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Review Article

Surgery Section

Barcelona Clinic Liver Cancer: A Narrative Review

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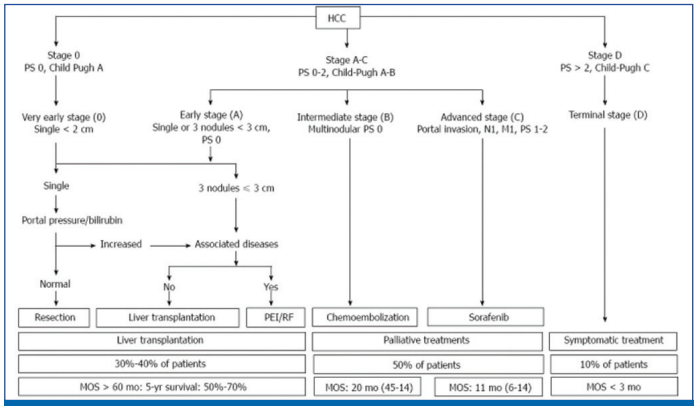
ABSTRACT

To plan therapies for Hepatocellular Carcinoma (HCC), staging methods are necessary. The most often employed HCC management recommendation is the Barcelona Clinic Liver Cancer (BCLC) staging system. Transarterial Chemoembolisation (TACE) is the go-to therapy for BCLC stage B (intermediate HCC). Numerous studies back the use of TACE in individuals with early and advanced HCC. TACE may be an option for individuals who are not candidates for Radiofrequency Ablation (RFA) or Hepatic Resection (HR) for BCLC stage 0 (very early HCC). TACE with RFA offers superior local tumour suppression than RFA alone in BCLC stage. Patients awaiting liver transplants may benefit from TACE as a bridging treatment. When compared to supportive care approaches, TACE improves survival for BCLC-B patients. Patients with BCLC-C stage HCC are treated in the first instance with sorafenib. The combination of sorafenib and TACE has demonstrated efficacy in slowing the development of tumours. Patients with HCC and portal venous thrombosis have superior survival results with TACE combined with radiation. Taking all of these facts into account, it is obvious that TACE, either alone or in conjunction with other therapies, plays a crucial part in the treatment of HCC at every stage. Patients with HCC should get a variety of treatments, and the best TACE candidates should be chosen using a more accurate patient classification approach.

Keywords: Clinical studies, Combinations, Hepatocellular carcinoma, Transarterial chemoembolisation, Trials

INTRODUCTION

The HCC is the fifth most frequent kind of cancer overall, is becoming more and more common among those who have liver cirrhosis [1]. Prognosis for HCC is unique among tumours since it relies on liver function in addition to tumour size [2]. As it combines hepatic function, general health status, and tumour characteristics to create a clinical algorithm, the BCLC staging System is the most widely used model in the world [3]. Notably, the BCLC staging system dictates that the mainstay of therapy for individuals with intermediate HCC is TACE. The use of TACE for patients with early-stage and advanced HCC is being increasingly supported by the available data [4]. Based on the BCLC staging system, this review provides a critical assessment of the information that is currently available about the use of TACE in the management of HCC. The clinical studies reported so far are also highlighted.



[Table/Fig-1]: Updated Barcelona Clinic Liver Cancer (BCLC) staging system and treatment strategy [6].
HCC: Hepatocellular carcinoma; PS: Performance status; PEI: Percutaneous ethanol injection; RF:Radiofrequency ablation; MOS: Performance status

BCLC STAGING SYSTEM

Only BCLC staging divides therapeutic options into the following five disease categories- very early, early, intermediate, advanced, and terminal- has received external validation. Importantly, the BCLC system is preferred for HCC staging, according to the liver expert groups {European Association for the Study of the Liver (EASL) and American Association for the Study of Liver Diseases (AASLD)}, as it helps predict survival outcomes and plan treatment options [5]. Each stage of the illness and the corresponding therapy options according to the BCLC staging system are shown in [Table/Fig-1] [6].

TACE is the recommended course of treatment for intermediate HCCs in the BCLC system. This group of patients exhibits a survival advantage from TACE, as per the BCLC criteria. TACE has, however, been extensively employed in clinical practice for several stages of HCC that go beyond those advised by the BCLC system. The phrase “traditional TACE” typically refers to the use of Lipiodol as an embolic substance, notwithstanding the variety in TACE procedures, chemotherapeutic drugs, and treatment intervals [7]. Lipiodol is used in conjunction with TACE to more effectively administer several anticancer drugs by acting as an embolic agent for microvessels, transporting chemotherapeutic agents, and increasing efflux of drugs into the portal vein [8]. Patients with HCC have another option besides the standard Lipiodol-based treatments: intra-arterial administration of non resorbable microspheres loaded with cytotoxic medications. According to reports, as compared to Lipiodol-based TACE, the amount of chemotherapeutic drugs that reach systemic circulation can be significantly reduced, considerably raising the local drug concentration [9].

Doxorubicin-loaded DEBs outperformed traditional TACE in the Phase-II PRECISION V study, which compared them, and showed a substantial decrease in liver damage and adverse medication reactions. However, no prospective investigation has yet revealed a discernible difference between Lipiodol-based TACE and DEB-TACE in terms of clinical effectiveness [10].

HEPATOCELLULAR CARCINOMA (HCC)

The potential role of TACE in the treatment of HCC is depicted in [Table/Fig-2] [11].

Stage	Potential role of TACE
BCLC 0	When RFA is not practical, TACE may be thought of as a workable substitute therapy for treating solitary HCCs that are 2 cm or less.
BCLC A	1: In the treatment of medium-sized HCC, the combination of TACE with RFA is safe and offers superior local tumour control than RFA alone (3-5 cm).
	2: When treating a large single HCC (> 5 cm), HR offers a superior Overall Survival (OS) rate than HCC, however TACE may be an option if HR is not practical.
	3: Before LT, TACE can be utilised to downstage the tumour according to the Milan criteria or act as a transitional treatment.
BCLC B	1: The recommended course of treatment for patients in this group is TACE.
	2: Better patient survival or local tumour control may result from the combination of RFA and sorafenib with other treatments.
BCLC C	1: When compared to supportive therapy, repeated TACE significantly increased patients' chances of survival with advanced HCC.
	2: There is evidence that sorafenib combined with TACE slows the development of tumours.
	3: Patients with HCC and PVT have greater survival rates when radiation is combined with them.

[Table/Fig-2]: Role of Transarterialchemoembolisation (TACE) in treating HCC [11]. RFA: Radiofrequency ablation; HCC:Hepatocellular carcinoma; BCLC: Barcelona clinic liver cancer; HR: Hepatic resection; LT:Liver transplantation; PVT: Portal venous thrombosis

Very Early Stage HCC (Stage 0)

In this phase, patients have a single tumour that is in situ or is less than two centimeters in diameter. Both the AASLD and the EASL recommend HR or Liver Transplantation (LT) as the first line of treatment for patients with BCLC 0 (EASL) [12]. Inadequate liver function, considerable blood loss, extra damage to the normal parenchyma and a paucity of liver donors are only some of the issues that might prevent certain patients from undergoing HR or LT [13]. Patients in stage 0 who are not good candidates for HR or LT may undergo one of many locoregional ablation treatments. There is consensus that RFA is the therapy of choice for these patients. Some researchers feel that RFA should be considered first for patients with a single 2 cm or smaller HCC, even if surgical removal is an option, because recent findings show RFA is as helpful as HR for micro HCCs in terms of Overall Survival (OS) [14]. RFA may not be theoretically possible in patients with HCCs that are subcapsular, dome-shaped, or located close to the main bile duct or intestinal loop due to the dangers involved, which include intestine perforation, severe bleeding, and bile leakage [15].

Remarkably, TACE was previously only considered in this patient population when HR, RFA, and LT were all impracticable due to various factors. While RFA showed greater tumour response and delayed tumour progression compared to TACE, no statistically significant difference in OS was reported between the two groups in a recent study of stage 0 HCC efficacy by Kim JH et al., [16]. When RFA is not practical, TACE may be regarded as a workable substitute therapy for treating solitary HCCs that are 2 cm or less.

Early Stage HCC (Stage A)

Patients with upto 3 cm nodules or a solitary HCC are included in this stage. Currently, HR is regarded as the gold standard of therapy for early HCCs in patients with well-preserved liver function and no significant lymphatic or vascular involvement. Unfortunately, a lot of patients at this point do not meet the BCLC requirements for HR since HCC typically develops in liver cirrhosis [17]. RFA has been shown to be a first-line therapy option for a single HCC with a maximum diameter of 5 cm which is both safe and effective, as was previously noted [18]. However, it was noted that tumours larger than 3 cm in size showed a substantial rise in the local tumour progression rate, a crucial prognostic indicator for RFA-treated HCC [19]. Particularly, total tumour ablation is seldom achieved. Notably, due to restrictions on the ablation zone, it is uncommon to accomplish full ablation for tumours bigger than 5 cm [20].

Because solitary HCC is classified as an early-stage illness by the BCLC staging system regardless of tumour size, massive single HCCs (>5 cm) without vascular invasion also fall within the BCLC A stage [21]. For a single big HCC, Jin YJ et al., investigated the effects of HR and TACE [22]. Regardless of tumour size, they observed that HR delivered a considerably higher five-year survival rate in the surgical group (65% vs. 17%) than in the TACE group. Comparing the surgical group with the TACE group using propensity score matching, the surgical group had a better five-year survival rate (41.3% vs. 18.5%) in the study by Zhu SL et al., [23]. There have been inconsistent results from the largest study to date, comparing long-term survival after HR and TACE as the first treatment for large solitary HCC (>5 cm), which was conducted recently by Lee YB et al., [24] (159 total patients: 91 patients for HR and 68 patients for TACE). The HR group had a longer Time To Progression (TTP), and their five-year OS rate was higher than that of the TACE group (66% vs. 50%). The OS of TACE patients was equivalent to that of HR patients after propensity score matching (58 pairs), whereas TTP lasted substantially longer in patients receiving HR. Instead of the kind of treatment, changes in baseline patient characteristics may be to blame for the disparity in OS between the two groups. They came to the conclusion that TACE, particularly in individuals with clinically suspected portal hypertension, might be taken into consideration as an alternate first therapy for large solitary HCCs if HR is not practical. It is necessary to examine the long-term effects of HR and TACE in the management of big solitary HCCs in a sizable, randomised, controlled trial.

Patients with cirrhosis and HCC may be chosen for LT on the basis of the Milan criteria (one lesion with a diameter of not more than 5 cm or upto three lesions with a diameter of 3 cm) [25]. But there are much more people seeking liver transplants than there are liver donors. It has been postulated that TACE may be used to downstage a tumour that fits the Milan criteria before transplantation. Additionally, in cirrhotic patients with HCC who meet the Milan criteria, TACE can be utilised as a bridge to LT.

Intermediate HCC (Stage B)

Asymptomatic, massive, or multifocal HCCs without vascular invasion or extrahepatic metastases are considered to be at the intermediate stage. The suggested therapeutic approach for this group of patients is TACE. Based on a meta-analysis of seven studies, it was found that TACE significantly improved 2-year survival relative to optimal supportive treatment (OR=0.53; 95%CI: 0.32-0.89) [26]. However, many patients with early HCCs were included in these trials because patients were not classified according to the BCLC staging criteria [27]. The usefulness of TACE in HCC patients with Child-Pugh class B is therefore very limited because a large number of patients have compensated liver function (Child-Pugh A). The significant population variation in terms of tumour burden, age, liver function, and probable co-morbidities is also one of the major issues with BCLC stage B [28]. However, there is no subgroup categorisation for this stage, making it challenging to offer the best treatment options [29]. TACE is so often employed in clinical settings in contravention of the most recent therapeutic recommendations.

Recently, a number of organisations have suggested patient stratification methods. A subclassification method for intermediate HCC was put out by Bolondi L et al., [30]. The primary determinants in these four-subgroup systems were the Child-Pugh score, the tumour load (within or beyond the up to seven criteria), ECOG performance, portal venous thrombosis, and the first and alternate therapy options offered to each category. The value of these subclassifications was assessed by Ha Y et al., [31]. The median OS for patients in their research who belonged to the B1 and B2 subtypes was 41 or 22 months, respectively. They recommended a modified subclassification approach by integrating the B3 and B4 patients to provide per-subclass-based treatment choices because

they found no difference in survival between the B3 (median OS: 16.6 months) and B4 groups (14.1 months vs. 17.2 months).

Combination Strategies

TACE+RFA: TACE offers a demonstrated survival benefit in patients with intermediate HCC; nevertheless, being a palliative therapy, it does not entirely eliminate the tumour, therefore tumour recurrence is common after treatment. Furthermore, repeated TACE might harm liver health and reduce patient survival. Nevertheless, RFA is able to completely destroy tiny HCCs and is believed to offer superior local disease management than TACE. Complete necrosis rates in patients with intermediate or large HCC range from 29-70%, making RFA ineffective even when used in conjunction with an overlapping approach or numerous surgeries. For intermediate HCC, Tanaka M et al., looked at the long-term consequences of combined therapy [32]. In all, 58 patients with BCLC stage B were included in the research (No vascular invasion or extrahepatic metastases; a single nodule >5 cm in size; two to three nodules, each >30 mm in size; more than three nodules). According to their findings, the combination treatment group had considerably higher 1-, 2-, 3-, and 5-year OS rates than the supportive care group. In prior trials, TACE alone was used to treat patients, although the OS rates for the combination treatment group were generally higher [33]. While large-scale randomised controlled research is needed to evaluate the results of TACE plus RFA with TACE alone, the combination treatment looks to be a safe and effective alternative for patients with intermediate HCC.

Systemic treatment with sorafenib: In BCLC C patients, sorafenib, an oral multikinase tyrosine inhibitor, is the preferred therapy. Independent of the patients' BCLC stage, sorafenib was shown to be safe and effective, according to a subanalysis of the (European Sorafenib Hepatocellular Carcinoma Assessment Randomised Protocol) study [34]. Researchers have shown that sorafenib may help BCLC B HCC patients who cannot get TACE or whose condition has worsened following TACE. If a person does not achieve the therapeutic criteria for a certain stage, the best course of action is to have them move up to the subsequent available therapy level [35]. Sorafenib may be helpful for patients with intermediate HCC who do not react to TACE.

Emergence of sorafenib: Patients who exhibit symptoms, vascular invasion, or extrahepatic spread fall into this group. For advanced HCC, there is no effective systemic treatment, and systemic chemotherapy may possibly have a negative impact on patient survival [36]. Antiproliferative and antiangiogenic effects of the oral multikinase inhibitor sorafenib have become a viable treatment option for advanced HCC treatments in this situation. In the SHARP trial, patients treated with sorafenib had an improved median OS without detectable drug toxicity; this improvement in survival was also seen in the Asian-Pacific population [37]. Sorafenib has now been regarded as the gold standard of treatment for BCLC stage C HCC.

TACE and its combination with sorafenib: The survival advantage following sorafenib treatment is restricted to less than three months, as shown by the aforementioned prior research, which emphasises the need for more effective treatment methods. Given these facts, a number of researchers have claimed that TACE may be advantageous for this patient population. The effectiveness and safety of TACE were examined by Chung GE et al., in patients with HCC who first displayed major portal venous invasion [38]. They demonstrated that both Child-Pugh classes A and B (median OS: 7.4 months vs. 2.6 months) exhibited a substantial survival advantage with repeated TACE in comparison to supportive treatment (median OS: 2.8 months vs. 1.9 months). Furthermore, it has been discovered that, in patients with HCC and extrahepatic dissemination, using TACE to reduce intrahepatic HCC offers survival advantages over conservative care, regardless of the use of sorafenib.

The release of angiogenic growth factors by TACE-induced hypoxia in surviving tumour cells leads to metastasis or tumour recurrence, which worsens the prognosis. Sorafenib has an antiangiogenic impact by inhibiting platelet-derived growth factor receptor tyrosine kinase, vascular endothelial growth factor receptors 2 and 3, and the Raf-MEK-ERK signaling cascade at the Raf kinase level [39]. Therefore, in principle, people with HCC may benefit from a TACE and sorafenib combo. When advanced HCC patients received sorafenib with TACE vs. sorafenib alone, Choi GH et al., compared the time to progression and OS [40]. Their data showed that the median TTP and OS for the combination group were significantly higher than those for the monotherapy group. Hence, adding TACE to standard sorafenib treatment has a proven impact in reducing tumour development in patients with advanced HCC, while the benefit to survival is debatable.

TACE Plus Radiotherapy: Patients with HCC with portal vein thrombosis had better results when TACE and radiation were combined. By maintaining appropriate portal flow and simplifying the eventual treatment of the original tumour, lowering Portal Vein Thrombosis (PVT) with RT can postpone the formation of intravascular tumours and the degradation of liver function [41]. For advanced HCC with portal vein thrombosis, Kim DY et al., recently assessed the effectiveness of TACE with or without RT against sorafenib [42]. Patients were split into three pairings in this single-centre study: TACE vs TACE+RT, TACE against sorafenib, and TACE+RT vs sorafenib. According to propensity score matched analysis, the TACE+RT group outlived the TACE-alone (102 pairs; TTP 8.7 months vs 3.6 months; OS, 11.4 months vs 7.4 months) and sorafenib (30 pairs; TTP, 3.4 months vs. 1.8 months; OS, 5.9 months vs 4.4 months) groups in terms of median time to progression and OS. Concurrent TACE and RT therapy may be an alternative to the currently recommended sorafenib therapy for the treatment of HCC with Portal Vein Thrombosis (PVT), albeit these results need to be confirmed in more randomised controlled studies.

DISCUSSION

Cillo U et al., prospectively included HCC patients for 175 consecutive days had their liver condition staged before starting treatment. Contrary to the BCLC treatment regimen, the quantity and size of nodules were not employed as strict exclusion factors for radical therapy. The Cox model was used to find survival predictors. The average length of survival was 23 months, whereas the Median Survival (MS) times for BCLC categories A, B, C, and D were 53, 16, 7, and 3 months, respectively. In cohort study, BCLC outperformed the Okuda, CLIP, UNOS-TNM, and JIS prognostic algorithms in terms of independent survival prediction (linear trend χ^2=43.01, likelihood χ^2=57.94, AIC 885.98). Furthermore, in surgical patients, the BCLC classification outperformed the AJCC-TNM 2002 system in terms of predictive accuracy. An Italian cohort of HCC patients mostly receiving radical therapy underwent a prospective assessment of the discriminating ability of BCLC staging [43].

Wang JH et al., evaluated the effectiveness of various treatment options for individuals with an initial HCC diagnosis, a retrospective analysis was done. Survival rates and MS times associated with different treatment options were analysed at each BCLC staging using the Kaplan-Meier method and the log-rank test. Total 3892 patients in all were enrolled. At one year, the OS rate was 46.2%, and at five years, it was 16.6%. MS times decreased from 57.7 months in the very first stage to 1.6 months in the very last stage. In very early, early, and even intermediate stages, surgical resection provided the best survival benefit for patients. For a subset of patients who were terminally ill, conformal radiation and TACE had improvements in survival. In conclusion, individuals with HCC who adhered to the prescribed treatment regimens based on BCLC staging had better survival rates [44].

Vitale A et al., measure the survival advantage of resection in comparison to non surgical treatments at each BCLC stage. Researchers identified 2090 BCLC A, B, and C HCC patients using the Italian Liver Cancer (ITA.LI.CA) database; 550 underwent resection, 1046 received Loco-Regional Treatment (LRT), and 494 received the Best Supportive Care (BSC). To compare the MS after resection to the MS after LRT or BSC, a multivariate log-logistic model was used to make the prediction. Net survival advantage of resection was used to represent the findings as follows: (MS resection-MS LRT)/MS BSC. The median net survival advantage of resection versus LRT was as follows after stratifying by BCLC stage: BCLC 0=62% (40%, 82%), A=45% (13%, 65%), B=46% (9%, 76%), and C=16% (55%, 33%). The three primary risk factors for liver resection were a Model for End-Stage Liver Disease (MELD) score >9, Child B class, and Performance Status (PST)=2. Independent of BCLC stage, resection usually provided a significant positive net survival advantage versus LRT for 1181 Child A patients (57%) with MELD 9 and PST 2: BCLC 0=64% (44%, 85%), A=59% (45%, 74%), B=71% (52%, 90%), and C=56% (36%, 78%). Resection did not provide any survival benefit versus LRT among the 909 (43%) patients with at least one risk factor (MELD >9 or PST=2 or Child B class). Regardless of the BCLC stage, resection may improve survival for HCC patients compared to LRT if there is no liver impairment (Child B or MELD >9) and PST >1 [45].

Vitale A et al., developed a prediction model that connects the BCLC stage of HCC patients to their 5-year benefit from LT. Large numbers of consecutive patients with HCC (n=1328) from the ITA.LI.CA database (n=2951) met the criteria for LT according to their age (70 or younger), the absence of relevant extrahepatic co-morbidities, and the lack of macroscopic vascular invasion or metastases. BCLC staging and non LT survival were analysed using Cox univariate and multivariate models with the following covariates: year of diagnosis, age, sex, aetiology of cirrhosis, the model for end-stage liver disease score, alpha fetoprotein concentrations, and therapy. The 5-year life expectancy with a liver transplant (as projected by the Metroticket model) was subtracted from the 5-year life expectancy without a liver transplant based on the BCLC stage to determine the benefit of LT for patients. A total of 1328 patients had a total of 83 (6%) BCLC-0 stage patients, 614 (46%) BCLC-A patients, 500 (38%) BCLC B-C patients, and 131 (10%) BCLC-D patients. Patients with HCC with advanced liver cirrhosis (BCLC stage D) and those with intermediate tumours may benefit from LT regardless of nodule number-size criteria (i.e., Milan criteria) (BCLC stages B-C), provided that there is no macroscopic vascular invasion or extrahepatic disease [46].

Tsilimigras DI et al., stated that BCLC staging approach has been widely used in clinical practice; however, new investigations have questioned the predictive stratification of this categorisation scheme and the indicated therapy allocation of patients with a single big tumour. Patients who had hepatectomy with the purpose of curing histologically proven HCC between 1998 and 2017 were identified using a global multi-institutional database. Patients were evaluated individually and assigned to BCLC stage A1 if they had a single big tumour. A total of 814 patients were divided into 68 (8.1%) BCLC-0, 310 (38.1%) BCLC-A, 279 (34.3%) BCLC-A1, and 157 (19.3%) BCLC-B. Patients with BCLC stage 0, A, A1, and B HCC had five-year OS rates of 86.2%, 69.0%, 56.9%, and 49.9%, respectively (p-value 0.001). Patients with BCLC stage A1 had the lowest OS (p=0.0016) among those with very early-stage and early-stage HCC (BCLC 0, A, and A1). Even after controlling for competing variables, there was no difference in survival between patients having surgery for BCLC stage A1 and B HCC (5-year OS: 56.9% vs. 49.9%) (hazard ratio 0.83, 95% confidence range 0.54-1.28). Patients with BCLC-A1 HCC had a comparable prognosis to those with BCLC-B tumours after having their livers removed. Among a few patients with BCLC-B HCC, surgery produced respectable long-term results. Surgery should not be regarded to be prohibited by stage B of the BCLC out of the gate [47].

Torzilli G et al., indicated that the BCLC categorisation of stage-B and stage-C illness is not a contraindication to employing an algorithm for selecting patients with HCC for surgery. The researchers carried out an anticipatory cohort study. 120 (73.6%) of 163 consecutive HCC patients received surgery, and 113 of those 120 (94.2%) underwent resection. Among the 113 patients, 61 (54%) had BCLC stage 0 or A disease, 24 (21%) had stage-B illness, and 28 (25%) had stage-C cancer. Mortality in hospitals was 0.9%. Major morbidity was 3.5%, and total morbidity was 27.4%. There was no cut-edge recurrence after a median follow-up of 24 months (range, 1-65 months). Three-year OS rates were 81%, 67%, and 74%, respectively, for patients with BCLC stages 0 or A, B, or C illness. Three-year Disease-Free Survival (DFS) rates were 30%, 35%, and 15%, respectively, and three-year hepatic DFS rates were 39%, 44%, and 17%, respectively. If the procedure is strictly guided by stringent intraoperative ultrasonographic supervision, patients with BCLC stage B and stage C HCC can survive HR with low mortality, tolerable morbidity, and survival advantages. These findings should encourage the BCLC guidelines to be updated [48].

Hsu CY et al., in order to enhance the BCLC system's performance, its distribution, determinants, and prognostic influence were studied. A total of 2,381 HCC patients in all were enrolled. According to the Eastern Cooperative Oncology Group scale, performance status was assessed. The Akaike Information Criteria (AIC) were used to examine the predictive capabilities of the original and three modified BCLC systems in HCC patients. Patients with performance statuses of 0, 1, 2, 3, and 4 were divided into 60%, 17%, 11%, 8%, and 4%, respectively. Age, alcoholism, hypoalbuminaemia, hyperbilirubinaemia, renal insufficiency, hyponatraemia, and prothrombin time lengthening were substantially linked with lower performance status. Patients with inferior performance status also had higher tumour burden, worse residual liver function, more frequent vascular invasion, and diabetes mellitus. More frequently, patients with lower performance status received the greatest supporting treatment. Performance status was a standalone prognostic predictor in the Cox proportional hazards model, and long-term survival tended to be poorer in patients with increasingly worse performance status. Among the four BCLC-based staging schemes, reassigning patients with performance status 0 or 1 to stage B produced the lowest AIC [49].

Kim H et al., contrasted surgical resection for BCLC-B HCC to non surgical therapies to establish the benefit of survival. The Korean Liver Cancer Association's national multicentre database was examined. Patients with BCLC-B HCC who were eligible for liver resection as first or second therapy within two years of diagnosis were randomly assigned to have surgery, while those who were not were given other treatments. The survival results of groups with matched propensity scores were contrasted. A total of 887 BCLC-B HCC patients were randomly chosen, 83 got liver resection as the first or second therapy, while 597 received non surgical care. Propensity score matching revealed that the two groups were evenly distributed (80 patients in each group). Patients receiving non surgical therapy had a worse overall MS than those who had resections (50 vs. 22 months, respectively). In the resection group, the 1-, 2-, 3-, and 5-year OS rates were 90, 88, 75, and 63 percent, vs. 79, 48, 35, and 22 percent in the group that underwent no surgery. In multivariable analysis, albumin levels below 3 g/dL (hazard ratio (HR) 1.96, 1.22 to 3.15), and the biggest tumour size higher than 5 cm (HR 1 81, 1.20 to 2.75) were independent predictors of poorer OS. When compared to non surgical therapies, therapy plans for BCLC-B HCC that may be surgically resectable give a survival advantage [50].

Sangro B et al., studied eight European centres looked into the primary prognostic markers influencing survival following radioembolisation utilising yttrium (Yr)-90-labeled resin microspheres in patients with

HCC. A total of 325 individuals received infusions with a median activity of 1.6 GBq between September 2003 and December 2009. These infusions were usually administered to the right lobe (38.5%) or the whole liver (45.2%). A little more than a quarter had intermediate staging (BCLC-B, 26.8%), and more than half had advanced BCLC staging (BCLC-C, 56.3%). The median OS, which varied considerably depending on the illness stage {BCLC A, 24.4 months (95% CI, 18.6-38.1 months); BCLC-B, 16.9 months (95% CI, 12.8-22.8 months); BCLC-C, 10.0 months (95% CI, 7.7-10.9 months)}, was 12.8 months (95% confidence range, 10.9-15.7). ECOG status, hepatic function (Child-Pugh class, ascites, and baseline total bilirubin), tumour burden (number of nodules, alpha-fetoprotein), and the presence of extrahepatic disease all substantially impacted survival, which is in keeping with this conclusion. In the context of BCLC staging, variables representing tumour burden and liver function contributed predictive information. With regard to survival, ECOG status, tumour burden (nodules >5), an international normalised ratio >1.2, and extrahepatic disease emerged as the most relevant independent prognostic factors via multivariate analysis. Fatigue, nausea/vomiting, and stomach discomfort were common side-effects. A 5.8% of patients showed bilirubin elevations of grade-3 or above. At 30 and 90 days, the all-cause death rate was 0.6% and 6.8%, respectively. Strong evidence of the survival attained with radioembolisation is shown by this analysis, including for patients with advanced illness and a few therapy alternatives [51].

Tsilimigras DI et al., established the results and recurrence patterns following resection both within and outside of the existing resection guidelines. A worldwide multi-institutional database was used to find patients who underwent resection for HCC between 2005 and 2017 and fell within the current resection criteria (BCLC-0/A or BCLC-B/C). Patients who underwent HCC resection within and outside of the BCLC recommendations were studied for patterns of recurrence, OS, DFS, and patterns of overall mortality. A 602 (79.5%) of the 756 patients were BCLC-0/A, whereas 154 (20.4%) were BCLC-B/C. Recurrences were primarily intrahepatic (inside BCLC: 74.3% versus beyond BCLC: 70.8%), and BCLC-B/C patients were more likely to have multiple tumours at relapse (69.6% *vs.* 49.4%) and to have recurrences within two years of the initial diagnosis (88.0% versus 75.5%). Annual recurrence in the first postoperative year was 38.3% in BCLC B/C patients and 21.3% in BCLC 0/A patients, respectively; 5-year OS was 76.9% in BCLC 0/A patients and 51.6% in BCLC B/C patients. Only AFP > 400 ng/mL (HR=1.84, 95% CI 1.07-3.15), and R1 resection (HR=2.36, 95% CI 1.32-4.23) were shown to be associated with a greater risk of recurrence among BCLC B/C patients after multivariable analysis. Certain BCLC B/C HCC patients may benefit from surgery and get satisfactory results. The findings emphasise the need of liver-specific monitoring measures, particularly for individuals undergoing resection who do not meet BCLC criteria, as well as the need to further develop the BCLC therapy algorithm [52].

Llovet JM et al., reported a prospective cohort of 22 BCLC patients treated with LDLT between 2001 and 2014 who had extended indications based on size/number (n=17) or downstaging (n=5) of their tumours. The patients' characteristics were as follows: median age, 57 years; male/female ratio, 20/2; Child-Pugh A/B ratio, 16/6; and alpha fetoprotein concentration below 100 ng/mL. Neoadjuvant localised treatments were given to 12 patients. Twelve patients had HCC staging that exceeded the Milan criteria at the time of transplantation, whereas 10 did not. According to pathological findings, 50% of patients had BCLC extended criteria. There was 0% perioperative mortality. The 1-, 3-, 5-, and 10-year survival rates were 95.5%, 86.4%, 80.2%, and 66.8%, respectively, after a median follow-up of 81 months. Overall, seven patients experienced recurrence (range: 9-108 months), and the actuarial recurrence rates at 5 and 10 years. Survival rates for HCC patients treated with expanded LDLT indications may be comparable to those achieved with the Milan criteria, however, these results need to be confirmed [53].

Yang T et al., studied short-terms and long-term outcomes of surgical resection in patients with advanced HCC were evaluated using BCLC staging. Based on a prospectively maintained database, this research comprised 511 Chinese patients with advanced HCC who had surgical resection at a hepatobiliary surgical institution between 2001 and 2007. Evaluations were made of mortality, morbidity, long-term OS, and DFS. Overall morbidity was 31.3%, and hospital mortality was 2.3%. The 1-, 3-, and 5-year OS rates were 69.9, 41.2, and 30.5%, respectively, after a median follow-up period of 27.8 months (range, 0-112 months), whereas the 1-, 3-, and 5-year DFS rates were 48.2, 30.3, and 24.0%. Patients with vascular invasion and/or extrahepatic dissemination had considerably worse 1-, 3-, and 5-year OS and DFS rates than those without these conditions, and patients with biliary invasion had much worse rates than patients without these conditions. Patients with advanced HCC (BCLC stage C) may be candidates for partial surgical resection due to its low mortality, tolerable morbidity, and significant survival advantages. These findings show that BCLC treatment schedule recommendations for advanced HCC need to be reassessed [54].

Chan AW et al., investigated if the albumin-bilirubin (ALBI) grade at the BCLC for HCC may replace the CP score. A cross-national multicentre cohort (n=3696) was assembled in order to evaluate the homogeneity, discriminatory ability, and monotonicity of gradients of the CP-based and ALBI-based BCLC systems. These metrics are represented numerically by homogeneity likelihood, linear trend Chi-squares, and c-indices, respectively. When the ALBI grade was included in the BCLC staging system, it predicted the clinical prognosis of HCC independent of the locations, aetiologies, and available treatments just as well as the CP score did. With a weighted kappa value of 0.917, the BCLC systems based on CP and ALBI were very concordant with one another. Clinical results for each restaged patient were considerably different from those for the individuals who were first staged. In instance, 83 (2.2%) patients with earlier stages of BCLC according to CP criteria were upstaged to ALBI-based BCLC stage-D, where their median OS was just three months. Predictive accuracy of the CP-based and ALBI-based BCLC systems was similar. Moreover, it may allow for better patient selection in clinical studies using systemic agents [55].

Kao WY et al., included 1265 treatment-naive HCC patients with BCLC stage 0 or A from 2007 to 2014 and compared survival rates across stages. Multivariate analysis was used to examine prognostic factors. In substage 0, A1-A4, there were 184, 446, 271, 92, and 272 patients. The prognosis of patients in stages 0 and A1 was comparable after a median follow-up of 21 months. Compared to those in phases A2-A4, they both had considerably greater OS rates. The best rate of OS was achieved with surgical resection, which was followed by TACE, RFA, and other therapies. Resection increased OS rates and decreased recurrence rates, notably in BCLC stages A2-A4 vs patients who received RFA. For early-stage HCC, the BCLC-staging approach offered reliable prognostic classification. Patients with a single tumour bigger than 2 cm who did not have portal hypertension or jaundice had a prognosis similar to that of stage 0 BCLC. In the case of early-stage HCC, curative therapy, in particular HR, is advised [56].

Lin CC et al., examined the effects of RFA with multiple electrodes (ME-RFA) for BCLC grade B and HCC tumours ranging in size from 3.1 to 7.0 cm. This retrospective analysis comprised 70 consecutive patients who underwent ME-RFA with a controller and developed 58 medium-sized (3.1-5.0 cm) and 17 large-sized (5.1-7.0 cm) HCCs. Results in terms of full response, the efficacy of the main approach, local tumour progression, and OS were examined. The rates of full response and Peritumoral edema (PTE) in medium-sized tumours were 79.3% and 91.4% after 1-4 treatments of ME-RFA, whereas in big tumours, they were 76.5% and 94.1%. The risk of significant complications was 5.7% overall. Both the two- and three-year projected OS rates were greater than 80% after a median follow-up of 21 months. Between

medium- and large-sized tumours, as well as between BCLC stages A, B1, and B2, there were no appreciable changes in OS and rates of local tumour progression. The only significant predictor associated with increased survival was a full response to ME-RFA. In conclusion, ME-RFA can successfully treat HCCs that range in size from 3.1 to 7.0 cm, with results that are equivalent for both medium- and large-sized tumours and BCLA stages A to B2 [57].

Tsilimigras DI et al., declared that the only possibly curative therapeutic option for those with HCC is surgery. There is considerable debate about how likely individuals are to be "cured" after undergoing liver resection for HCC. Patients who had hepatectomy with the hope of curing HCC were identified using a worldwide, multi-institutional database. After comparing patients to the general population on the basis of age, race, and sex, a non mixture cure model was used to calculate cure fractions. The median and 5-year DFS among 1,010 patients was 2.8 years and 36.6%, respectively. Following the excision of the HCC, the likelihood of recovery was 42.2%, and recovery took an average of 3.35 years. The preoperative alpha-fetoprotein level, tumour size, tumour number, and margin status were identified by the multivariable cure model as independent predictors of cure. Patients with an alpha-fetoprotein level under 10 ng/mL, the biggest tumour measuring less than 5 cm, three or less nodules and R0 resections had a cure percentage of 61.6%. Patients with all four adverse prognostic markers, such as an alpha-fetoprotein level greater than 11 ng/mL, nodules that are larger than 5 cm, and R1 resection, had a cure fraction of 15.8%. Although patients with BCLC-A had a 47.6% chance of survival, those with BCLC-B HCC had a cure percentage of 37.6%. Among patients with Liver Cancer-B treated at the Barcelona Clinic, only alpha-fetoprotein levels predicted the likelihood of recovery. After liver resection for HCC, around four out of 10 patients might be deemed "cured." Surgery nonetheless offered a good chance of cure among certain patients with BCLC-B HCC, even if cure was more frequently attained following resection for BCLC-A HCC [58].

CONCLUSION(S)

As it divides patients into groups based on outcomes and assigns treatments, the BCLC staging system has been the foundation of HCC treatment techniques. Notably, TACE has been crucial in the management of intermediate HCC despite the significant variability of the HCC patient group with BCLC stage B. TACE has also been employed as an alternate or combination treatment in patients with early or advanced HCC. For the benefit of patients with HCC, many therapeutic approaches should be used. Future research should also improve the patient stratification technique, to choose TACE candidates and determine the best alternative therapies for individuals who do not respond to TACE.

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