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Curative therapies are superior to standard of care (transarterial chemoembolization) for intermediate stage hepatocellular carcinoma

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Abstract

Background & Aims: The Barcelona Clinic Liver Cancer intermediate stage (BCLC-B) of hepatocellular carcinoma (HCC) includes extremely heterogeneous patients in terms of tumour burden and liver function. Transarterial-chemoembolization (TACE) is the first-line treatment for these patients although it may be risky/useless for

See Appendix for other members of the ITA.LI.CA group.

someone, while others could undergo curative treatments. This study assesses the treatment type performed in a large cohort of BCLC-B patients and its outcome.

Methods: Retrospective analysis of 485 consecutive BCLC-B patients from the ITA.LI.CA database diagnosed with naïve HCC after 1999. Patients were stratified by treatment.

Results: 29 patients (6%) were lost to follow-up before receiving treatment. Treatment distribution was: TACE (233, 51.1%), curative treatments (145 patients, 31.8%), sorafenib (18, 3.9%), other (39, 8.5%), best supportive care (BSC) (21, 4.6%). Median survival (95% CI) was 45 months (37.4–52.7) for curative treatments, 30 (24.7–35.3) for TACE, 14 (10.5–17.5) for sorafenib, 14 (5.2–22.7) for other treatments and 10 (6.0–14.2) for BSC ($P<.0001$). Independent prognosticators were gender and treatment. Curative treatments reduced mortality (HR 0.197, 95%CI: 0.098–0.395) more than TACE (HR 0.408, 95%CI: 0.211–0.789) ($P<.0001$) as compared with BSC. Propensity score matching confirmed the superiority of curative therapies over TACE.

Conclusions: In everyday practice TACE represents the first-line therapy in an half of patients with naïve BCLC-B HCC since treatment choice is driven not only by liver function and nodule characteristics, but also by contraindications to procedures, comorbidities, age and patient opinion. The treatment type is an independent prognostic factor in BCLC-B patients and curative options offer the best outcome.

KEYWORDS

BCLC-B, HCC, intermediate stage, treatment

1 | INTRODUCTION

Hepatocellular carcinoma (HCC) accounts for more than 700 000 deaths per year worldwide and is a leading cause of mortality among cirrhotic patients.[1] In most geographical areas the annual HCC mortality almost equals its incidence, highlighting the high lethality rate of this cancer. The dismal prognosis is because of the frequent detection of HCC at an advanced stage, that precludes access to curative treatments such as liver transplant (LT), hepatic resection or percutaneous ablation techniques.[2]

Two breakthrough advancements have greatly contributed to improving HCC prognosis in recent years: the implementation of surveillance programs with liver ultrasound (US) in patients at risk – which can detect most HCCs at an early stage – and the availability of the Barcelona Clinic Liver Cancer (BCLC) staging system that indicates the first-line therapy for each cancer stage in an evidence-based manner.[3] Indeed, the BCLC staging system is a cornerstone in the management of HCC and, as such, has been endorsed by Western practice guidelines[2, 4] and has inspired the therapeutic recommendations released by the Japanese Society of Hepatology.[5]

However, increasing evidence suggests that the BCLC system is an imperfect tool in selecting the best treatment option for HCC, and the advancements in HCC management prompts the refinement of an algorithm created more than 10 years ago. The current inadequacy of the BCLC staging system is widely perceived so that both Japanese and Italian guidelines propose, instead of a single stage-specific first-line treatment, a "box" of therapeutic options allowing a more flexible and individualized decision,[5, 6] and a number of referral centres report frequent deviations from the BCLC indications.[7–13] The therapeutic boundaries are perceived as especially narrow for the intermediate stage (BCLC B), which includes an extremely heterogeneous population so that the standard-of-care treatment –transarterial chemoembolization (TACE) – may represent an "undertreatment" for some patients and an "overtreatment" for others. In order to overcome this imperfection, a treatment-oriented subclassification of the

Key points

- In clinical practice, the treatment choice for intermediate HCC frequently deviates from Barcelona Clinic Liver Cancer (BCLC) algorithm, that recommends chemoembolization.
- Curative treatments gave better results than chemoembolization in our population of intermediate patients.
- This superiority was confirmed after adjustment for possible confounding factors using multivariate analysis and propensity score analysis.
- For well-selected intermediate patients, curative treatments represent a favourable "treatment migration" phenomenon rather than an "overtreatment".

intermediate stage has been recently proposed by an International panel of experts.[14]

This field-practice study reports the 2000–2012 experience of the Italian Liver Cancer (ITA.LI.CA) group regarding the treatment type and the outcome of patients with a newly diagnosed intermediate stage HCC.

2 | PATIENTS AND METHODS

We retrospectively analysed the Italian Liver Cancer (ITA.LI.CA) database, which includes the prospectively collected data of 5140 patients affected by HCC, consecutively managed at 21 different Italian medical institutions from January 1987 to December 2012. Details on the ITA.LI.CA database have already been reported.[15]

Among the ITA.LI.CA patients, 837 (16.3%) belonged to the intermediate BCLC stage at the time of diagnosis.[2] Of these patients, 485 fulfilled the inclusion criterion of the study, i.e. tumour detection from January 2000 to December 2012 (Figure 1).

Liver cirrhosis was present in 440 patients (90.7%) whereas HCC ensued in the setting of a normal liver in four cases (0.8%), fatty liver in 3 (0.6%), chronic hepatitis in 17 (3.5%), hepatic fibrosis in 3 (0.6%), and other conditions (haemochromatosis and Wilson disease) in 2 (0.4%). In 16 (3.3%) patients, this piece of information was missing. The diagnosis of cirrhosis was based on histology in 57 (11.7%) patients and on clinical, US and endoscopic features in the remaining cases.

Liver disease was considered because of hepatitis C virus (HCV) or B virus (HBV) infection if patients were positive for serum anti-HCV antibody or HBV surface antigen respectively. Cirrhosis was considered because of alcohol if daily alcohol intake was >60 g in males and >40 g in females for >10 years and no other causes of liver damage were identified.

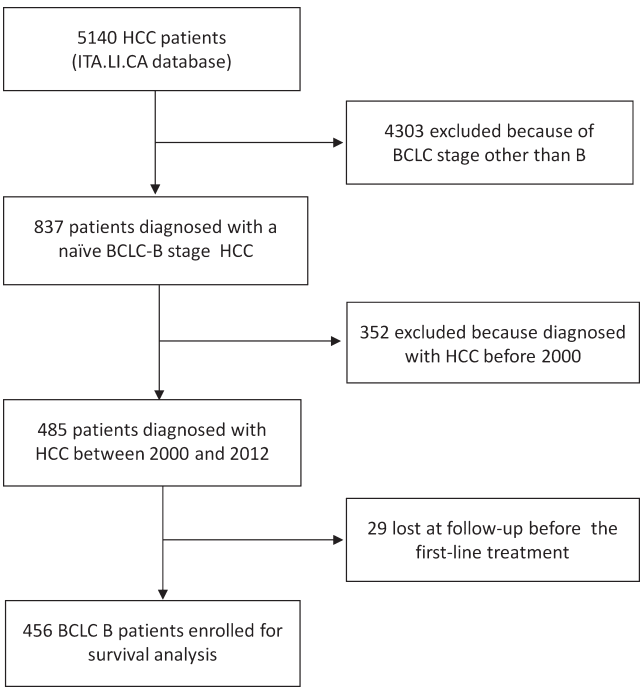

FIGURE 1 CONSORT diagram of the study. ITA.LI.CA, Italian Liver Cancer; HCC, hepatocellular carcinoma; BCLC, Barcelona Clinic Liver Cancer

The diagnosis of HCC was based on histology in 45 (9.3%) patients. In the remaining cases, the diagnosis relied on the radiological criteria at multiphase CT or MRI proposed by the Italian (before 2012), European and American guidelines for the management of HCC.[16–18]

Patients were divided into four treatment subgroups:

1. curative treatments (LT, resection and percutaneous ablation with radiofrequency [RF] or ethanol injection)
2. TACE
3. sorafenib
4. non-evidenced-based treatments such as systemic therapy with doxorubicin or capecitabine (indicated as "other")
5. best supportive care (BSC).

Patients who underwent a combined therapy were included in the group managed with the most effective treatment of the combination, according to the above reported hierarchy. In each centre, treatment decisions were made by a multidisciplinary team, taking into account liver function, tumour burden and location, comorbidities, specific contraindications for each procedure and patient's opinion. We considered the following as alternative treatments to TACE: (i) LT in the setting of a down-staging protocol or a program using expanded selection criteria[18, 19]; (ii) resection for a few nodules in the presence of a preserved liver function [Child-Pugh class A, Model for End-stage Liver Disease (MELD) score ≤10]; (iii) percutaneous ablation (radiofrequency [RF] whenever possible) in patients with non-resectable nodules ≤4 cm and with no more than four lesions; (iv) sorafenib (after 2008) in patients in whom TACE was contraindicated or considered useless because of the presence of a bilobar, disseminated HCC; (v) other treatments or BSC in patients not amenable to (or refusing) TACE and the above mentioned treatments. These selection criteria were followed by all the ITA.LI.CA centres with the exception of the amenability to OLT, which was possible for Barcelona Clinic Liver Cancer intermediate stage (BCLC-B) patients only in the Bologna and Padua centers.[19,20]

Patients were followed with serial out-clinic evaluations, multiphase computed tomography (CT) or magnetic resonance (MR) performed 1 month after each treatment, and repeated at 3–4 month intervals. In the case of cancer persistence/recurrence after treatment, management was decided according to the clinical features of the patient by the local multidisciplinary team for HCC management.

The following variables were also analysed: gender, age, aetiology of liver disease, underling liver disease, type of diagnosis (during/outside surveillance), Child-Pugh and MELD scores, tumour features (size of the largest nodule and number), serum alpha-foetoprotein (AFP), creatinine, blood urea nitrogen (BUN), sodium, bilirubin, albumin, international normalized ratio (INR), aspartate aminotransferase (AST), gamma-glutamiltranspeptidase (GGT), platelets count, ascites, encephalopathy, pain and comorbidities (expressed as Charlson score).[21]

2.1 | Statistical analysis

Continuous variables are expressed as mean±standard deviation (SD) and categorical variables as number of cases and proportions. Variable distribution was assessed by the Kolmogorov–Smirnov test, and continuous variables were compared using the analysis of variance (ANOVA). Categorical variables were compared using Chi-square test with Yates' correction.

Survival was calculated from HCC diagnosis to death or the last follow-up visit and expressed as median and 95% confidence interval (95% CI) estimated as 1.96 × SE.[22] A second survival analysis was performed by censoring patients who underwent OLT as second-line treatment at the time of transplant. Survival curves were generated by using the Kaplan–Meier method and compared with the log rank test.

Cox univariate analysis was carried out to assess the degree of association between survival and the above-mentioned variables. Variables associated ($P \leq .10$) with survival at the univariate analysis were tested with the Cox multivariate regression model. Before entering into the multivariate analysis model, the variance inflation factor (VIF) was calculated to check multicollinearity among variables, and a VIF value <5 was considered indicative of no collinearity. The hazard ratio (HR) and 95% CI were calculated for independent predictors of survival.

Propensity analysis was performed using logistic regression to create a propensity score for patients belonging to the treatment groups showing a significant survival benefit over BSC (curative treatments and TACE). The model was then used to one-to-one match these patients by using the nearest neighbour matching method.[23] This enabled us to test the treatment efficacy in term of survival after adjustment for the confounding factors.

A two-tailed $P < .05$ was considered statistically significant. All statistical analyses were performed using the SPSS 21.0 statistical package (SPSS Incorporated, Chicago, IL, USA).

3 | RESULTS

Demographic and clinical characteristics of patients are summarized in Table 1. The mean age of patients was 67.6±9.4 years and most of them were male. Hepatitis C virus infection was the main cause of liver disease, followed by alcohol abuse. HCC was detected during a surveillance program in 47.9% of patients, and developed in a setting of well-compensated cirrhosis in 55.0% of cases.

Twenty-nine patients (6.0%) were lost to follow-up before receiving the treatment. Of the remaining 456 patients, 233 (51.1%) received TACE, 145 (31.8%) curative treatments (9 LT, 41 resection, 38 RF and 57 ethanol injection), 18 (3.9%) sorafenib, 39 (8.5%) other treatments, and 21 (4.6%) BSC (Figure 2). All non-curative treatments were performed more frequently in tertiary referral centres.

Considering the period 2009–2012, when sorafenib became available in clinical practice, the percentages of patients undergoing TACE, curative approaches, sorafenib, other treatment and BSC were 54.2%, 20.3%, 10.4%, 3.1% and 7.3% respectively.

Best supportive care was associated with the highest prevalence of a poor liver function (Child-Pugh B8-9, $P = .003$).

3.1 | Survival analyses

The median follow-up was 21 months (range: 1–138), during which 152 (21.8%) patients underwent one or more different treatments after the first-line therapy (Table S2). During the follow-up 315 patients died (64.9%). The cause of death was tumour progression in 186 cases (59.0%), liver failure in 23 (7.3%), other tumours in 4 (1.3%), infections in 5 (1.6%), gastrointestinal/peritoneal bleeding in 4 (1.3%), cardiovascular disease in 5 (1.6%), and unknown in 88 (27.9%). No perioperative (90 days) mortality was observed among the 41 patients treated with hepatic resection. The distribution of death causes did not significantly differ among treatment groups ($P = .174$).

Median overall survival (OS) was 31 months (95% CI: 26.7–35.2). Median survival by treatment was: curative, 45 months (95% CI: 37.4–52.7); TACE, 30 months (95% CI: 24.7–35.3); sorafenib, 14 months (95% CI: 10.5–17.5); other treatments, 14 months (95% CI: 5.2–22.7); BSC, 10 months (95% CI: 6.0–14.2). The 1-, 3- and 5-year survival rates were: 90.5%, 63.0% and 37.1% for curative therapies, 89.0%, 39.9% and 11.9% for TACE, 66.6%, 0% and 0% for sorafenib, 57.6%, 11.1% and 5.5% for other treatments, and 45.6%, 15.2% and 0% for BSC (Figure 3 panel A).

As in five patients the retreatment was OLT (three cases after ablative procedures and two after TACE), the survival analyses were repeated in the whole population and in the subgroups of curative and TACE treatment after censoring these five patients at the time of OLT. Median OS for the whole population was 31 months (95% CI: 26.8–35.2), that of the curative group 45 months (95% CI: 38.0–51.9 and that of TACE group 30 months (95% CI: 24.7–35.3). The 1-, 3- and 5-year survival rates were: 90.5%, 62.4% and 36.6% for curative therapies and 88.9%, 39.5% and 11.7% for TACE.

After removing the 29 patients lost to follow-up before receiving treatment, the univariate analysis showed that gender, cirrhosis, Child-Pugh score, MELD score, pain, nodule number >3, and treatment type were associated with survival (Table 2). These variables were tested with the multivariate analysis: gender, cirrhosis, Child-Pugh score, and treatment type were selected as independent prognostic factors. Namely, curative treatments and TACE significantly reduced the mortality risk as compared with BSC, and curative therapies were significantly superior to TACE (Table 2).

Since Child-Pugh score was not available in all patients, we performed a second univariate and multivariate analysis without this variable and MELD score (in order to avoid statistical redundancy) that included bilirubin, albumin, INR, creatinine, ascites and encephalopathy. In this second model gender, cirrhosis, ascites, bilirubin, pain, nodule number >3 and treatment type were associated with survival at the univariate analysis (Table S1). The multivariate analysis selected, as prognosticators, gender, cirrhosis, bilirubin and treatment type.

Moreover, we performed a sensitive analysis (univariate and multivariate) in patients stratified for Child-Pugh class (A or B) and for

TABLE 1 Baseline characteristics of patients

Variable	All patients (n=485)	Curative (n=145)	TACE (n=233)	Sorafenib (n=18)	Other (n=39)	BSC (n=21)	*P* value
Age (years)	67.6±9.4	67.2±9.9	67.1±8.6	66.3±10.3	72.9±8.3	66.2±13.1	.007
Male gender (N, %)	364 (75.0)	117 (32.1)	189 (51.9)	15 (4.1)	26 (7.1)	17 (4.8)	.325
Aetiology[a]							.044
Viral (N, %)	315 (70.1)	104 (33.0)	162 (51.4)	12 (3.8)	26 (8.2)	11 (3.6)	.494
Alcohol (N, %)	87 (19.4)	27 (31.1)	46 (52.9)	0	5 (5.7)	9 (10.3)	.013
Others (N, %)	41 (9.1)	10 (24.5)	20 (48.8)	4 (9.7)	6 (14.6)	1 (2.4)	.122
Diagnosis and management							
Surveillance[b] (N, %)	203 (47.9)	65 (32.0)	116 (57.1)	8 (3.9)	10 (4.9)	4 (2.1)	.031
Liver function							
Child-Pugh class[c]							
A (N, %)	267 (72.2)	89 (33.4)	135 (50.6)	11 (4.0)	24 (9.0)	8 (3.0)	.038
B7 (N, %)	50 (13.8)	10 (20.0)	31 (62.0)	0	7 (14.0)	2 (4.0)	.117
B8-9 (N, %)	53 (14.3)	18 (34)	24 (45.2)	1 (2.0)	2 (3.8)	8 (15.0)	.003
MELD ≤ 9[d] (N, %)	176 (47.3)	66 (37.5)	89 (50.6)	8 (4.5)	9 (5.1)	4 (2.3)	<.0001
Laboratory tests							
AFP[e]							
≤200 ng/mL	314 (80.0)	110 (35.0)	157 (50.0)	12 (3.8)	22 (7.0)	13 (4.2)	.005
>200 ng/mL	79 (20.0)	15 (19.0)	42 (53.2)	2 (2.5)	14 (17.7)	6 (7.6)	.005
Creatinine mg/dL	1.05±0.5	1.0±0.3	1.0±0.7	1.1±0.3	1.2±0.5	1.1±0.4	.430
Sodium mEq/dL	138.6±3.8	137.7±4.2	139.2±3.0	137.2±2.9	138.4±5.7	137.1±3.9	.008
Comorbidities							
Charlson score ≤2 (N, %)	294 (60.6)	104 (35.4)	142 (48.3)	12 (4.1)	28 (9.5)	8 (2.7)	.018
Tumour burden							
Size of largest nodule (cm)	4.5±2.1	4.4±1.9	4.4±2.0	3.9±3.7	5.7±2.0	5.2±2.7	.003
No. of nodules >3[f] (N, %)	342 (73.9)	100 (29.2)	181 (52.9)	13 (3.8)	34 (10.0)	14 (4.1)	.019

HBV, hepatitis B virus; HCV, hepatitis C virus; MELD, model for end-stage liver disease; AFP, alpha-foetoprotein; TACE, transarterial chemoembolization; BSC, best supportive care.
[a]Data available in 449 (98.5%) patients.
[b]Data available in 424 (93.0%) patients.
[c]Data available in 370 (81.1%) patients.
[d]Data available in 372 (81.6%) patients.
[e]Data available in 393 (81.0%) patients.
[f]Data available in 463 (95.5%) patients.

the median value of the Charlson index. The independent prognostic meaning of treatment was confirmed by these subanalyses (*P*<.0001) (data not shown).

3.2 | Propensity score analysis

The propensity score analysis was performed for patients undergoing curative treatments or TACE. Variables entered in the propensity model were: age (cut-off ≤68 years), gender, MELD, AFP > 200 ng/mL, number of nodules >3, and Charlson score (Table 3). This model matched 71 pairs of patients (Table 4). After matching, the median survival remained better in patients undergoing curative therapies than in the TACE group (52 months [95% CI: 45.6–58.3] vs 34 months [95% CI: 29.5–38.5], *P*<.0001), with survival rates at 1, 3 and 5 years of 95.4%, 66.1% and 41.8%, vs 90.9%, 43.3% and 7.5% respectively (Figure 3 panel B).

4 | DISCUSSION

A considerable proportion of HCCs is diagnosed at an intermediate stage and most patients treated for early stage HCC progress to intermediate stage over time. Therefore, the optimal management of intermediate stage HCCs represents an important task for hepatologists. This stage includes patients who may greatly differ for two crucial prognostic and treatment-driving factors, i.e. tumour burden and liver function. Nevertheless, the BCLC system suggests TACE as "one-size-fits-all" treatment for all these patients. Considering the

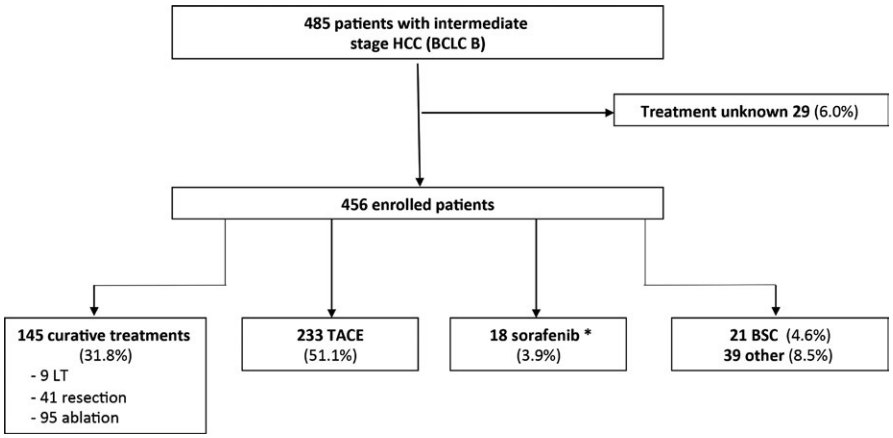

FIGURE 2 Treatment distribution in patients with intermediate stage hepatocellular carcinoma. 24 patients received a combined treatment and were classified according to the most effective therapy of the combination. LT, liver transplant; TACE, transarterial chemoembolization; BSC, best supportive care. *available after 2008

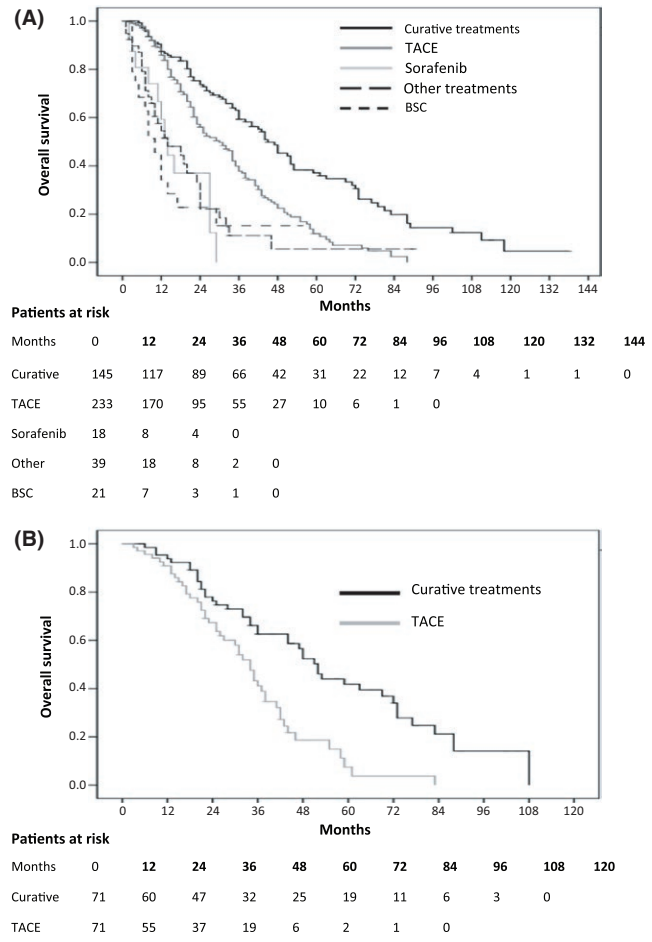

FIGURE 3 Panel A: overall survival by treatments (curative vs TACE: *P*<.0001, TACE vs sorafenib: *P*<.0001, sorafenib vs other treatments: *P*=.815, other treatment vs BSC: *P*=.078). Panel B: overall survival in patients treated with curative therapies or TACE, after matching with the propensity score analysis method

advancement of HCC management in the last years, this indication sounds too restrictive and somehow obsolete. Therefore, it is frequently disregarded in clinical practice[7–12] in favour of a more flexible and individually tailored therapeutic approach.[5, 6, 14]

In addressing this hot topic, we selected patients with: (i) a *naïve* HCC, in order to avoid unintended influences on treatment decision by the response and/or adverse effects of previous treatment(s); (ii) a tumour diagnosed in the new century, in order to explore the modern field-practice management of intermediate stage HCC.

Our study shows that in our country the "real word" management of intermediate stage HCC deviates from the BCLC recommended strategy in an half of cases and, more importantly, that the treatment choice has a paramount importance for the prognosis of these patients. In fact, survival progressively decreased from curative to palliative treatments, with a striking difference between curative approaches and TACE (median survival 45 vs. 30 months, *P*<.0001). Similar results had already been reported by two field-practice single centre studies[7, 13] and our exploratory survey including patients observed from 1987 to 2008.[24] However, all these studies did not adjust the results by potential confounding factors because of a different distribution of several prognostic factors among therapeutic subgroups. Instead, we addressed this bias using several multivariate models and the propensity score analysis, showing that treatment choice maintains its prognostic importance in BCLC B patients even after adjustment for the other variables affecting survival in both Child-Pugh class A and B patients, as well as in patients with comorbidities.

These findings come from a multicentric experience involving institutions with different degrees of expertise in liver disease management. Noteworthy, all non-curative treatments were performed more frequently in tertiary referral centres. This may be attributed to a higher proportion of "fragile" BCLC-B patients gathering in specialized centres and their greater acquaintance with sorafenib use, rather than to a greater adherence to guideline recommendations that, instead, would have resulted in a selective increase in TACE application.

Thus, TACE cannot be considered the first-line treatment for all intermediate HCCs and, whenever specific contraindications are excluded, patients should be addressed towards more radical therapies, such as surgical or percutaneous ablation procedures. This suggestion is indeed supported by several lines of evidence coming from: (i) cohort and propensity–matched studies showing the superiority of surgery over other treatments[25–29]; (ii) cohort studies that tested extended criteria or down-staging strategy aimed at opening LT doors to BCLC B patients[19, 20, 30, 31]; (iii) a randomized controlled trial demonstrating that hepatic resection is superior to TACE in patients with resectable multiple HCCs beyond Milan criteria.[32] Therefore, in well-selected

TABLE 2 Factors associated with survival

Variable	Univariate analysis			Multivariate analysis	
	HR	95% CI	*P* value	HR	95% CI
Treatment					
Best Supportive Care	Reference			Reference	
Other treatments	0.721	0.387–1.344	.304	1.011	0.461–2.220
Sorafenib	0.880	0.411–1.885	.743	0.802	0.293–2.195
TACE	0.349	0.204–0.595	.037	0.408	0.211–0.789
Curative	0.185	0.106–0.324	<.001	0.197	0.098–0.395
Age	1.005	0.993–1.018	.399		
Male Gender	1.335	1.013–1.759	.021	1.502	1.074–2.100
Aetiology	0.963	0.875–1.060	.438		
Viral	1.113	0.862–1.438	.411		
Alcohol	1.124	0.838–1.506	.436		
Others	1.190	0.747–1.897	.465		
Surveillance	1.154	0.910–1.464	.236		
Size of the largest nodule	1.020	0.963–1.080	.503		
Number of nodules >3	1.287	0.959–1.727	.093	1.117	0.787–1.585
Cirrhosis	2.331	1.454–3.735	<.0001	1.957	1.002–3.823
Child-Pugh score	1.052	1.001–1.105	.045	1.275	1.004–1.619
MELD score	1.033	1.009–1.058	.007	0.999	0.950–1.052
AFP mg/dL	1.000	1.000–1.000	.318		
Sodium mg/dL	0.977	0.942–1.013	.203		
Sodium ≤139 mmol/L*	1.152	0.865–1.534	.334		
AST UI/L	0.948	0.960–1.010	.223		
GGT UI/L	1.003	0.988–1.019	.679		
ALP UI/L	0.999	0.989–1.009	.787		
BUN mg/dL	1.004	0.995–1.012	.410		
Platelets	0.999	0.997–1.001	.496		
Charlson score	1.024	0.934–1.124	.611		
Charlson score >2*	1.118	0.874–1.430	.015		
Pain	1.435	0.977–2.109	.066	1.070	0.670–1.707

TACE, transarterial chemoembolization; MELD, model for end-stage liver disease; AFP, alpha-foetoprotein; ALT, alanine aminotransferase; AST, aspartate aminotransferase; GGT, gamma-glutamiltranspeptidase; ALP, alkaline phosphatase; BUN, blood urea nitrogen.

*Median value.

BCLC B patients, surgery and ablative treatment should be considered a possible and favourable "treatment migration" phenomenon rather than an "overtreatment". This phenomenon is not uncommon, occurring in 31.8% of our cases, as well as in 35% and 39% of cases reported by two single centre studies.[7, 13]

On the other hand, TACE may be an "overtreatment" for patients with a high risk of iatrogenic liver decompensation, such as those with a Child-Pugh score >7,[4, 7] severe comorbidities, and those with disseminated nodules, or for patients showing a poor response to this treatment.[33–35] Indeed, our BSC-treated patients more frequently had a Child-Pugh score 8–9, large tumours and comorbid illnesses than those treated with surgery or locoregional therapies. For these patients –representing a minority of BCLC B cases– sorafenib, whenever feasible or BSC may represent the most appropriate first-line therapy and, not an "undertreatment" in a setting where "less is more". The subanalysis of treatment distribution after 2008 reveals that sorafenib almost entirely replaced non-evidence-based therapies.

Our study has several limitations. Firstly, its retrospective nature makes result potentially contaminated by unintended selection biases,

TABLE 3 Characteristics of patients treated with curative approaches (surgery or percutaneous ablation) and transarterial chemoembolization

Variable	All patients (n=378)	Curative (n=145)	TACE (n=233)	*P* value
Age (mean; SD)	67.0±9.1	67.2±9.9	67.1±8.6	.878
Age ≤ 68 (N, %)	208 (55.0)	79 (54.5)	129 (55.4)	.915
Male gender (N, %)	306 (80.9)	117 (80.7)	189 (81.1)	1
Aetiology[a]				.907
Viral (N, %)	266 (72.1)	104 (71.7)	162 (69.5)	.724
Alcohol (N, %)	73 (19.8)	27 (18.6)	46 (19.7)	.893
Others (N, %)	30 (8.1)	10 (6.9)	20 (8.6)	.696
Diagnosis and management				
Surveillance (N, %)	181 (47.9)	65 (44.8)	116 (49.8)	.328
Liver function				
Child-Pugh class[b]				.141
A (N, %)	224 (73.0)	89 (61.4)	135 (57.9)	.357
B7 (N, %)	41 (13.3)	10 (6.9)	31 (13.3)	.058
B8-9 (N, %)	42 (13.7)	18 (12.4)	24 (10.3)	.499
MELD ≤ 9 (N, %)	150 (39.7)	42 (29.0)	108 (46.3)	.009
Laboratory test				
AFP[c]				
≤200 ng/mL (N, %)	267 (82.4)	110 (75.9)	157 (67.8)	.037
>200 ng/mL (N, %)	57 (17.6)	15 (10.3)	42 (18.0)	.037
Comorbidities				
Charlson score ≤2 (N, %)	246 (65.1)	104 (71.7)	142 (60.9)	.035
Tumour burden				
Size of largest nodule (mean, SD)	4.4±2.0	4.5±2.0	4.4±2.0	.767
Number of nodules >3 (N, %)	281 (74.3)	100 (69.0)	181 (77.7)	.069

HBV, hepatitis B virus; HCV, hepatitis C virus; MELD, model for end-stage liver disease; AFP, alpha-foetoprotein; TACE, transarterial chemoembolization; BSC, best supportive care.
[a]Data available in 369 (97.6%) patients.
[b]Data available in 307 (81.2%) patients.
[c]Data available in 324 (85.7%) patients.

such as factors other than those we considered to guide the treatment choice, i.e. the patient opinion, local facilities for specific options and the personal and arbitrary conviction of the HCC team leader. However, our data are in line with those found in single expert centres, where HCC management relies on a specific skill and the availability of all therapeutic options.[7, 13]

Secondly, the therapeutic groups were different for a number of clinical features. Therefore, to overcome this bias, we used the propensity score which is largely used in the literature to simulate random experiments, although this method is not yet universally accepted.[36]

Thirdly, the survival of one-fifth of our patients was the result of the first-line therapy and subsequent different treatments. However, the sequential application of different treatments represents an unavoidable confounding factor for the results coming from both clinical practice and randomized controlled trials.[13]

Fourthly, our results cannot be applicable to patients previously treated for an early HCC that progressed to BCLC B stage since they were obtained in *naïve* BCLC B patients.

Fifthly, the low number of sorafenib-treated cases did not allow us to perform a reliable analysis of sorafenib efficacy, and this may explain the lack of its superiority over BSC.

To conclude, in Italy the modern field-practice approach to patients with a newly diagnosed intermediate stage HCC relies on several therapeutic options, ranging from LT to BSC, in a setting of a *personalized medicine* that takes into account a number of clinical features. Our study indicates that, whenever possible, curative treatments should be preferred to palliative ones, as they offer the best outcome. These results are in line with the "treatment benefit" policy –currently tested only for surgical approaches[37, 38] –and support the recommendation of the Italian Association for the Study of the Liver to consider TACE as the first-line treatment for BLCC B patients

TABLE 4 Characteristics of patients treated with curative approaches and TACE after propensity score match

Variable	All patients (n=142)	Curative (n=71)	TACE (n=71)	*P* value	*d* value
Age (mean, SD)	67.4±9.6	66.6±10.6	68.1±8.4	.338	−.157
Age ≤ 68 (N, %)	70 (49.3)	32 (45.1)	38 (53.5)	.401	−.120
Male gender (N, %)	116 (81.7)	59 (83.1)	57 (80.3)	.829	.052
Aetiology					
Viral (N, %)	99 (70.2)	48 (67.6)	51 (71.8)	.715	−.065
Alcohol (N, %)	30 (21.1)	13 (18.3)	17 (23.9)	.538	−.098
Others (N, %)	10 (7.0)	7 (9.8)	3 (4.2)	.208	.157
Diagnosis and management					
Surveillance (N, %)	59 (41.5)	25 (35.2)	34 (47.9)	.169	−.183
Liver function					
Child-Pugh class					
A (N, %)	100 (70.4)	52 (73.2)	48 (67.6)	1	.087
B7 (N, %)	19 (13.4)	7 (9.8)	12 (16.9)	.217	−.147
B8-9 (N, %)	18 (12.7)	12 (16.9)	6 (8.4)	.211	.181
MELD ≤9 (N, %)	72 (50.7)	36 (50.7)	36 (50.7)	1	.000
Laboratory test					
AFP					
≤200 ng/mL (N, %)	125 (88.0)	62 (87.3)	63 (88.7)	1	−.031
>200 ng/mL (N, %)	17 (12.0)	9 (12.7)	8 (11.3)	1	.031
Comorbidities					
Charlson score ≤2 (N, %)	53 (37.3)	27 (38.0)	26 (36.6)	1	.021
Tumour burden					
Size of largest nodule (mean, SD)	4.1±1.7	4.0±1.7	4.3±1.7	.176	−.176
Number of nodules >3 (N, %)	95 (66.9)	47 (66.2)	48 (67.6)	1	−.021

HBV, hepatitis B virus; HCV, hepatitis C virus; MELD, model for end-stage liver disease; AFP, alpha-foetoprotein; TACE, transarterial chemoembolization; BSC, best supportive care.

not deemed eligible for surgery or ablation by a multidisciplinary HCC team.[6]

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CONFLICT OF INTEREST

None of the authors have a condition that could be construed as a conflict of interest.

ABBREVIATIONS

AASLD, American Association for the study of the liver; AFP, alpha-foetoprotein; ANOVA, analysis of variance; BCLC-B, Barcelona Clinic Liver Cancer intermediate stage; BSC, best supportive care; CI, confidence interval; CT, computed tomography; EASL, European Association for the Study of the Liver; HBV, hepatitis B virus; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; HR, hazard ratio; ITA.LI.CA., Italian Liver Cancer; LT, liver transplant; MELD, Model for End-stage Liver Disease; MR, magnetic resonance; RF, radiofrequency; SD, standard deviation; TACE, Transarterial-chemoembolization; US, ultrasound; VIF, variance inflation factor.

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SUPPORTING INFORMATION

Additional Supporting Information may be found online in the supporting information tab for this article.

APPENDIX

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