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Review

Management of patients with intermediate stage hepatocellular carcinoma

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***Abstract*:** Hepatocellular carcinoma (HCC) causes a significant health burden globally and its impact is expected to increase in the coming years. Intermediate stage HCC, as defined by the Barcelona Clinic Liver Cancer (BCLC) system stage B, represents up to 30% of patients at diagnosis and encompasses a broad spectrum of tumor burden. Several attempts have been made to further subclassify this heterogenous group. The current standard of care recommended by BCLC for intermediate stage HCC patients is transarterial chemoembolization (TACE), with modest outcomes reported. While refinements have been made to TACE technique and patient selection, it remains non-curative. In the real-world setting, only 60% of patients with intermediate stage HCC receive TACE, with the remainder deviating to a range of other therapies that have shown promise in select patient subgroups. These include curative treatments (resection, ablation, and liver transplantation), radiotherapy (stereotactic and radioembolization), systemic therapies, and their combination. In this review, we summarize the classifications and current management for patients with intermediate stage HCC as well as highlight recent key developments in this space.

Keywords: BCLC staging, hepatocellular carcinoma, intermediate stage, locoregional therapy, transarterial chemoembolization

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Introduction

Liver cancer is currently the sixth most common malignancy and second most common cause of cancer-related death globally.[1,2] Its incidence is growing and it is predicted that more than 1 million people will die annually from the disease by 2030.[1] Hepatocellular carcinoma (HCC) is the leading type of primary liver cancer, accounting for more than 90% of cases.[3] HCC has a poor prognosis with an overall 5-year survival of less than 20% and patient survival is determined by disease stage.[4] Several staging systems for HCC have been proposed, which involve simultaneous assessment of tumor extent, liver function, and performance status.[2] The most widely accepted staging system adopted by major liver and oncology societies is the Barcelona Clinic Liver Cancer (BCLC) system.[3,5,6] This review will focus on intermediate stage (BCLC stage B) HCC. Approximately 30% of HCC patients present with intermediate stage disease and treatment in this group has historically been limited to transarterial chemoembolization (TACE).[7,8] In this review, we summarize the classification and current management for this heterogeneous group of patients and highlight key recent developments in this field.

What is intermediate stage HCC?

The tumor burden in intermediate stage HCC can be highly variable (Figure 1). Patients can present with as few as two tumors (with one larger than 3 cm) or up to any number of tumors in the absence of extra-hepatic or vascular invasion. Similarly, the disease may be confined to one to two liver segments or be multi-lobar and widespread. Patients in the intermediate stage are required to have preserved liver function [Child-Turcotte-Pugh (CTP) A or B], and good

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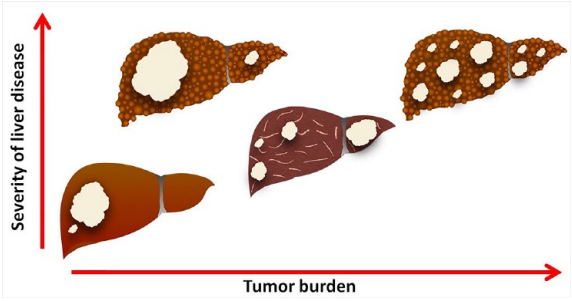

Figure 1. Clinical spectrum of intermediate stage HCC.
HCC, hepatocellular carcinoma.

performance status. More simplistically, these are patients who have disease beyond resectability or Milan liver transplant (LT) criteria (one tumor ⩽5 cm or up to three tumors each ⩽3 cm) but have not yet reached advanced or terminal stages (characterized by macrovascular invasion, metastasis or CTP C). Prognostically, historical cohorts of intermediate stage HCC patients have shown that, without treatment, their 1-year survival is 50% and their median survival is 10 months.[9,10] This has improved slightly due to management and treatment advances; however, there remains considerable heterogeneity, with untreated median survival times ranging from 5 to 25 months between the worst and best intermediate stage patient subgroups.[7] Furthermore, current treatments recommended for patients with intermediate stage HCC are considered to be non-curative.

Other classifications of BCLC-B patients

The aforementioned heterogeneity in the BCLC-B group has made it difficult to study in clinical trials, individualize treatment, and prognosticate.[11] This has led to several attempts to subclassify these patients further (Table 1). The most validated alternative classification is the Bolondi system, which categorizes patients into four groups based on their tumor extent and their CTP score.[7,12–16] This classification has been shown to correspond with prognosis, and suggests different treatment recommendations based on sub-stages B1–4 [ranging from LT, transarterial radioembolization (TARE), systemic therapy, to best supportive care].[7,13,14] The Kinki criteria[17,18] simplifies the Bolondi system by combining the B3 and B4 subgroups and differentiates patients within the BCLC-B class who may be appropriate for a curative approach. These Kinki B1 patients (B1) are recommended for hepatic resection and ablation as first-line therapies alongside TACE.[17,19] The Japanese Society for Transcatheter Hepatic Arterial Embolization system similarly uses tumor burden and CTP status to divide the intermediate stage into three groups.[20,21] None of these sub-staging systems have been adopted internationally.

It has been suggested that Asian patients may require a different staging system to those used in Western countries as the vast majority of HCCs in Asia relate to chronic hepatitis B virus (HBV) infection.[22,23] Asian patients may have less severe underlying hepatic impairment (particularly if they are taking anti-viral therapy), and, therefore, a more aggressive approach to therapy may be appropriate.[22] The most well-validated staging system for Asian patients is the Hong Kong Liver Cancer (HKLC). This recommends resection in a sub-group of Asian patients with BCLC intermediate stage disease (discussed later). HKLC has been shown to be equivalent to the BCLC system in predicting prognosis and marginally superior in terms of real-world clinician adherence to treatment recommendations.[24,25]

Standard management of intermediate stage HCC: TACE

There have been many recent advances in the treatment of HCC, particularly for patients with advanced BCLC-C disease. Although refinements to locoregional therapy have also been made for patients with BCLC-B HCC, TACE remains the first-line treatment prescribed in international guidelines for these patients.[3,5,6] TACE involves intra-arterial infusion of a cytotoxic agent into the feeding arteries of a HCC followed by embolization of those vessels.[26] Its efficacy is mediated through both ischemic and cytotoxic effects on the HCC, with ischemia probably contributing more.[27] Indeed, embolization of the feeding artery without administration of a cytotoxic agent [transarterial embolization (TAE) or so called 'bland-embolization'] has similar efficacy to TACE.[28] Conversely, injection of chemotherapy without embolization appears to be inferior to both TACE and TAE and is not recommended.[29] A range of cytotoxic agents (cisplatin, doxorubicin alone, or doxorubicin in combination with other agents) and embolizing materials (gelatin sponges or polyvinyl alcohol particles) has been used to perform TACE.[26,28,30,31] As such, the approach to TACE can be variable and institution-dependent.[26]

Table 1. Proposed sub-classifications of the BCLC intermediate stage.

		Bolondi system[12]	Kinki criteria[17]	Japanese society for transcatheter hepatic arterial embolization system[20,21]
Components	Tumor burden	Within or outside 'up-to-7' criteria	Within or outside 'up-to-7' criteria	4 lesions of ⩽7 cm criteria
	Liver function	CTP 5–7 or 8–9	CTP 5–7 or 8–9	CTP <9 or 9
Number of subcategories		4 or 5 (B1–4 +/– quasi C)	3/4 (B1–3 with further sub-staged into B3A and B3B)	3
Areas of overlap with BCLC C class		Minor impairments of performance status (B4) Sub-segmental and segmental tumor thrombus (Quasi C)	Not allowed	Not allowed
Demonstrated different prognosis by subclasses		Yes	Yes	Yes
Treatment aim defined by sub-stage		No	Yes – curative or palliative intent	No
First-line treatment recommendation by subclass		Yes	No. Instead lists a range of options	Appropriate or inappropriate for TACE
Other alternative options		Yes		No

BCLC, Barcelona Clinic Liver Cancer; CTP, Child-Turcotte-Pugh; TACE, transarterial chemoembolization.

In 2002, two landmark randomized controlled trials (RCT) were published that reported a benefit of TACE over supportive care for unresectable HCC.[32,33] These positive findings were subsequently confirmed by two meta-analyses,[29,34] and TACE was endorsed by major clinical practice guidelines.[8,35] Although a Cochrane review in 2011 reported no benefit from TACE over no treatment,[36] this meta-analysis has been criticized for including trials that recruited early and advanced stage HCC patients.[37] Across 101 studies of over 10,000 patients, the objective response rate after TACE (defined as either a complete or partial response) is reported to be 52.5% [95% confidence interval (CI): 43.6–61.5].[30] The 1-year and 5-year overall survival (OS) rate after TACE treatment is 70% and 32%, respectively, with a median survival time of 19.4 months (95% CI: 16.2–22.6).

To date, no cytotoxic agent or dose has shown superiority over others; however, lower doses may be associated with fewer side effects.[28] In conventional TACE (c-TACE), cytotoxic agents are usually mixed with an iodinated oily contrast agent known as Lipiodol® (ethiodized oil) which is selectively retained by HCCs and enhances drug delivery into the tumor.[26] Lipiodol® may also act as a microembolic agent for very small tumor vessels.[30] As Lipiodol® is hyperdense, it can mask residual disease vascularity on follow-up computed tomography (CT) imaging.[28,38] In cTACE there is also a delay between the administration of cytotoxic and embolic agents, which may result in a larger volume of cytotoxic drug entering the systemic circulation.[39] To address these disadvantages of cTACE, TACE using drug-eluting beads (DEB-TACE) was developed. This technique involves the administration of microspheres (usually 100–300 μm in size) coated with a macromere most commonly comprised of polyvinyl alcohol.[31] These spheres are loaded with a chemotherapeutic agent (most commonly doxorubicin) and cause simultaneous chemotherapy delivery and vessel embolization.[31,40] DEB-TACE may theoretically allow for higher doses of the chemotherapeutic agent to be administered and a more sustained release to the target HCC.[39,40]

Table 2. Proposed scoring systems to predict TACE response.

	'Six-and-twelve' score[46]	ALBI-TAE[48]	STATE score[51]
Components	Largest tumor diameter (cm) + number of nodules	ALBI grade (0 or 2–3) AFP (⩽200 or >200 ng/ml) Up to 11 criteria	Albumin (g/l) Up-to-7 criteria CRP (<1 mg/dl or ⩾1 mg/dl)
Groups [median survival (months)]	<6–49.1 6–12 to 32.0 >12–15.8	A (score 0) – 65.9 B (score 1) – 30.2 C (score 2) – 17.4 D (score 3) – 6.0	<18–5.3 ⩾18–19.5
Study cohort	24 Chinese tertiary referral centers (n = 1604)	Single Taipei Veterans Hospital (n = 570)	Two Austrian centers (n = 277)
Cohort characteristics	Mean age – 57 years Hepatitis B – 85%	Mean age – 69 years Hepatitis B – 45% Hepatitis C 34%	Mean age – 66.5 years Alcohol – 45% Viral hepatitis – 35%

AFP, alpha-fetoprotein; ALBI, albumin to bilirubin grade; CRP, C-reactive protein.

Despite initial enthusiasm for DEB-TACE, its benefit over cTACE remains controversial. An early RCT of 201 patients found that DEB-TACE resulted in a higher overall response rate in a sub-group of patients with more advanced disease (CTP B, Eastern Cooperative Oncology Group Performance Status 1, bilobar or recurrent disease) and fewer severe adverse events compared with cTACE.[41] A retrospective Korean cohort of 129 patients demonstrated a higher response rate and increased survival in patients with BCLC-B stage disease.[42] However, two subsequent studies (n = 249 and 177) have since failed to demonstrate any benefit of DEB-TACE over cTACE, although both included significant proportions of patients with non-BCLC stage B disease.[43,44] A meta-analysis comparing the two techniques showed a non-significant trend towards increased OS favoring DEB-TACE.[45] Of note, due to significant heterogeneity between studies, it was not possible to compare the techniques in BCLC-B patients specifically in this meta-analysis.[45] It appears that DEB-TACE is at least equivalent to cTACE and may have a benefit in patients with more advanced disease or those at increased risk of side effects. The substantially increased cost of DEB-TACE compared with cTACE is another consideration.

Patient selection for TACE

Due to the heterogeneity of response to TACE, several scoring systems have been proposed to predict patients who are likely to achieve a good outcome (Table 2). The "six-and-twelve" score is derived from the sum of the largest tumor diameter and the number of tumor nodules. Based on this score, patients are divided into three prognostic groups: score less than 6 (median OS 49.1 months), between 6 and 12 (OS 32.0 months), and greater than 12 (OS 15.8 months).[46] The authors suggest that the last group may instead benefit from early introduction of systemic therapy.[47] The ALBI-TAE model[48] is more complex, and categorizes patients into four groups based on albumin-bilirubin (ALBI) grade,[49] alpha-fetoprotein (AFP) and tumor burden as measured by the 'up-to-11' criteria (largest tumor + number of nodules ⩽ 11).[50] This model provides better discrimination than the six-and-twelve score, with the best group having a median OS of more than 5 years and the worst group having OS of 6 months. However, both scores need further validation in other cohorts. The STATE score uses albumin and C-reactive protein levels and tumor burden (within or outside of the up-to-7 criteria) to classify patients into a favorable group (post-TACE median OS of 19.5 months) and an unfavorable group (median OS 5.3 months).[51] Patients in the poor prognostic group (with STATE score <18) were also more likely to experience a grade 3/4 adverse event or die within 3 months following TACE and the number needed to harm from TACE in this group was four.[51] While these scoring systems have a role in defining patients inappropriate for TACE, they do not answer the question of which treatment (TACE or otherwise) is best for intermediate stage HCC patients.

Table 3. Post-TACE treatment models to predict response to repeat TACE.

	ART score[53]	SNACOR model[56]	ABCR score[55]	mHAP-III score[57]
Components	AST 25% increase (4 points) Tumor response (absent = 1 point) CTP increase (1+ = 1.5, 2+ = 3)	Tumor size (<5 cm or ⩾5 cm) Tumor number (<4 or ⩾4) Baseline AFP (<400 ng/mL or ⩾400 ng/mL) CTP (A or B) Response to 1st TACE (CR/PR or SD/PD)	AFP (⩾200 ng/mL = 1) BCLC stage (B = 2, C = 3) CTP increase by ⩾2 (2) Tumor response (present -3, absent = 0)	Tumor number Albumin Bilirubin AFP Maximum tumor size
Groups [median survival (months)]	0–1.5 = 23.7 ⩾2.5 = 6.6	0–2 = 49.8 3–6 = 30.7 7–10 = 12.4	⩽0 = 37.8 1–3 = 17.1 ⩾4 = 7.5	Continuous variable using web-based calculator
Study cohort	Two Austrian centers (*n* = 222)	Two Korean centers (*n* = 485)	Two French centers (*n* = 317)	Two Italian centers (*n* = 385)
Cohort characteristics	Mean age – 64 years Alcohol – 46% Viral hepatitis – 34%	Mean age – 58 years Hepatitis B – 70% Hepatitis C – 13%	Mean age – 68 years Alcohol = 44% Viral hepatitis = 42%	Mean age – 68 years Hepatitis C – 62% Hepatitis B – 15%

AFP, alpha-fetoprotein; AST, Aspartate aminotransferase; BCLC, Barcelona Clinic Liver Cancer; CR, complete response; CTP, Child-Turcotte-Pugh; PD, progressive disease; PR, partial response; SD, stable disease; TACE, transarterial chemoembolization.

Models to assess initial response to TACE and determine if further TACE is appropriate have also been developed (Table 3). On average, the duration of response after initial TACE is roughly 8.5 months before repeat TACE is required.[52] The ART score is calculated based on aspartate aminotransferase increase >25%, radiological tumor response and CTP increase.[53] Patients with a higher ART score (⩾2.5) have reduced OS (6.6 *versus* 23.7 months) and are more likely to experience adverse events after TACE compared with those with lower scores. It can also be applied sequentially prior to a third or fourth TACE to predict good responders.[54] The ABCR score consists of four components (AFP, BCLC stage, CTP, and tumor response) to be calculated prior to the second TACE. Possible scores range from −3 to 6 and patients are separated into three prognostic groups (⩽0 = 37.8 months, 1–3 = 17.1 months and ⩾4 = 7.5 months).[55] Compared with the ART score, the ABCR score was shown to better correlate with prognosis.[55] Other models such as SNACOR and mHAP-III model also assess similar variables.[56,57]

TACE adverse events

In the largest meta-analysis of c-TACE outcomes, the most common adverse events were fever (57% of patients), liver enzyme abnormalities (52%), abdominal pain (42%), fatigue (40%), and nausea and vomiting (34%).[30] This collection of symptoms is often referred to as the post-embolization syndrome, which is thought to be due to systemic cytokine release.[58] More serious adverse effects of c-TACE are less common, but include hepatic artery complications (7.2%), new ascites (6.1%), hepatic decompensation or failure (1.0%), hepatic abscess (0.9%), and acute renal impairment (0.6%).[30] Patients with more advanced liver disease or biliary obstruction are at increased risk of serious complications.[22] Death has been estimated to occur in 0.6% of patients following TACE, with the leading causes being hepatic decompensation, sepsis, and gastrointestinal bleeding.[30] Complication rates between DEB-TACE and c-TACE appear to be similar.[45]

Combination therapies with TACE

The combination of TACE and ablative therapies has also been pursued, especially in patients where a more curative approach to treatment is desired, such as those on the boarder of early and intermediate stage (Bolondi subclass B1) HCC. In a small proof-of-concept study, radiofrequency ablation (RFA) was combined with TACE in 10 patients with multinodular disease with a target lesion greater than 3 cm. This resulted in a complete response in 7/10 patients.[59] In a meta-analysis of six RCTs with 534 patients, the addition of TACE to RFA resulted in significantly improved OS and recurrence-free survival compared with RFA alone.[60] However, it should be noted that

not all of the included studies in this meta-analysis recruited intermediate-stage patients. There is also emerging data to support microwave ablation either alone or in combination with TACE in patients with intermediate stage HCC.[61,62]

To date no adjuvant systemic agent has been shown to consistently improve outcomes above TACE alone in intermediate stage disease, and, as such, their use is not recommended. In an exploratory phase II RCT, sorafenib in combination to DEB-TACE had no impact on time to progression and OS compared with DEB-TACE alone. Concerningly, this approach was associated with a shorter time to "untaceable" progression.[63] A recent multicenter RCT (156 patients, 50% BCLC-B) showed a significantly longer modified progression-free survival (PFS) (25.2 months *versus* 13.5 months) and time to untaceable progression (26.7 *versus* 20.6 months) in favor of TACE plus sorafenib *versus* TACE alone.[64] OS was not analyzed. However, it should be noted that 40% of these patients had previously received TACE (maximum two treatments and none within the last 6 months) and the same beneficial effects of combination therapy on PFS was not seen among TACE naïve patients. A meta-analysis of four other RCTs comparing TACE plus sorafenib with TACE plus placebo similarly revealed a longer time to progression with combination therapy, no impact on OS, and more frequent adverse events.[65] Clinical trials of either bevacizumab or brivanib in combination with TACE demonstrated no impact on OS and increased serious side effects compared with TACE alone.[66,67] Recent promising results from trials of immunotherapy (especially in combination with bevacizumab) in advanced HCC has led to clinical trials investigating this combination as an adjuvant therapy post-TACE [ClinicalTrials.gov identifier: NCT03778957]. The results of these studies are eagerly awaited.[68,69]

Management of intermediate stage HCC: other treatments

Liver resection

Experience with liver resection for intermediate stage HCC comes mainly from Asian countries. As mentioned above, the HKLC system recommends liver resection as first-line therapy for intermediate tumors in patients with CTP A disease (HKLC stage IIb).[70] Liver resection has been shown to be safe and effective in carefully selected patients with preserved liver function, even in the presence of portal hypertension or multiple tumor nodules. A review of 434 consecutive liver resections in a Japanese center reported 5-year OS rates of 58% and 56% in CTP A patients with portal hypertension or multinodular disease, respectively.[71] Comparatively, the 5-year OS rate in patients with CTP B disease was only 19%. In a study of 146 propensity score matched patients from Taiwan with HCC beyond Milan LT criteria, those who received surgical resection were shown to have better 5-year survival compared with those who underwent TACE.[72] A meta-analysis of 18 studies comparing resection with TACE similarly found significantly improved 1- and 5-year OS rates of 84% and 45% *versus* 68% and 23%, respectively, favoring resection.[73] However, this study has been criticized for including trials which recruited patients with large solitary HCCs within the intermediate stage.[74] A series of 2046 patients (737 BCLC-B) undergoing liver resection across 10 centers from "both East and West" reported similar 1- and 5-year survival for BCLC-B patients (88% and 57%, respectively).[75] Independent factors found to be predictive for reduced survival were impaired liver function, tumor size >5 cm, and the presence of macrovascular invasion. Notably, tumor multiplicity was not a significant predictor, suggesting that surgery still has a role in the patients with multifocal disease as long as the aforementioned adverse prognostic factors are absent. Clearly, resection is feasible (and curative) for a subset of BCLC-B patients with CTP A cirrhosis. More studies are needed, particularly in Western patients, to see if this approach can be generalized.

Liver transplantation

Although intermediate stage HCC is classified by BCLC as beyond (Milan) LT criteria, transplantation may still have a role through newer expanded LT criteria and the use of downstaging.

Expanded criteria. Since the original Milan criteria was established in 1996, several more liberal LT criteria have been proposed. The University of California, San Francisco (UCSF) liver cancer system allows for a single tumor $\leqslant 6.5$ cm or up to three tumors $\leqslant 4.5$ cm in size and a total tumor diameter $\leqslant 8$ cm in the absence of macroscopic vascular invasion or extra-hepatic spread to be considered for LT.[76] These expanded criteria resulted in a 1- and 5-year post-LT survival of 90% and 75%, respectively. These are comparable with

outcomes from transplanting with the Milan criteria, but, importantly, allow for a 10% increase in the number of HCC patients eligible for LT.[77] The up-to-7 criteria (diameter of largest lesion + number of lesions add up to seven or less in the absence of vascular invasion) was developed after analysis of 1556 patients transplanted for HCC in 36 centers worldwide. This also showed similar 5-year post-LT survival compared with transplanting within the Milan criteria (71.2% *versus* 73.3%).[15] Most recently, this model was further refined to include AFP to create a new prediction model (Metroticket 2.0), which identifies patients who would have a >70% post-LT 5-year survival. This model was shown to be superior at predicting 5-year post-LT survival compared with the three other criteria mentioned above.[78] Thus, a BCLC-B patient previously deemed to be ineligible for LT due to tumor burden in excess of the Milan criteria may now fulfil the Metroticket 2.0 criteria and safely undergo LT.

Downstaging. Downstaging refers to treatments administered with the aim of reducing HCC tumor burden to fall within LT criteria.[79] Selecting which intermediate stage HCC patients to attempt downstaging is difficult. The original UCSF protocol included patients with either one lesion >5 cm, 2–3 lesions >3 cm but ⩽5 cm or 4–5 lesions each ⩽3 cm, all with a total tumor diameter ⩽8 cm.[80] In their study, 70% of patients were successfully downstaged to within Milan criteria, and 86% underwent transplantation (after a minimum wait of 3 months after downstaging) with excellent 1- and 4-year survival rates of 96% and 92%, respectively.[80] An initial AFP level of greater than 1000 ng/ml was predictive of downstaging failure. These criteria were further validated in larger cohort which showed similar 3-year post-LT survival compared with patients transplanted within traditional Milan criteria (79% UCSF *versus* 83% Milan) at the cost of a slightly higher rate of HCC recurrence (13% UCSF *versus* 7% Milan).[81] Elevated baseline AFP (>100 ng/ml) and shorter duration (<12 months) on the waiting list after successful downstaging were predictive of post-LT recurrence, reflecting that it is not only tumor volume but also tumor biology that determines the most appropriate LT candidates.[81]

Multipolar radiofrequency ablation

Multipolar RFA has been described as alternative technique for treating large lesions (up to 8 cm) and involves the insertion of three separate ablation probes within the same lesion.[82] In a small retrospective study, lesions greater than 5 cm (median size 57 mm) were treated in 27 patients using this technique and resulted in an initial complete response rate of 81%. This technique universally resulted in a post-ablation syndrome but was otherwise relatively safe. Multipolar RFA has been shown to be superior to monopolar RFA in tumors between 25 mm and 45 mm in terms of less residual disease and fewer local recurrences.[83] Although these results need to be replicated in larger studies, they could suggest that multifocal RFA may have a role in carefully selected intermediate stage patients with low tumor burden (e.g., two tumors with one >3 cm), especially in those deemed not suitable for resection or LT.

Transarterial radioembolization

TARE (also referred to as Selective Internal Radiation Therapy) is another alternative therapy for intermediate stage HCC. TARE is a form of brachytherapy where microspheres (either glass or resin) loaded with radioactive isotopes are injected intra-arterially in the feeding vessels of a HCC.[84] Yttrium-90 (^{90}Y) is the most commonly studied and used radioisotope; however, other isotypes (holmium-166 and iodine-131) have been trialled. Up to 15–20% of patients are ineligible for TARE due to significant arteriovenous shunting.[26,85] The microspheres used in TARE are much smaller than those used in TACE (30 μm *versus* >100 μm). Thus TARE does not assert its efficacy by creating ischemia from vessel occlusion. It can be administered either in a lobar or whole liver fashion in the case of bilobar or multifocal disease. ^{90}Y has a short half-life and short tissue penetration, meaning a relatively high dose of internal radiation can be administered locally to the target lesions.[84] Almost all of the radiation is delivered within the first 2 weeks but the maximal radiological response may not be apparent until 3–6 months after treatment.[84]

There is a lack of high-quality evidence comparing TARE with TACE, particularly in patients with intermediate HCC. It has been estimated that a non-inferiority RCT would require at least 1000 patients enrolled to be sufficiently powered.[26] In a small randomized trial (n = 45), TARE demonstrated longer time to progression (>26 *versus* 6.8 months) but similar OS (18.6 *versus* 17.7 months) and safety profile compared with c-TACE.[86] Two large real-world TARE cohort studies have reported median OS in BCLC-B

patients to be numerically similar to those seen in TACE cohorts.[87,88] In a prospective cohort of 86 patients with intermediate stage HCC undergoing locoregional therapy, TARE-treated patients had a similar median OS compared with TACE-treated patients (16.4 *versus* 18 months, respectively) despite having objectively greater tumor burden in the TARE group.[89] A subsequent meta-analysis of comparative trials between TARE *versus* TACE across all stages of HCC also demonstrated similar OS.[90] It is also recognized that TARE (but not TACE) may, in addition to treatment of the targeted tumor, cause hypertrophy of the contralateral (untreated) liver lobe, and, hence, help facilitate subsequent liver resection if appropriate.[91]

TARE has a similar side effect profile to TACE, with the addition of radioembolization induced liver injury, which typically occurs 4–8 weeks after radioembolization. This is characterized by jaundice and ascites with mild transaminase derangements.[26,92] The frequency of grade 3/4 hyperbilirubinemia varies from 5 to 15% within TARE studies[87,93] and its risk likely relates to the severity of the underlying liver disease. Compared with TACE, TARE has lower rates of post-procedural abdominal pain, vomiting, and fatigue.[89,90] However, TARE is substantially more costly than TACE.[94]

Systemic therapy

First line. Lenvatinib has recently been proposed as first-line therapy prior to TACE in patients with intermediate stage HCC. In a proof-of-concept retrospective study, 30 patients with intermediate Bolondi B2 disease (CTP A cirrhosis and tumor burden outside the up-to-7 criteria) treated with lenvatinib (15/30 were part of a clinical trial) were propensity matched with 60 patients who underwent c-TACE.[95] Lenvatinib-treated patients exhibited significantly better progression-free survival (16.0 *versus* 3.0 months), objective response rates (73.3% *versus* 33.3%), and OS (37.9 *versus* 21.3 months) compared with c-TACE-treated patients, respectively. Furthermore, two (7%) lenvatinib-treated patients achieved significant disease downstaging to allow for curative therapy (resection and ablation) compared with none in the c-TACE group. These results should be interpreted with caution since propensity score matching does not substitute for a well-conducted RCT, and patient selection biases almost certainly exist in both groups. However, these results are promising, and, if replicated in a large RCT, they would challenge the primacy of TACE in this subgroup of intermediate disease patients.

TACE refractory disease. TACE has been shown to lose effectiveness with each subsequent treatment.[96] Although many criteria have been proposed, no unified definition of TACE failure or refractoriness currently exists. Several studies have assessed the use of systemic therapy in patients with TACE-refractory intermediate disease. In a retrospective study of 56 patients, those who were switched to sorafenib instead of repeated TACE had longer median time to progression to advanced stage (26.7 *versus* 7.9 months) and improved OS (25.4 *versus* 11.5 months).[97] These findings were confirmed in a second retrospective cohort.[98] Of note, in both these series, the survival after commencement of sorafenib was better than what was initially demonstrated in RCTs of patients with advanced disease suggesting that early introduction after onset of TACE refractoriness may be advantageous. RCTs to determine the best therapy for intermediate stage TACE-refractory patients are clearly needed.

Radiotherapy

Technological advancements in external beam radiotherapy has led to the development of stereotactic body radiotherapy (SBRT), which can deliver high-dose radiation accurately in a small number of fractions to HCCs with acceptable damage to surrounding normal liver, which is highly radiosensitive.[99,100] In a study of 108 patients with incurable HCC non-responsive to TACE (BCLC A to C), lesions up to 7 cm in size were treated with three fractions of SBRT.[101] Local control and OS rates at 2 years were 87% and 63%, respectively. The response was dose-dependent, with those who received greater than 54 Gray achieving local control in 100% of cases and a 71% survival rate at 2 years. Notable adverse events included gastrointestinal ulceration and worsening liver function, particularly in patients with impaired liver function (CTP B or C).[102] SBRT can theoretically be combined with TACE for synergistic effect since TACE may shrink the area requiring radiotherapy and promote radiosensitization, although this has not been adequately studied.[102] A retrospective study of patients with unresectable HCC from the Surveillance, Epidemiology, and End Results registry database compared 112 patients who received SBRT with 77 who received TARE. After

adjusting for confounders, the authors detected no significant difference in OS or disease-specific survival between the two modalities.[103] A recent systematic review and meta-analysis studied 2513 patients with HCC and portal vein tumor thrombus (i.e., advanced stage disease) from 37 studies who received either external beam radiotherapy, TARE, or SBRT.[104] Pooled results demonstrated no significant differences in 1- and 2-year OS between the three radiotherapy modalities. However, patients who received SBRT exhibited the highest response rates (71% *versus* 51% for external beam radiotherapy and 33% for TARE). Whether this result is transferable to intermediate stage HCC is unclear. Although these studies suggest SBRT is a promising therapy for intermediate stage HCC, further prospective RCTs comparing it with other modalities are required.[100]

Current challenges and future perspectives

Better sub-staging to facilitate clinical trials and eventually personalized medicine

The BCLC staging system was initially developed in an era when treatment options for HCC were limited. With rapidly expanding therapies for HCC, the BCLC system may represent an oversimplification, which is reflected in reports that real-world clinical practice deviates from BCLC recommendations in more than 50% of the time (40% among BCLC-B patients).[24,25,105] Furthermore, at least 11 different staging systems (each with their deficiencies) have been described.[106] As we move towards personalized medicine, it becomes increasingly important to match well-characterized patient (sub)groups to specific treatments. Despite the numerous other effective first-line treatments discussed above, TACE has been the sole first-line treatment recommended by BCLC for the past decade. As discussed, the current classification of intermediate stage HCC is too heterogeneous, hampering the comparison between different therapies. The majority of prior studies comparing TACE with other treatments have been retrospective studies (with or without propensity score matching), and contain dissimilar BCLC-B patients or even patients outside of BCLC-B.[11] The positive signals from these studies need to be further investigated by prospective RCTs of appropriately subclassified patient groups.

Going forward, a more concerted effort is required to reach a global consensus on how to best subclassify (or even reclassify) this group. Although any classifications would be based entirely on clinical variables initially, genomic signatures may eventually be added in the future to determine which type of intermediate stage HCC responds best to which type of therapy (embolization *versus* radiation *versus* chemotherapy). Indeed, comprehensive molecular classification of surgically resected (presumably early stage) HCCs has already begun.[107] Furthermore, current staging and sub-staging classifications do not consider tumor biology or aggressiveness, which is far more complex than its size and number. Currently, our best surrogate maker of tumor biology is a period of monitoring for tumor response after locoregional therapy.[79] The inclusion of surrogate markers such as AFP level or radiomic signatures in future sub-classification systems also warrants further study.[108]

As HCC treatment becomes even more complex in the future, there will be an increasing reliance on decisions to be made through multidisciplinary tumor board meetings, which has already been shown to improve patient outcomes and is considered standard of care.[109] It should also be kept in mind that, although effective treatments exist for intermediate stage HCC, they are non-curative for the large majority of patients. Early involvement of the palliative care service has been shown to improve symptoms (physical and psychological) and quality of life related to both the disease and its treatment adverse events in these patients.[110] An overall treatment approach for BCLC-B HCC subgroups is suggested in Figure 2.

Lessons from advanced HCC trials

We are entering a new era of systemic therapy for advanced HCC with an explosion of clinical trial activity. It would be prudent to see if the introduction of promising systemic therapies from these trials at an earlier (intermediate) stage will be beneficial in the pre-TACE setting (to reduce the tumor treatment area or even permit curative therapy) or the post-TACE setting (to prevent tumor recurrence). Initial data with lenvatinib seems to support this approach and it is likely that more regimens will be studied in the future.[95,96] The search for biomarkers which predict response to systemic therapies (especially immunotherapies) in patients with advanced HCC is ongoing.[68] Once we are able to accurately identify these responders, these biomarkers may be applied to intermediate stage patients who may be better off commencing systemic therapy

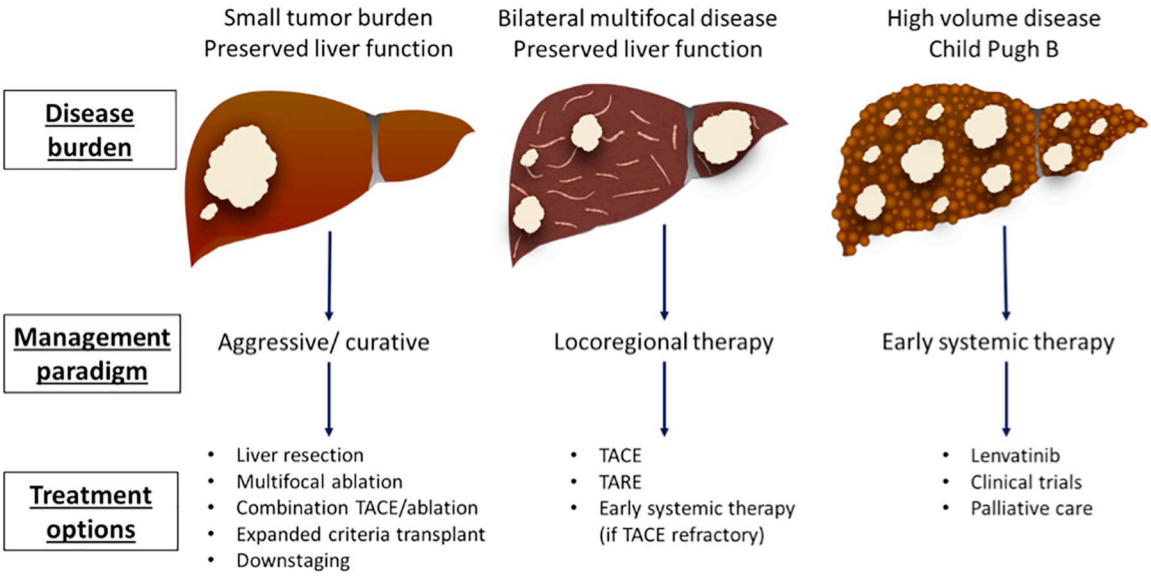

Figure 2. Possible treatment guide for intermediate stage HCC.
HCC, hepatocellular carcinom; TACE, transarterial chemoembolization; TARE, transarterial radioembolization.

personalized to them instead of undergoing a "one size fits all" approach with TACE.

Several molecular pathways involved in hepatocarcinogenesis have been specifically targeted in advanced HCC with modest results. In a study of sorafenib refractory patients, treatment with tivantinib (an oral c-MET receptor tyrosine kinase inhibitor) led to prolonged median time to progression compared with placebo in a subgroup of patients with high tumor expression of MET (with no difference for patients overall).[111] However, this drug was associated with death due to severe neutropenia in four patients, limiting its applicability. Despite showing early promise in phase II clinical trials,[112] agents targeting vascular endothelial growth factor (VEGF) and/or platelet derived growth factor receptor in advanced HCC have failed to demonstrate non-inferiority to sorafenib in phase III trials.[113–115] They were also less well-tolerated than sorafenib. More recently, regimens containing bevacizumab (targeting VEGF) in combination with a checkpoint inhibitor or ramucirumab alone (targeting VEGF receptor) have yielded positive results for advanced HCC patients in first- and second-line settings, respectively.[69,116] Drugs targeting other pathways such as erlotinib (epidermal growth factor receptor pathway), temsirolimus (PI3K/Akt/mTOR pathway), and linsitinib (insulin-like growth factor pathway) have not progressed beyond phase II clinical trials as monotherapy in HCC.[117–119] Inhibitors of the sonic hedgehog and Wnt/β-catenin pathways remain largely in the pre-clinical realm for now.[120,121] Whether targeting these specific pathways has a role in intermediate stage HCC is yet to be determined and needs further study.

Addressing tumor hypoxia

Although HCC is a hypervascular cancer, its feeding vessels are abnormal in structure and function. This results in intra-tumoral hypoxia, which is further worsened by TACE. Hypoxia has detrimental consequences including the induction of a more aggressive tumor phenotype, an immunosuppressive tumor microenvironment and resistance to future chemo- or radiotherapies.[27] Indeed, locally recurrent tumors after TACE have significantly shorter doubling times compared with primary HCCs and take on a more aggressive tumor phenotype.[122–124] There is growing pre-clinical evidence to support vascular normalization (instead of starvation) as a paradigm for treating advanced cancer and several agents including immune checkpoint inhibitors and even bevacizumab (traditionally thought of as anti-angiogenic) have demonstrated vascular normalizing properties when administered at appropriate doses.[125,126] This can result in improved intra-tumoral delivery of co-administered cytotoxic therapies and anti-tumor immune cells. Interestingly, the combination of atezolizumab

(checkpoint inhibitor) with bevacizumab has recently proved to be the first systemic therapy in over a decade to improve on sorafenib as first-line treatment in advanced HCC.[69] Whether this combination or more broadly the vascular normalization approach, is effective in intermediate stage HCC is unknown and worth exploring.

Other novel therapies

Given the current interest in checkpoint inhibitors for HCC, other immunotherapies such as immune cell-based therapies (dendritic cells, natural killer cells, chimeric antigen receptor-engineered T cells) and peptide vaccines would also be worth exploring.[68] In particular, immunotherapy using dendritic cells (DCs) has been proposed as a potential therapy for HCC.[127] It is theorized that DC exposed to liver tumor may subsequently present tumor antigens to T cells and result in the production of tumor-specific CD8 T cells.[128] In several phase II clinical trials, autologous DCs exposed to liver tumor cell lines were administered (either intravenously or subcutaneously).[127–129] Autologous DCs have resulted in reductions in AFP levels and partial radiological responses in a minority of patients. They have also been shown to be relatively safe with only minor injection site reactions and no significant autoimmunity documented. These trials to date have predominantly focused on patients with advanced stage disease or those who are not eligible for other therapies. One study evaluating autologous DCs as an adjuvant therapy demonstrated variable results. When DCs were combined with RFA, poorer survival was observed compared with placebo whereas improved survival occurred when they were used as an adjuvant to other therapies (including TACE).[130] Clearly, larger randomized trials are required in intermediate stage disease.

Targeting liver cancer stem cells (LCSCs) is another novel and promising strategy going forward for HCC treatment. This subpopulation of cells within an HCC (identified by their specific surface markers) has been shown to be responsible for the initiation, progression, recurrence, metastasis, and chemoresistance of HCCs, making them prime targets for therapeutic strategies.[131] Indeed, several treatments directed against LCSCs have been studied in the preclinical setting including targeting their associated surface markers, signaling pathways, microenvironment, epigenetic regulation, microRNAs, and transporters. A handful of agents have made it to phase I/II clinical trials (e.g. OMP-54F28 [ClinicalTrials.gov identifier: NCT02069145], LED225 [ClinicalTrials.gov identifier: NCT02151864], gefintinib [Clinical Trials.gov identifier: NCT00071994]) although their results were either negative or not reported. However, a recent phase II study of galunisertib [transforming growth factor (TGF)-β1 receptor type I inhibitor] in combination with sorafenib in 47 patients with advanced stage HCC demonstrated a promising median OS of 18.8 months.[132] The TGF-β pathway has been considered to be crucial in the self-renewal and differentiation of LCSCs. A subsequent trial of galunisertib in combination with nivolumab (checkpoint inhibitor) is currently under way [ClinicalTrials.gov identifier: NCT02423343]. Again, any promising results in advanced stage HCC cannot be extrapolated to intermediate stage HCC without specific clinical trials in that setting.

Conclusion

According to current BCLC staging, intermediate stage HCC consists of a potpourri of patients with different tumor burdens. While significant recent developments have been made in advanced stage HCC, TACE remains the mainstay of therapy for the intermediate group and is considered a palliative therapy. An armamentarium of other treatments ranging from curative therapies (resection, LT, ablation) to those used in advanced disease (systemic agents) have all shown promise in select patient subgroups, making it difficult to generalize recommendations across the whole stage. Further studies to determine when and how to use these treatments and how to best subclassify the intermediate stage are needed to optimize patient outcomes in this group.

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