ref.	
	R1	19	17	3.06 (1.74–5.23)	< 0.0001	12	2.43 (1.31–4.53)	0.005
Microvascular invasion	No	74	45	Ref.		40	Ref.	
	Yes	57	34	0.98 (0.63–1.54)	0.882	39	1.40 (0.90–2.17)	0.139

Intra- and postoperative outcomes

Operative time was longer in BCLC-B group compared with BCLC-A/0 (195 min IQR: 150–255 min vs 170 min, IQR: 130–210 min; $p = 0.0002$).

Despite a higher complication rate in BCLC-B group (49.6% vs 32.9%; $p = 0.001$), the incidence of clinically relevant complications did not differ significantly between the two groups (16.0% vs 10.1%; $p = 0.079$), as well as postoperative mortality (4.6% vs 2.7%; $p = 0.309$).

Moreover, BCLC-B patients experienced a longer postoperative course (10 vs 8 days; $p < 0.0001$) (Table 2).

Survival analysis

The 1-, 3-, and 5-year relapse-free survival was 74, 43, and 31% for BCLC-0/A patients and 59, 38, and 34% for BCLC-B patients ($p = 0.180$) (Fig. 1a).

The 1-, 3-, and 5-year overall survival was 89, 70, and 52% for BCLC-A/0 patients and 77, 51, and 44% for BCLC-B patients ($p = 0.004$) (Fig. 1b).

The median follow-up was 2.9 years (IQR 1.4–5.1) for the entire cohort; 3.0 years (IQR 1.6–5.1) for the BCLC-0/A group, and 2.4 years (IQR 1.1–5.5) for BCLC-B patients.

Subanalysis of BCLC-B group

Prognostic factors affecting relapse-free survival and overall survival in the BCLC-B group were analyzed using univariate Cox-regression models (Table 3).

Analyzing relapse-free survival, growing number of nodules (HR 3.04; $p = 0.003$—Fig. 2), bilobar disease (HR 1.93; $p = 0.014$), CTP-B (HR 2.47; $p = 0.003$), and R1 resection (HR 2.43; $p = 0.005$) were associated with a higher risk of tumor recurrence following resection.

An MELD score > 9 (HR 2.26; $p = 0.001$), CTP-B (HR 3.04; $p = 0.0002$), the presence of more than two nodules (HR 3.66; $p = 0.0001$), and R1 resection (HR 3.06; $p < 0.0001$) negatively affected overall survival.

Notably, the presence of a large (> 5 cm) single lesion showed a protective effect on relapse-free survival (HR 0.60; $p = 0.005$) and overall survival (HR 0.53; $p = 0.014$).

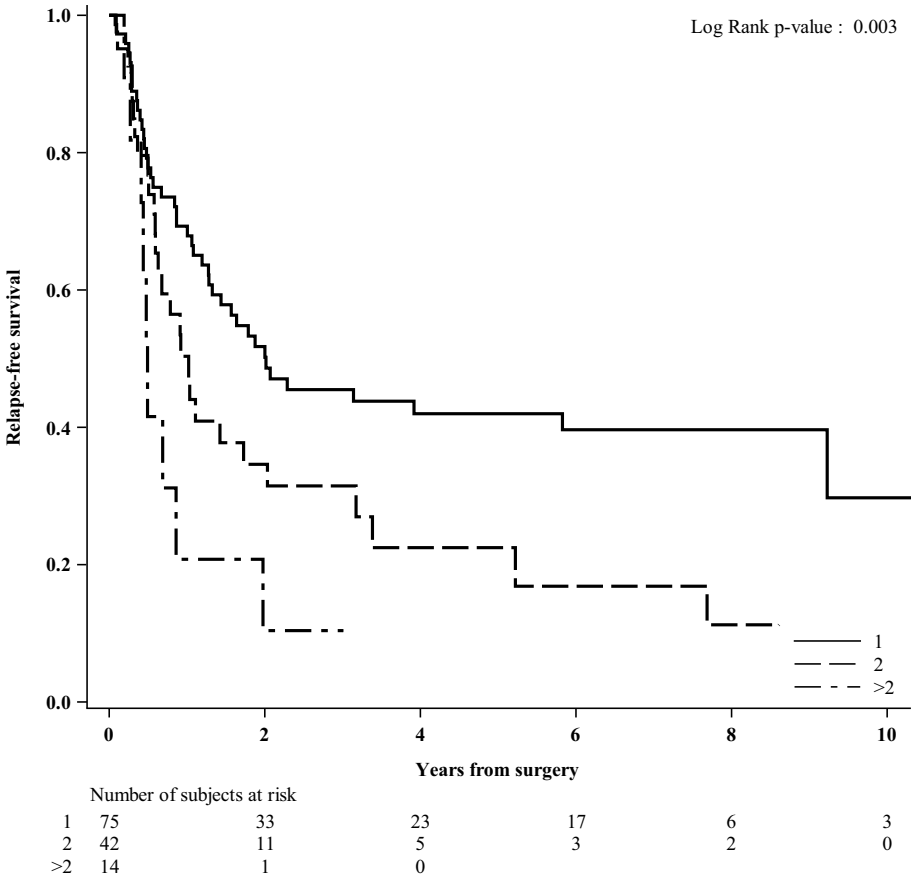


Fig. 2 Relapse-free survival for BCLC-B patients after resection for HCC stratified by number of resected lesions

Discussion

Recent advances in surgical technique, perioperative care, and accurate patient selection have gradually reduced the morbidity and mortality of hepatic resection [23, 24], which has started to be proposed to intermediate-stage HCC with encouraging results in terms of postoperative and oncological outcomes.

In our population, BCLC-B patients presented with more numerous and bigger tumors compared to BCLC-0/A group, which is implicit in the use of BCLC classification, while underlying liver function was similar between the two groups.

Our study highlighted a significantly higher rate of postoperative complications in BCLC-B cohort of patients compared to BCLC-0/A group, which may be justified by the higher rate of major hepatectomies, more frequent pedicle clamping, less use of laparoscopy, and longer operative times for intermediate-stage HCC.

Notably, our analysis did not show any increased risk of clinically relevant complications perioperative mortality despite a longer hospital stay.

These results confirm that surgical resection represent a more complex but still appealing treatment option for BCLC-B patients.

This conclusion is also supported by a large multicenter analysis of 2046 patients carried out by Torzilli et al. [25], which found no difference in postoperative morbidity and mortality between BCLC-0/A and BCLC-B patients.

Focusing on oncological outcomes of our study population, the 1-, 3-, and 5-year relapse-free survival was 74, 43, and 31% for BCLC-0/A patients and 59, 38, and 34% for BCLC-B patients, without any statistically significant difference between the two groups.

These results do not differ from other series where 1-, 3-, and 5-year relapse-free survival for BCLC-B patients range between 60 and 63%, 32 and 38%, and 15 and 30% [8, 12, 25].

On the other hand, 1-, 3-, and 5-year overall survival was 89, 70, and 52% for BCLC-A/0 patients and 77, 51, and 44% for BCLC-B patients, respectively, highlighting only a slightly worse prognosis of BCLC-B group when compared to BCLC-A/0.

Our results are again similar to those from other groups where the reported overall survival for resected BCLC-B ranges between 76 and 88%, 48 and 75%, and 33 and 64% [8, 13, 25–27].

The last part of our study focused on survival analysis of BCLC-B group; the effect of a multifocal and bilobar tumor as well as an R1 resection on relapse-free survival is quite

intuitive and confirms the observations from other authors [28, 29], while the association between a CTP-B and a worse relapse-free survival could be explained by higher tumorigenesis in more advanced stages of liver cirrhosis [30].

Focusing on overall survival, higher MELD and CTP score represented two risk factors for a worse OS, reflecting a higher risk of liver failure and cancer-unrelated death.

Notably, the presence of more than two nodules and R1 resection was associated with a worse overall survival, while a tumor size of more than 5 cm exerted a protective effect.

The main limitations of our study are its retrospective nature and the utilization of the 2003 BCLC classification due to prospective data entry: despite that, the results of subgroup analysis of BCLC-B patients strongly support the recent re-classifications of large uninodular tumors as BCLC-A [3].

In conclusion, hepatic resection for intermediate-stage HCC is a safe procedure with acceptable postoperative morbidity and mortality rates, and should be encouraged in patients with preserved liver function and low number of nodules; importantly, the results of our study support the recent re-classification of large (> 5 cm) single HCC nodules in the BCLC-A subgroup, along with the indication for their surgical resection, as long as a complete (R0) resection could be achievable.

Lay summary for general audience

Hepatocellular carcinoma is the most frequent tumor of the liver. Surgery along with liver transplantation is the best cure for this cancer. Following BCLC guidelines, only patients in early stage should be treated with surgery. However, selected patients with intermediate- or advanced-stage HCC could benefit from surgical treatment.

Acknowledgements We thank the NTF Research Group, Enrico Pinotti MD [MONZA], Laura Benuzzi MD [MILANO], Isabella Pezzoli MD [MILANO], Maria Danieli MD [MILANO], Arianna Ciravegna MD [MONZA]) for its efforts in data managing and statistical analysis. The members of the NTF Research Group are: Tiziana Cena [NOVARA], Vincenzo Bagnardi PhD [MILANO], Laura Benuzzi MD [MILANO], Isabella Pezzoli MD [MILANO], Maria Danieli MD [MILANO], and Arianna Ciravegna MD [MONZA].

Compliance with ethical standards

Conflict of interest The authors certify that there is no conflict of interest with any financial organization regarding the material discussed in the manuscript.

Ethical approval Ethical approval was no necessary because of the retrospective nature of this study.

Informed consent Informed consent was obtained for all the patients enrolled in clinical research studies.

References

1. Bray F, Ferlay J, Soerjomataram I et al (2018) Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin 68:394–424
2. Lafaro KJ, Demirjian AN, Pawlik TM (2015) Epidemiology of hepatocellular carcinoma. Surg Oncol Clin N Am 24:1–17
3. Forner A, Reig M, Bruix J (2018) Hepatocellular carcinoma. Lancet 391:1301–1314
4. Ruzzenente A, Guglielmi A, Sandri M et al (2012) Surgical resection versus local ablation for HCC on cirrhosis: results from a propensity case-matched study. J Gastrointest Surg 16:301–311 **(discussion 311)**
5. Qi X, Tang Y, An D et al (2014) Radiofrequency ablation versus hepatic resection for small hepatocellular carcinoma. J Clin Gastroenterol 48(5):450–457
6. De Carlis L, Di Sandro S, Centonze L et al (2016) Liver-allocation policies for patients affected by HCC in Europe. Curr Transplant Rep 3:313–318
7. Ota K, Teraoka S, Kawai T (1995) Donor difficulties in Japan and Asian countries. Transplant Proc 27:83–86
8. Ho M-C, Huang G-T, Tsang Y-M et al (2009) Liver resection improves the survival of patients with multiple hepatocellular carcinomas. Ann Surg Oncol 16:848–855
9. Garancini M, Pinotti E, Nespoli S et al (2016) Hepatic resection beyond Barcelona clinic liver cancer indication: when and how. World J Hepatol 8:513–519
10. Forner A, Gilabert M, Bruix J, Raoul J-L (2014) Treatment of intermediate-stage hepatocellular carcinoma. Nat Rev Clin Oncol 11:525–535
11. Kapitanov T, Neumann UP, Schmeding M (2015) Hepatocellular carcinoma in liver cirrhosis: surgical resection versus transarterial chemoembolization—a meta-analysis. Gastroenterol Res Pract 2015:696120
12. Jianyong L, Lunan Y, Wentao W et al (2014) Barcelona clinic liver cancer stage B hepatocellular carcinoma: transarterial chemoembolization or hepatic resection? Medicine 93:e180
13. Lin C-T, Hsu K-F, Chen T-W et al (2010) Comparing hepatic resection and transarterial chemoembolization for barcelona clinic liver cancer (BCLC) stage B hepatocellular carcinoma: change for treatment of choice? World J Surg 34:2155–2161
14. von Elm E, Altman DG, Egger M et al (2007) Strengthening the reporting of observational studies in epidemiology (STROBE) statement: guidelines for reporting observational studies. BMJ 335:806–808
15. Llovet JM, Burroughs A, Bruix J (2003) Hepatocellular carcinoma. Lancet 362:1907–1917
16. Dindo D, Demartines N, Clavien P-A (2004) Classification of surgical complications: a new proposal with evaluation in a cohort of 6336 patients and results of a survey. Ann Surg 240:205–213
17. European Association For The Study Of The Liver, European Organisation For Research And Treatment Of Cancer (2012) EASL-EORTC clinical practice guidelines: management of hepatocellular carcinoma. J Hepatol 56:908–943
18. Mazzaferro V, Llovet JM, Miceli R et al (2009) Predicting survival after liver transplantation in patients with hepatocellular

carcinoma beyond the Milan criteria: a retrospective, exploratory analysis. Lancet Oncol 10:35–43
19. Verslype C, Rosmorduc O, Rougier P, ESMO Guidelines Working Group (2012) Hepatocellular carcinoma: ESMO-ESDO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol 23(Suppl 7):vii41–vii48
20. Guerrini GP, Gerunda GE, Montalti R et al (2014) Results of salvage liver transplantation. Liver Int 34:e96–e104
21. Felli E, Cillo U, Pinna AD et al (2015) Salvage liver transplantation after laparoscopic resection for hepatocellular carcinoma: a multicenter experience. Updates Surg 67:215–222
22. Di Sandro S, Bagnardi V, Najjar M et al (2018) Minor laparoscopic liver resection for hepatocellular carcinoma is safer than minor open resection, especially for less compensated cirrhotic patients: propensity score analysis. Surg Oncol 27:722–729
23. Sharma R, Gibbs JF (2010) Recent advances in the management of primary hepatic tumors refinement of surgical techniques and effect on outcome. J Surg Oncol 101:745–754
24. Day RW, Brudvik KW, Vauthey J-N et al (2016) Advances in hepatectomy technique: toward zero transfusions in the modern era of liver surgery. Surgery 159:793–801
25. Torzilli G, Belghiti J, Kokudo N et al (2013) A snapshot of the effective indications and results of surgery for hepatocellular carcinoma in tertiary referral centers. Ann Surg 257:929–937
26. Kim H, Ahn SW, Hong SK et al (2017) Survival benefit of liver resection for Barcelona clinic liver cancer stage B hepatocellular carcinoma. Br J Surg 104:1045–1052
27. Cucchetti A, Djulbegovic B, Tsalatsanis A et al (2015) When to perform hepatic resection for intermediate-stage hepatocellular carcinoma. Hepatology 61:905–914
28. Shah SA, Cleary SP, Wei AC et al (2007) Recurrence after liver resection for hepatocellular carcinoma: risk factors, treatment, and outcomes. Surgery 141:330–339
29. Lafaro K, Grandhi MS, Herman JM, Pawlik TM (2016) The importance of surgical margins in primary malignancies of the liver. J Surg Oncol 113:296–303
30. Di Sandro S, Sposito C, Lauterio A et al (2018) Proposal of prognostic survival models before and after liver resection for hepatocellular carcinoma in potentially transplantable patients. J Am Coll Surg 226:1147–1159