Management of patients with intermediate stage hepatocellular carcinoma

David Prince*, Ken Liu*, Weiqi Xu, Minjiang Chen, Jin-Yu Sun, Xiao-Jie Lu and Jiansong Ji

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 refinementes 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

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
equally

*These authors contributed equally

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

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Minjiang Chen
Key Laboratory of Imaging Diagnosis and Minimally Invasive Intervention Research, The Fifth Affiliated Hospital of Wenzhou Medical University/Affiliated Lishui Hospital of Zhejiang University/The Central Hospital of Zhejiang Lishui, Lishui, China

Jin-Yu Sun
Department of Radiology, The Fifth Affiliated Hospital of Wenzhou Medical University/Affiliated Lishui Hospital of Zhejiang University/The Central Hospital of Zhejiang Lishui, Lishui, China

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 criteria17,18 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
In 2002, two landmark randomized controlled trials (RCT) were published that reported a benefit of TACE over supportive care for unresectable HCC. These positive findings were subsequently confirmed by two meta-analyses, and TACE was endorsed by major clinical practice guidelines. Although a Cochrane review in 2011 reported no benefit from TACE over no treatment, this meta-analysis has been criticized for including trials that recruited early and advanced stage HCC patients. 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). 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. 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. Lipiodol® may also act as a microembolic agent for very small tumor vessels. As Lipiodol® is hyperdense, it can mask residual disease vascularity on follow-up computed tomography (CT) imaging. 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. To address these disadvantages of cTACE, TACE using drug-eluting beads (DEB-TACE) was developed. This technique involves the administration of microspheres (usually 100–300µm in size) coated with a macromere most commonly comprised of polyvinyl alcohol. These spheres are loaded with a chemotherapeutic agent (most commonly doxorubicin) and cause simultaneous chemotherapy delivery and vessel embolization. DEB-TACE may theoretically allow for higher doses of the chemotherapeutic agent to be administered and a more sustained release to the target HCC.

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

| Components | Bolondi system | Kinki criteria | Japanese society for transcatheter hepatic arterial embolization system |
|------------|----------------|---------------|-----------------------------------------------|
| 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.
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 model48 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 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) | 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 | A (score 0) – 65.9 | < 18–5.3 | ALBI grade (0 or 2–3) | Up to 11 criteria | ALBI grade (0 or 2–3) | Up to 11 criteria | CRP (<1 mg/dl or ≥ 1 mg/dl) |
| | 6–12 to 32.0 | B (score 1) – 30.2 | ≥ 18–19.5 | ALBI grade (0 or 2–3) | Up to 11 criteria | ALBI grade (0 or 2–3) | Up to 11 criteria | CRP (<1 mg/dl or ≥ 1 mg/dl) |
| | > 12–15.8 | C (score 2) – 17.4 | | ALBI grade (0 or 2–3) | Up to 11 criteria | ALBI grade (0 or 2–3) | Up to 11 criteria | CRP (<1 mg/dl or ≥ 1 mg/dl) |
| | | D (score 3) – 6.0 | | ALBI grade (0 or 2–3) | Up to 11 criteria | ALBI grade (0 or 2–3) | Up to 11 criteria | CRP (<1 mg/dl or ≥ 1 mg/dl) |
| 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 | Mean age – 69 years | Mean age – 66.5 years |
| | Hepatitis B – 85% | Hepatitis B – 45% | Alcohol – 45% |
| | | Hepatitis C 34% | Viral hepatitis – 35% |

AFP, alpha-fetoprotein; ALBI, albumin to bilirubin grade; CRP, C-reactive protein.
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 (0–1.5 = 23.7 months, 1.5–2.5 = 6.6 months, ≥2.5 = 6.6 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

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

| ART score53 | SNACOR model56 | ABCR score55 | mHAP-III score57 |
|-------------|----------------|--------------|-----------------|
| **Components** | | | |
| AST 25% increase (4 points) | Tumor size (<5 cm or ⩾5 cm) | AFP (≥200 ng/mL = 1) | Tumor number (1–3) | | | | |
| Tumor response (absent = 1 point) | Tumor number (1–3) | BCLC stage (B = 70%, C = 42%) | CTP increase by ⩾2 (2) | | | | |
| CTP increase (1+ = 1.5, 2+ = 3) | Baseline AFP (<400 ng/mL or ⩾400 ng/mL) | Hepatitis B = 70% | Tumor response (present -3, absent = 0) | | | | |

**Groups [median survival (months)]**

- ART score: 0–1.5 = 23.7 months, 1.5–2.5 = 6.6 months
- ABCR score: ≤0 = 37.8 months, 1–3 = 17.1 months, 4–7,5 = 7.5 months

**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
- Alcohol − 46%
- Hepatitis C − 13%
- Mean age − 68 years
- Alcohol − 44%
- Hepatitis C − 42%
- Mean age − 68 years
- Alcohol − 62%
- Hepatitis B − 15%

**Study summary (median survival, months)**

- ART score: 0–1.5 = 23.7 months, 1.5–2.5 = 6.6 months
- ABCR score: ≤0 = 37.8 months, 1–3 = 17.1 months, 4–7,5 = 7.5 months

**Study cohort characteristics**

- Mean age − 64 years
- Alcohol − 46%
- Viral hepatitis − 34%
- Mean age − 58 years
- Alcohol − 46%
- Hepatitis C − 13%
- Mean age − 68 years
- Alcohol − 44%
- Hepatitis C − 42%
- Mean age − 68 years
- Alcohol − 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.

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%).50 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%).50 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 \textit{versus} 13.5 months) and time to untaceable progression (26.7 \textit{versus} 20.6 months) in favor of TACE plus sorafenib \textit{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 resection with TACE similarly found significantly improved 1- and 5-year OS rates of 84\% \textit{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.

**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\% \textit{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 \(<=6.5\) cm or up to three tumors \(<=4.5\) cm in size and a total tumor diameter \(<=8\) 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. 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%). 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. Thus, a BCLC-B patient previously deemed to be ineligible for LT due to tumor burden in excess of the Milan criteria may now fulfill 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. 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. 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. An initial AFP level of greater than 1000 ng/ml was predictive of downstaging failure. These criteria were further validated in a 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). 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.

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. 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. 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. Yttrium-90 (90Y) is the most commonly studied and used radioisotope; however, other isotopes (holmium-166 and iodine-131) have been trialled. Up to 15–20% of patients are ineligible for TARE due to significant arteriovenous shunting. 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. 90Y 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. 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. 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. 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. 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.\textsuperscript{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 \textit{versus} 18 months, respectively) despite having objectively greater tumor burden in the TARE group.\textsuperscript{99} A subsequent meta-analysis of comparative trials between TARE \textit{versus} TACE across all stages of HCC also demonstrated similar OS.\textsuperscript{96} 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.\textsuperscript{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.\textsuperscript{26,92} The frequency of grade 3/4 hyperbilirubinemia varies from 5 to 15\% within TARE studies\textsuperscript{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.\textsuperscript{89,90} However, TARE is substantially more costly than TACE.\textsuperscript{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.\textsuperscript{95} Lenvatinib-treated patients exhibited significantly better progression-free survival (16.0 \textit{versus} 3.0 months), objective response rates (73.3\% \textit{versus} 33.3\%), and OS (37.9 \textit{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.\textsuperscript{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 \textit{versus} 7.9 months) and improved OS (25.4 \textit{versus} 11.5 months).\textsuperscript{97} These findings were confirmed in a second retrospective cohort.\textsuperscript{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.\textsuperscript{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.\textsuperscript{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).\textsuperscript{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.\textsuperscript{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. A recent systematic review and meta-analysis studied 2513 patients with HCC and portal vein thrombus (i.e., advanced stage disease) from 37 studies who received either external beam radiotherapy, TARE, or SBRT. 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.

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). Furthermore, at least 11 different staging systems (each with their deficiencies) have been described. 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. The positive signals from these studies need to be further investigated by prospective RCTs of appropriately subclassified patient groups.

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. 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. 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. The search for biomarkers which predict response to systemic therapies (especially immunotherapies) in patients with advanced HCC is ongoing. 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.
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). 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, 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. They were also less well-tolerated than sorafenib. More recently, regimens containing bevacizumab (targeting VEGF) and/or platelet derived growth factor receptor in advanced HCC have failed to demonstrate non-inferiority to sorafenib in phase III trials. 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. 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. Inhibitors of the sonic hedgehog and Wnt/β-catenin pathways remain largely in the pre-clinical realm for now. 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. Indeed, locally recurrent tumors after TACE have significantly shorter doubling times compared with primary HCCs and take on a more aggressive tumor phenotype. 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. 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. 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. In particular, immunotherapy using dendritic cells (DCs) has been proposed as a potential therapy for HCC. 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. In several phase II clinical trials, autologous DCs exposed to liver tumor cell lines were administered (either intravenously or subcutaneously). 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). 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. 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], gefinitib [ClinicalTrials.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. 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.

Conflict of interest statement
The authors declare that there is no conflict of interest.

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References

1. World Health Organization. Projections of mortality and causes of death, 2016 to 2060, https://www.who.int/healthinfo/global_burden_disease/projections/en/ (2019, accessed 9 April 2020).

2. Villanueva A. Hepatocellular carcinoma. N Engl J Med 2019; 380: 1450–1462.

3. European Association for the Study of the Liver. EASL clinical practice guidelines: management of hepatocellular carcinoma. J Hepatol 2018; 69: 182–236.

4. Jemal A, Ward EM, Johnson CJ, et al. Annual report to the nation on the status of cancer, 1975–2014, featuring survival. J Natl Cancer Inst 2017; 109: djx030.

5. Vogel A, Cervantes A, Chau I, et al. Hepatocellular carcinoma: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol 2018; 29: iv238–iv255.

6. Marrero JA, Kulik LM, Sirlin CB, et al. Diagnosis, staging, and management of hepatocellular carcinoma: 2018 practice guidance by the American Association for the study of liver diseases. Hepatology 2018; 68: 723–750.

7. Giannini EG, Moscatelli A, Pellegatta G, et al. Application of the intermediate-stage subclassification to patients with untreated hepatocellular carcinoma. Am J Gastroenterol 2016; 111: 70–77.

8. European Association for the Study of the Liver. EASL–EORTC clinical practice guidelines: management of hepatocellular carcinoma. J Hepatol 2012; 56: 908–943.

9. Cabibbo G, Enea M, Attanasio M, et al. A meta-analysis of survival rates of untreated patients in randomized clinical trials of hepatocellular carcinoma. Hepatology 2010; 51: 1274–1283.

10. Giannini EG, Farinati F, Ciccarese F, et al. Prognosis of untreated hepatocellular carcinoma. Hepatology 2015; 61: 184–190.

11. Roccarina D, Majumdar A, Thorburn D, et al. Management of people with intermediate-stage hepatocellular carcinoma: an attempted network meta-analysis. Cochrane Database Syst Rev 2017; 3: CD011649.

12. Bolondi L, Burroughs A, Dufour J-F, et al. Heterogeneity of patients with intermediate (BCLC B) hepatocellular carcinoma: proposal for a subclassification to facilitate treatment decisions. In: Seminars in Liver Disease. New York, NY: Thieme Medical Publishers, 2012, pp.348–359.

13. Scaffaro LA, Stella SF, Alvares–Da–Silva MR, et al. Survival rates according to barcelona clinic liver cancer sub-staging system after transarterial embolization for intermediate hepatocellular carcinoma. World J Hepatol 2015; 7: 628–632.

14. Ha Y, Shim JH, Kim SO, et al. Clinical appraisal of the recently proposed barcelona clinic liver cancer stage B subclassification by survival analysis. J Gastroenterol Hepatol 2014; 29: 787–793.

15. Mazzaferrero V, Llovet JM, Miceli R, et al. Predicting survival after liver transplantation in patients with hepatocellular carcinoma beyond the Milan criteria: a retrospective, exploratory analysis. Lancet Oncol 2009; 10: 35–43.

16. Weinmann A, Koch S, Sprinzl M, et al. Survival analysis of proposed BCLC-B subgroups in hepatocellular carcinoma patients. Liver Int 2015; 35: 591–600.

17. Kudo M, Arizumi T, Ueshima K, et al. Subclassification of BCLC B stage hepatocellular carcinoma and treatment strategies: proposal of modified Bolondi’s subclassification (Kinki criteria). Dig Dis 2015; 33: 751–758.

18. Arizumi T, Ueshima K, Iwanishi M, et al. Validation of a modified substaging system (Kinki criteria) for patients with intermediate-stage hepatocellular carcinoma. Oncology 2015; 89: 47–52.

19. Kudo M. Heterogeneity and subclassification of barcelona clinic liver cancer stage B. Liver Cancer 2016; 5: 91–96.

20. Yamakado K, Miyayama S, Hirota S, et al. Prognosis of patients with intermediate-stage hepatocellular carcinomas based on the Child–Pugh score: subclassifying the intermediate stage (barcelona clinic liver cancer stage B). Jpn J Radiol 2014; 32: 644–649.

21. Yamakado K, Miyayama S, Hirota S, et al. Subgrouping of intermediate-stage (BCLC stage B) hepatocellular carcinoma based on tumor number and size and Child–Pugh grade correlated with prognosis after transarterial chemoembolization. Jpn J Radiol 2014; 32: 260–265.

22. Omata M, Cheng A-L, Kokudo N, et al. Asia–Pacific clinical practice guidelines on the management of hepatocellular carcinoma: a 2017 update. Hepatol Int 2017; 11: 317–370.

23. Yang JD, Hainaut P, Gores GJ, et al. A global view of hepatocellular carcinoma: trends, risk, prevention and management. Nat Rev Gastroenterol Hepatol 2019; 16: 589–604.
24. Kim KM, Sinn DH, Jung SH, et al. The recommended treatment algorithms of the BCLC and HKLC staging systems: does following these always improve survival rates for HCC patients? Liver Int 2016; 36: 1490–1497.

25. Wallace MC, Huang Y, Preen DB, et al. HKLC triages more hepatocellular carcinoma patients to curative therapies compared to BCLC and is associated with better survival. Dig Dis Sci 2017; 62: 2182–2192.

26. Sangro B, D’Avola D, Íñarraíraegui M, et al. Transarterial therapies for hepatocellular carcinoma. Expert Opin Pharmacother 2011; 12: 1057–1073.

27. Liu K, Zhang X, Xu W, et al. Targeting the vasculature in hepatocellular carcinoma treatment: starving versus normalizing blood supply. Clin Transl Gastroenterol 2017; 8: e98.

28. Marelli L, Stigliano R, Triantos C, et al. Transarterial therapy for hepatocellular carcinoma: which technique is more effective? A systematic review of cohort and randomized studies. Cardiovasc Intervent Radiol 2007; 30: 6–25.

29. Camma C, Schepis F, Orlando A, et al. Transarterial chemoembolization for unresectable hepatocellular carcinoma: meta-analysis of randomized controlled trials. Radiology 2002; 224: 47–54.

30. Lencioni R, de Baere T, Soulen MC, et al. Lipiodol transarterial chemoembolization for hepatocellular carcinoma: a systematic review of efficacy and safety data. Hepatology 2016; 64: 106–116.

31. Vogl TJ and Lee C. Doxorubicin-eluting beads in the treatment of liver carcinoma. Expert Opin Pharmacother 2014; 15: 115–120.

32. Lo CM, Ngan H, Tso WK, et al. Randomized controlled trial of transarterial lipiodol chemoembolization for unresectable hepatocellular carcinoma. Hepatology 2002; 35: 1164–1171.

33. Llovet JM, Real MI, Montaña X, et al. Arterial embolisation or chemoembolisation versus symptomatic treatment in patients with unresectable hepatocellular carcinoma: a randomised controlled trial. Lancet 2002; 359: 1734–1739.

34. Llovet JM and Bruix J. Systematic review of randomized trials for unresectable hepatocellular carcinoma: chemoembolization improves survival. Hepatology 2003; 37: 429–442.

35. Bruix J and Sherman M. Management of hepatocellular carcinoma. Hepatology 2005; 42: 1208–1236.

36. Oliveri RS, Wetterslev J and Gluud C. Transarterial (chemo) embolisation for unresectable hepatocellular carcinoma. Cochrane Database Syst Rev 2011; CD004787.

37. Forner A, Llovet JM and Bruix J. Chemoembolization for intermediate HCC: is there proof of survival benefit? J Hepatol 2012; 56: 984–986.

38. Brown KT, Do RK, Gonen M, et al. Randomized trial of hepatic artery embolization for hepatocellular carcinoma using doxorubicin-eluting microspheres compared with embolization with microspheres alone. J Clin Oncol 2016; 34: 2046–2053.

39. Varela M, Real MI, Burrel M, et al. Chemoembolization of hepatocellular carcinoma with drug eluting beads: efficacy and doxorubicin pharmacokinetics. J Hepatol 2007; 46: 474–481.

40. Lencioni R, De Baere T, Burrel M, et al. Transcatheter treatment of hepatocellular carcinoma with doxorubicin-loaded DC Bead (DEBDOX): technical recommendations. Cardiovasc Intervent Radiol 2012; 35: 980–985.

41. Lammer J, Malagari K, Vogl T, et al. Prospective randomized study of doxorubicin-eluting-bead embolization in the treatment of hepatocellular carcinoma: results of the PRECISION V study. Cardiovasc Intervent Radiol 2010; 33: 41–52.

42. Song MJ, Chun HJ, Kim HY, et al. Comparative study between doxorubicin-eluting beads and conventional transarterial chemoembolization for treatment of hepatocellular carcinoma. J Hepatol 2012; 57: 1244–1250.

43. Facciorusso A, Mariani L, Sposito C, et al. Drug-eluting beads versus conventional chemoembolization for the treatment of unresectable hepatocellular carcinoma. J Gastroenterol Hepatol 2016; 31: 645–653.

44. Golferi R, Giampalma E, Renzulli M, et al. Randomised controlled trial of doxorubicin-eluting beads vs conventional chemoembolisation for hepatocellular carcinoma. Br J Cancer 2014; 111: 255–264.

45. Facciorusso A, Di Maso M and Muscatelli N. Drug-eluting beads versus conventional chemoembolization for the treatment of unresectable hepatocellular carcinoma: a meta-analysis. Dig Liver Dis 2016; 48: 571–577.

46. Wang Q, Xia D, Bai W, et al. Development of a prognostic score for recommended TACE candidates with hepatocellular carcinoma: a multicentre observational study. J Hepatol 2019; 70: 893–903.
47. Wang Q, Xia D, Bai W, et al. Reply to: “the "six-and-twelve score" for TACE treatment: does it really help us?” J Hepatol 2019; 71: 1053–1054.

48. Lee IC, Hung YW, Liu CA, et al. A new ALBI-based model to predict survival after transarterial chemoembolization for BCLC stage B hepatocellular carcinoma. Liver Int 2019; 39: 1704–1712.

49. Johnson PJ, Berhane S, Kagebayashi C, et al. Assessment of liver function in patients with hepatocellular carcinoma: a new evidence-based approach—the ALBI grade. J Clin Oncol 2015; 33: 550.

50. Kim JH, Shim JH, Lee HC, et al. New intermediate-stage subclassification for patients with hepatocellular carcinoma treated with transarterial chemoembolization. Liver Int 2017; 37: 1861–1868.

51. Hucke F, Pinter M, Graziaidei I, et al. How to STATE suitability and START transarterial chemoembolization in patients with intermediate stage hepatocellular carcinoma. J Hepatol 2014; 61: 1287–1296.

52. Terzi E, Golfieri R, Piscaglia F, et al. Response rate and clinical outcome of HCC after first and repeated cTACE performed “on demand”. J Hepatol 2012; 57: 1258–1267.

53. Sieghart W, Hucke F, Pinter M, et al. The ART of decision making: retreatment with transarterial chemoembolization in patients with hepatocellular carcinoma. Hepatology 2013; 57: 2261–2273.

54. Hucke F, Sieghart W, Pinter M, et al. The ART-strategy: sequential assessment of the ART score predicts outcome of patients with hepatocellular carcinoma re-treated with TACE. J Hepatol 2014; 60: 118–126.

55. Adhoute X, Penaranda G, Naude S, et al. Retreatment with TACE: the ABCR SCORE, an aid to the decision-making process. J Hepatol 2015; 62: 855–862.

56. Kim BK, Shim JH, Kim SU, et al. Risk prediction for patients with hepatocellular carcinoma undergoing chemoembolization: development of a prediction model. Liver Int 2016; 36: 92–99.

57. Cappelli A, Cucchetti A, Cabibbo G, et al. Refining prognosis after trans-arterial chemoembolization for hepatocellular carcinoma. Liver Int 2016; 36: 729–736.

58. Piscaglia F, Tovoli F, Pini P, et al. A new horizon in the prevention of the postembolization syndrome after transcatheter arterial chemoembolization for hepatocellular carcinoma. Hepatology 2018; 67: 467–469.

59. Iezzi R, Cesario V, Siciliani L, et al. Single-step multimodal locoregional treatment for unresectable hepatocellular carcinoma: balloon-occluded percutaneous radiofrequency thermal ablation (BO-RFA) plus Transcatheter Arterial Chemoembolization (TACE). Radiol Med 2013; 118: 555–569.

60. Wang X, Hu Y, Ren M, et al. Efficacy and safety of radiofrequency ablation combined with transcatheter arterial chemoembolization for hepatocellular carcinomas compared with radiofrequency ablation alone: a time-to-event meta-analysis. Korean J Radiol 2016; 17: 93–102.

61. Giorgio A, Gatti P, Montesarchio L, et al. Microwave ablation in intermediate hepatocellular carcinoma in cirrhosis: an Italian multicenter prospective study. J Clin Transl Hepatol 2018; 6: 251–257.

62. Xu Z, Xie H, Zhou L, et al. The combination strategy of transarterial chemoembolization and radiofrequency ablation or microwave ablation against hepatocellular carcinoma. Anal Cell Pathol (Amst) 2019; 2019: 8619096.

63. Lencioni R, Llovet JM, Han G, et al. Sorafenib or placebo plus TACE with doxorubicin-eluting beads for intermediate stage HCC: the SPACE trial. J Hepatol 2016; 64: 1090–1098.

64. Kudo M, Ueshima K, Ikeda M, et al. Randomised, multicentre prospective trial of Transarterial Chemoembolisation (TACE) plus sorafenib as compared with TACE alone in patients with hepatocellular carcinoma: TACTICS trial. Gut. Epub ahead of print 4 December 2019. DOI: 10.1136/gutjnl-2019-318934.

65. Zeng J, Lv L and Mei Z-C. Efficacy and safety of transarterial chemoembolization plus sorafenib for early or intermediate stage hepatocellular carcinoma: a systematic review and meta-analysis of randomized controlled trials. Clin Res Hepatol Gastroenterol 2016; 40: 688–697.

66. Kudo M, Han G, Finn RS, et al. Brivanib as adjuvant therapy to transarterial chemoembolization in patients with hepatocellular carcinoma: a randomized phase III trial. Hepatology 2014; 60: 1697–1707.

67. Pinter M, Ulbrich G, Sieghart W, et al. Hepatocellular carcinoma: a phase II randomized controlled double-blind trial of transarterial chemoembolization in combination with biweekly intravenous administration of
bevacizumab or a placebo. *Radiology* 2015; 277: 903–912.

68. Xu W, Liu K, Chen M, et al. Immunotherapy for hepatocellular carcinoma: recent advances and future perspectives. *Ther Adv Med Oncol* 2019; 11: 1–15.

69. Finn RS, Qin S, Ikeda M, et al. Atezolizumab plus bevacizumab in unresectable hepatocellular carcinoma. *N Engl J Med* 2020; 382: 1894–1905.

70. Yau T, Tang VY, Yao T-J, et al. Development of Hong Kong Liver Cancer staging system with treatment stratification for patients with hepatocellular carcinoma. *Gastroenterology* 2014; 146: 1691–1700.

71. Ishizawa T, Hasegawa K, Aoki T, et al. Comparison of surgical resection and transarterial chemoembolization for hepatocellular carcinoma beyond the Milan criteria: a propensity score analysis. *Ann Surg Oncol* 2012; 19: 842–849.

72. Hyun MH, Lee YS, Kim JH, et al. Hepatic resection compared to chemoembolization in intermediate- to advanced-stage hepatocellular carcinoma: a meta-analysis of high-quality studies. *Hepatology* 2018; 68: 977–993.

73. Labgaa I, Demartines N and Melloul E. Surgical resection versus transarterial chemoembolization for intermediate stage hepatocellular carcinoma (BCLC-B): an unsolved question. *Hepatology* 2019; 69: 923.

74. Torzilli G, Belghiti J, Kokudo N, et al. A snapshot of the effective indications and results of surgery for hepatocellular carcinoma in tertiary referral centers: is it adherent to the EASL/AASLD recommendations? An observational study of the HCC East-West study group. *Ann Surg* 2013; 257: 929–937.

75. Yao FY, Ferrell L, Bass NM, et al. Liver transplantation for hepatocellular carcinoma: expansion of the tumor size limits does not adversely impact survival. *Hepatology* 2001; 33: 1394–1403.

76. Chen JW, Kow L, Verran DJ, et al. Poorer survival in patients whose explanted hepatocellular carcinoma (HCC) exceeds Milan or UCSF Criteria. An analysis of liver transplantation in HCC in Australia and New Zealand. *HPB* 2009; 11: 81–89.

77. Mazzaferro V, Sposito C, Zhou J, et al. Metroticket 2.0 model for analysis of competing risks of death after liver transplantation for hepatocellular carcinoma. *Gastroenterology* 2018; 154: 128–139.

78. Liu K and McCaughan GW. How to select the appropriate “neoadjuvant therapy” for hepatocellular carcinoma. *Expert Opin Pharmacother* 2018; 19: 1167–1170.

79. Mehta N, Dodge JL, Grab JD, et al. National experience on down-staging of hepatocellular carcinoma before liver transplant: influence of tumor burden, alpha-fetoprotein, and wait time. *Hepatology* 2020; 71: 943–954.

80. Seror O, N’Kontchou G, Ibraheem M, et al. Large (≥5.0-cm) HCCs: multipolar RF ablation with three internally cooled bipolar electrodes—initial experience in 26 patients. *Radiology* 2008; 248: 288–296.

81. Cartier V, Boursier J, Lebigot J, et al. Radiofrequency ablation of hepatocellular carcinoma: mono or multipolar? *J Gastroenterol Hepatol* 2016; 31: 654–660.

82. Bolondi L and Piscaglia F. Yttrium 90 radioembolization: the horizon is changing for patients with intermediate and advanced hepatocellular carcinoma. *Hepatology* 2013; 57: 1694–1696.

83. Salem R, Gordon AC, Mouli S, et al. Y90 radioembolization significantly prolongs time to progression compared with chemoembolization in patients with hepatocellular carcinoma. *Gastroenterology* 2016; 151: 1155–1163.

84. Sangro B, Carpanese L, Cianni R, et al. Survival after yttrium-90 resin microsphere radioembolization of hepatocellular carcinoma across Barcelona clinic liver cancer stages: a European evaluation. *Hepatology* 2011; 54: 868–878.

85. Salem R, Lewandowski RJ, Mulcahy MF, et al. Radioembolization for hepatocellular carcinoma using yttrium-90 microspheres: a comprehensive report of long-term outcomes. *Gastroenterology* 2010; 138: 52–64.

86. El Foul A, Ertle J, El Dorry A, et al. In intermediate stage hepatocellular carcinoma:
radioembolization with yttrium 90 or chemoembolization? Liver Int 2015; 35: 627–635.

90. Lobo L, Yakoub D, Picado O, et al. Unresectable hepatocellular carcinoma: radioembolization versus chemoembolization: a systematic review and meta-analysis. Cardiovasc Intervent Radiol 2016; 39: 1580–1588.

91. Garlipp B, de Baere T, Damm R, et al. Left-liver hypertrophy after therapeutic right-liver radioembolization is substantial but less than after portal vein embolization. Hepatology 2014; 59: 1864–1873.

92. Sangro B, Gil-Alzugaray B, Rodriguez J, et al. Liver disease induced by radioembolization of liver tumors: description and possible risk factors. Cancer 2008; 112: 1538–1546.

93. Salem R, Lewandowski RJ, Kulik L, et al. Radioembolization results in longer time-to-progression and reduced toxicity compared with chemoembolization in patients with hepatocellular carcinoma. Gastroenterology 2011; 140: 497–507.

94. Rostambeigi N, Dekarske AS, Austin EE, et al. Cost effectiveness of radioembolization compared with conventional transarterial chemoembolization for treatment of hepatocellular carcinoma. J Vasc Interv Radiol 2014; 25: 1075–1084.

95. Kudo M, Ueshima K, Chan S, et al. Lenvatinib as an initial treatment in patients with intermediate-stage hepatocellular carcinoma beyond up-to-seven criteria and Child–Pugh a liver function: a proof-of-concept study. Cancers (Basel) 2019; 11: 1084.

96. Kudo M. A new treatment option for intermediate-stage hepatocellular carcinoma with high tumor burden: initial lenvatinib therapy with subsequent selective TACE. Liver Cancer 2019; 8: 1–13.

97. Ogasawara S, Chiba T, Ooka Y, et al. Efficacy of sorafenib in intermediate-stage hepatocellular carcinoma patients refractory to transarterial chemoembolization. Oncology 2014; 87: 330–341.

98. Arizumi T, Ueshima K, Minami T, et al. Effectiveness of sorafenib in patients with transcatheter arterial chemoembolization (TACE) refractory and intermediate-stage hepatocellular carcinoma. Liver Cancer 2015; 4: 253–262.

99. Kalogeridi M-A, Zygogianni A, Kyrgias G, et al. Role of radiotherapy in the management of hepatocellular carcinoma: a systematic review. World J Hepatol 2015; 7: 101–112.

100. Yu Y and Feng M. Radiotherapy for hepatocellular carcinoma. In: Seminars in Radiation Oncology. Elsevier, 2018, pp.277–287.

101. Jang WI, Kim M-S, Bae SH, et al. High-dose stereotactic body radiotherapy correlates increased local control and overall survival in patients with inoperable hepatocellular carcinoma. Radiat Oncol 2013; 8: 250.

102. Murray LJ and Dawson LA. Advances in stereotactic body radiation therapy for hepatocellular carcinoma. In: Seminars in Radiation Oncology. Elsevier, 2017, pp.247–255.

103. Oladeru OT, Miccia JA, Yang J, et al. Conformal external beam radiation or selective internal radiation therapy—a comparison of treatment outcomes for hepatocellular carcinoma. J Gastrointest Oncol 2018; 129: 112–122.

104. Rim CH, Kim CY, Yang DS, et al. Comparison of radiation therapy modalities for hepatocellular carcinoma with portal vein thrombosis: a meta-analysis and systematic review. Radiother Oncol 2018; 129: 112–122.

105. Golﬁeri R, Bargellini I, Spreamico C, et al. Patients with barcelona clinic liver cancer stages B and C hepatocellular carcinoma: time for a subclassification. Liver cancer 2019; 8: 78–91.

106. Liu P-H, Hsu C-Y, Hsia C-Y, et al. Prognosis of hepatocellular carcinoma: assessment of eleven staging systems. J Hepatol 2016; 64: 601–608.

107. Ally A, Balasundaram M, Carlsen R, et al. Comprehensive and integrative genomic characterization of hepatocellular carcinoma. Cell 2017; 169: 1327–1341.

108. Wakabayashi T, Ouhmich F, Gonzalez-Cabrera C, et al. Radiomics in hepatocellular carcinoma: a quantitative review. Hepatol Int 2019; 13: 546–559.

109. Agarwal PD, Phillips P, Hillman L, et al. Multidisciplinary management of hepatocellular carcinoma improves access to therapy and patient survival. J Clin Gastroenterol 2017; 51: 845–849.

110. Laube R, Sabih AH, Strasser SI, et al. Palliative care in hepatocellular carcinoma. J Gastroenterol Hepatol. Epub ahead of print 6 July 2020. DOI: 10.1111/jgh.15169.

111. Santoro A, Rimassa L, Borbath I, et al. Tivantinib for second-line treatment of advanced hepatocellular carcinoma: a randomised, placebo-controlled phase 2 study. Lancet Oncol 2013; 14: 55–63.

112. Toh HC, Chen PJ, Carr BI, et al. Phase 2 trial of linifanib (ABT-869) in patients with
unresectable or metastatic hepatocellular carcinoma. *Cancer* 2013; 119: 380–387.

113. Johnson PJ, Qin S, Park J-W, et al. Brivanib versus sorafenib as first-line therapy in patients with unresectable, advanced hepatocellular carcinoma: results from the randomized phase III BRISK-FL study. *J Clin Oncol* 2013; 31: 3517–3524.

114. Cainap C, Qin S, Huang W-T, et al. Linifanib versus sorafenib in patients with advanced hepatocellular carcinoma: results of a randomized phase III trial. *J Clin Oncol* 2015; 33: 172–179.

115. Cheng A-L, Kang Y-K, Lin D-Y, et al. Sunitinib versus sorafenib in advanced hepatocellular cancer: results of a randomized phase III trial. *J Clin Oncol* 2013; 31: 4067–4075.

116. Zhu AX, Kang Y-K, Yen C-J, et al. Ramucirumab after sorafenib in patients with advanced hepatocellular carcinoma and increased α-fetoprotein concentrations (REACH-2): a randomised, double-blind, placebo-controlled, phase 3 trial. *Lancet Oncol* 2019; 20: 282–296.

117. Philip PA, Mahoney MR, Allmer C, et al. Phase II study of erlotinib (OSI-774) in patients with advanced hepatocellular cancer. *J Clin Oncol* 2005; 23: 6657–6663.

118. Enguita-Germán M and Fortes P. Targeting the insulin-like growth factor pathway in hepatocellular carcinoma. *World J Hepatol* 2014; 6: 716–737.

119. Yeo W, Chan SL, Mo FK, et al. Phase I/II study of temsirolimus for patients with unresectable Hepatocellular Carcinoma (HCC)- a correlative study to explore potential biomarkers for response. *BMC Cancer* 2015; 15: 395.

120. Vilchez V, Turcios L, Marti F, et al. Targeting Wnt/β-catenin pathway in hepatocellular carcinoma treatment. *World J Gastroenterol* 2016; 22: 823–832.

121. Jeng KS, Jeng CJ, Jeng WJ, et al. Sonic Hedgehog signaling pathway as a potential target to inhibit the progression of hepatocellular carcinoma. *Oncol Lett* 2019; 18: 4377–4384.

122. Lai JP, Conley A, Knudsen BS, et al. Hypoxia after transarterial chemoembolization may trigger a progenitor cell phenotype in hepatocellular carcinoma. *Histopathology* 2015; 67: 442–450.

123. Kim YB, Park Y and Park C. Increased proliferation activities of vascular endothelial cells and tumour cells in residual hepatocellular carcinoma following transcatheter arterial embolization. *Histopathology* 2001; 38: 160–166.

124. Tezuka M, Hayashi K, Kubota K, et al. Growth rate of locally recurrent hepatocellular carcinoma after transcatheter arterial chemoembolization: comparing the growth rate of locally recurrent tumor with that of primary hepatocellular carcinoma. *Dig Dis Sci* 2007; 52: 783–788.

125. Tian L, Goldstein A, Wang H, et al. Mutual regulation of tumour vessel normalization and immunostimulatory reprogramming. *Nature* 2017; 544: 250–254.

126. Jain RK. Normalizing tumor vasculature with anti-angiogenic therapy: a new paradigm for combination therapy. *Nat Med* 2001; 7: 987–989.

127. Palmer DH, Midgley RS, Mirza N, et al. A phase II study of adoptive immunotherapy using dendritic cells pulsed with tumor lysate in patients with hepatocellular carcinoma. *Hepatology* 2009; 49: 124–132.

128. Ghafar MTA, Morad MA, El-Zamarany EA, et al. Autologous dendritic cells pulsed with lysate from an allogeneic hepatic cancer cell line as a treatment for patients with advanced hepatocellular carcinoma: a pilot study. *Int Immunopharmacol* 2020; 82: 106375.

129. El Ansary M, Mogawer S, Abd Elhamid S, et al. Immunotherapy by autologous dendritic cell vaccine in patients with advanced HCC. *J Cancer Res Clin Oncol* 2013; 139: 39–48.

130. Lee J-H, Tak WY, Lee Y, et al. Adjuvant immunotherapy with autologous dendritic cells for hepatocellular carcinoma, randomized phase II study. *Oncoimmunology* 2017; 6: e1328335.

131. Wang N, Wang S, Li M-Y, et al. Cancer stem cells in hepatocellular carcinoma: an overview and promising therapeutic strategies. *Ther Adv Med Oncol* 2018; 10: 1–25.

132. Kelley RK, Gane E, Assenat E, et al. A phase 2 study of galunisertib (TGF-B1 receptor type I inhibitor) and sorafenib in patients with advanced hepatocellular carcinoma. *Clin Transl Gastroenterol* 2019; 10: e00056.