Consensus Statement

Hong Kong Consensus Statements for the Management of Unresectable Hepatocellular Carcinoma

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Abstract
Background: Hepatocellular carcinoma (HCC) is highly prevalent in Hong Kong due to the high prevalence of chronic hepatitis B infection. Liver cancer is the fourth most common cancer and the third most common cause of cancer death. Due to the high case load, there is a high level of local expertise in treating HCC, and the full spectrum of treatment modalities is available. This document summarizes how these modalities should be used based on the latest evidence. ***Summary:*** In 2 meetings held in early 2017, a multidisciplinary group of Hong Kong clinicians, including liver surgeons, interventional radiologists, clinical oncologists, and medical oncologists, met to update local consensus statements for management of HCC. These statements are based on the latest evidence and give detailed guidance on how to deploy these modalities, in particular for cases of HCC which are not suited to surgical resection.

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Key Messages: These statements give detailed information on how to decide if a patient is a candidate for resection, methods to improve candidacy for resection, and guidance for use of various nonsurgical interventions to manage patients ineligible for resection.

Introduction

Hepatocellular carcinoma (HCC) accounts for 80% of liver cancer and is the third most common cause of cancer death in the Asia Pacific region [1]. In Hong Kong, liver cancer is the fourth commonest cancer and the third commonest cause of cancer death [2], and HCC is highly prevalent in Hong Kong due to the high prevalence of chronic hepatitis B infection.

Treating HCC is challenging, as the patient needs to be treated for both a highly malignant tumor with a propensity for venous invasion, and impaired liver function or cirrhosis. HCC is treated in Hong Kong by surgical approaches, including liver resection, liver transplantation, and local ablation, and nonsurgical approaches such as transcatheter arterial chemoembolization (TACE), transcatheter arterial radioembolization (TARE), stereotactic body radiation therapy (SBRT), systemic chemotherapy, and the multikinase inhibitor sorafenib.

Several staging systems have been developed and applied to HCC to provide prognosis and guide treatment. The Barcelona Clinic Liver Cancer (BCLC) staging system [3] is widely endorsed and used in Western countries, but is not commonly used in Asia. BCLC staging was developed in Western countries where hepatitis C virus (HCV) infection, alcohol-related cirrhosis, and nonalcoholic fatty liver disease are the main attributable factors for HCC. In Asian populations, HCC is associated with endemic hepatitis B virus (HBV) infection, resulting in a higher case volume. The treatment recommendations from BCLC staging are perceived by physicians in Asia as too conservative, and with the high level of local expertise, a more aggressive treatment approach is taken, particularly the broader use of surgical resection.

The Hong Kong Liver Cancer (HKLC) staging system is a locally developed prognostic classification scheme that includes treatment guidance for Asian patients with HCC, validated using data from 3,856 patients treated in Hong Kong [4]. Additional local guidance comes from consensus recommendations published by Poon et al. [5] in 2015. The objective of this new consensus document is to update the 2015 recommendations according to the latest data, with a focus on treatment of unresectable HCC.

Methods

In 2 meetings held in February and March 2017, a multidisciplinary group of Hong Kong clinicians – hepatobiliary surgeons, medical oncologists, clinical oncologists, and interventional radiologists – met to formulate consensus statements on management of unresectable HCC. Local clinicians known to have a special clinical and/or research interest in HCC management were invited from the universities and major public hospitals of Hong Kong to form a panel that was broadly representative in terms of institutions and specialties.

Consensus statements were developed by designated group members prior to the meetings. Statements and the supporting evidence were presented to the group members and the statements modified according to the feedback. Each statement was assessed using a Likert scale (1 – Accept completely; 2 – Accept with some reservations; 3 – Accept with major reservations; 4 – Reject with reservations; 5 – Reject completely), and voting was performed anonymously to encourage independent responses. Acceptance was defined as 80% of the group accepting a statement completely or with some reservations. Where a consensus was not met, statements were revised and voted on until a consensus was met. The group evaluated each statement's level of evidence as per the 2011 Oxford criteria [6]. Where applicable, the levels are given in parentheses at the end of the statements.

Consensus Statements

The Role of Liver Cancer Staging Systems

1. The BCLC staging system is not conventionally used to stratify HCC patients for treatment in Hong Kong.
2. The HKLC staging system provides a better prognostic classification and treatment algorithm than BCLC in a HBV-predominant population (Level 2).
3. In patients from an HBV-predominant population with intermediate and locally advanced HCC, HKLC staging is better than BCLC in stratifying patients into various treatment modalities (Level 2).

The HKLC staging system incorporates parameters such as Eastern Cooperative Oncology Group (ECOG) status, presence of extrahepatic vascular invasion/metastasis, tumor size and number of nodules to stage liver cancer and guide treatment. HKLC staging has been compared with BCLC using data from almost 4,000 patients with HCC treated in Hong Kong between 1995 and 2008 [4]. HKLC staging showed superior ability to distinguish between patients with specific overall survival (OS) times and HKLC-assigned subsets of BCLC intermediate- and advanced-stage patients to more aggressive treatments which improved survival [4]. A comparison of BCLC and HKLC in 668 Chinese HCC patients confirmed HKLC to be superior for prognosis [7], and a comparison in a North American cohort of patients who received intra-arterial therapy for unresectable HCC found HKLC outperformed BCLC for survival separation, survival time, calibration, and discrimination[8].

Definition of Unresectable

4. Liver resection should be considered as a first-line curative treatment for HKLC intermediate-stage HCC, and with satisfactory liver function reserve.
5. Liver resection should be considered in HKLC locally advanced HCC when adequate function of future liver remnant (FLR) is anticipated.
6. Resection of both isolated extrahepatic metastasis and hepatic tumor may be considered in selected patients.
7. Selected patients with bilobar tumor may benefit from combined resection of the predominant tumor and resection or ablation of the contralateral nodules (Level 4).

Approximately 45% of patients with HCC in Hong Kong receive some form of surgery, a proportion that would fall to approximately 25%, if the more conservative BCLC recommendations were followed. Major and minor resection carries a mortality risk of approximately 5 and 1–2%, respectively. While transplantation is an effective option, donation rates in Hong Kong are lower than in the West.

Indications for partial hepatectomy include unilobar disease, and absence of invasion into the portal vein or inferior vena cava. Some patients with thrombus of the portal vein main branch have received resection and portal vein reconstruction [9], but long-term survival data are limited; such patients may be candidates for yttrium 90 (Y-90) radioembolization. Patients with severe chronic illness or decompensated cirrhosis are not resectable.

Prior to resection, liver function should be assessed with tests of bilirubin, alanine aminotransferase, aspartate aminotransferase, alkaline phosphatase, platelet count, Child-Pugh grade, and indocyanine green (ICG) retention. ICG retention should be performed in addition to Child-Pugh grading to better assess liver function in the future remnant [10]. The volume of the FLR should be assessed, with 20% considered acceptable for normal liver [10], 30% for postchemotherapy patients [11], and 40% for patients with cirrhosis [12]. Combined resection and intraoperative radiofrequency ablation (RFA) was analyzed in a retrospective case comparison study of 200 patients with HCC, with combination therapy found to be safe and effective in multifocal HCC, and an attractive option for bilobar disease [13]. The efficacy of

resection of predominant tumor and combined liver resection and RFA is supported by a cohort study that included 1,198 patients over a 20-year period [14].

In Hong Kong, the primary treatment for bilobar tumor is resection with the aim of achieving adequate liver reserve after the operation. Tumor size of 10 cm or more is not considered a contraindication to surgery; resection in patients with tumors of this size is supported by a retrospective study comparing surgical outcomes in patients grouped by tumor size which found a median survival of 38.0 months in patients with curative resection of solitary HCC larger than 10 cm [15].

8. For patients with inadequate FLR, portal vein embolization (PVE) can increase the chance of resection (Level 3).

PVE can be used to induce atrophy in the part of the liver to be resected and compensatory hypertrophy in the remnant part. A systematic review of 40 studies including 2,144 patients found that PVE is effective in increasing the FLR, allowing resection in patients who may otherwise be ineligible [16]. ALPPS, an alternative procedure, can produce more rapid liver growth, but with a higher risk of mortality compared with PVE (approximately 10 vs. 2%, respectively) [16, 17].

The Role of Local Ablation

9. Local ablation is an acceptable alternative to resection for small HCC (<3 cm) in Child-Pugh A/B patients (Level 4).

10. For resectable tumors 3–5 cm in patients with Child-Pugh A liver function, resection is the preferred option over ablation (Level 1).

A 2013 systematic review and meta-analysis covering 2 randomized controlled trials (RCTs) and 10 non-RCTs comparing RFA and resection in early-stage HCC up to 5 cm in size found that disease-free survival and OS are better with resection compared with RFA [18]; however, ablation was associated with fewer posttreatment complications and shorter hospital stays [18].

11. For HCC nodules 3–5 cm in diameter, the combination of TACE and ablation may be more beneficial than ablation alone (Level 1).

12. For solitary tumors 5–7 cm, ablation combined with TACE may be beneficial in selected patients (Level 4).

A recent meta-analysis of 7 RCTs found that RFA plus TACE significantly improved survival rates at 1, 3, and 5 years compared with RFA alone in patients with tumors >3 cm, but not in patients with tumors <3 cm [19]. The safety and efficacy of RFA in larger HCC was assessed in a study that compared the safety and efficacy of RFA in patients with smaller (≤3 cm) and larger (3.1–8.0 cm) tumors, finding RFA to be safe and effective for larger HCC [20].

13. RFA via the surgical approach is preferred when tumor location incurs a high risk of biliary or visceral injury by percutaneous approach, and may offer a survival benefit for patients with large HCC >3 cm (Level 3).

14. An ablative margin of <5 mm was significantly correlated with local recurrence in HCC (Level 4).

Percutaneous and surgical RFA have been compared in 162 patients with HCC in dangerous locations. Curative rates were similar in both groups, but the incidence of severe postoperative complications and local tumor progression was lower in the surgical RFA group [21]. Another case series found that while complete ablation rates are similar when performing the percutaneous approach versus the surgical approach for HCC (3.1–5 cm), 1- and 3-year survival rates are significantly higher in patients managed via the surgical approach [22]. A case series of patients who received computed tomography-guided RFA found an ablation zone with a minimal margin uniformly larger than 5 mm was associated with the best local tumor control [23].

15. Percutaneous ethanol injection still has a role in small HCC <2 cm not suitable for thermal ablation (Level 5).

    Although a meta-analysis of 5 randomized trials has shown that RFA is superior to ethanol injection in the treatment of small HCC in terms of treatment response, recurrence and OS, not all lesions are suitable for RFA (e.g., tumors near biliary tree or large vessels) [24]. For these, ethanol injection may be attempted. In Hong Kong centers, this is typically performed by injecting 90% absolute alcohol mixed with lipiodol under a general anesthesia or conscious sedation.

16. Microwave ablation is a safe and effective modality for treatment of HCC. It is an alternative option to RFA (Level 4).

    In Asia, microwave ablation is used as an alternative to RFA, with several studies reporting similar safety and efficacy outcomes [25–28]. In animal models, lesions that have been subjected to microwave ablation showed significantly less blood vessel-mediated cooling than lesions after RFA, suggesting that microwave ablation may lead to fewer tumor recurrences in the long term [29, 30].

17. High-intensity focused ultrasound (HIFU) ablation is safe and effective in the treatment of small HCCs. It can achieve survival outcomes comparable to those of RFA and thus serves as a good alternative treatment (Level 4).

18. HIFU ablation is generally well tolerated in HCC patients with Child-Pugh A/B cirrhosis. It may have some advantage in selected patients, such as those with ascites or with tumors close to major bile ducts (Level 4).

19. HIFU may be used as an alternative bridging therapy for HCC patients awaiting liver transplantation (Level 4).

    HIFU has been compared to RFA in 2 case series with small or recurrent HCC, with similar outcomes between the 2 techniques [31, 32]. HIFU is a well-tolerated treatment for HCC in patients with cirrhosis and ascites [31], and data from a retrospective study showed that significantly more HIFU-bridged patients had a complete response to treatment compared with TACE-treated patients [33].

20. Patients with a predominant large mass in one lobe and 1 or 2 small tumor nodules in the other lobe may benefit from combined resection of the predominant tumor and resection or ablation of the contralateral nodules (Level 4).

    Recent studies have shown that hepatectomy combined with RFA [13, 34] or other forms of ablation [35] is an effective, well-tolerated treatment for selected patients with multifocal disease.

    Role of TACE
21. TACE is recommended as a first-line treatment for patients with unresectable, large/multifocal HCCs, with no vascular invasion or extrahepatic spread, and with satisfactory liver function (Child-Pugh A or B) (Level 1).

22. Selective or super-selective TACE should be attempted in order to preserve nontumorous liver parenchyma, maximize treatment effect, and minimize complications (Level 5).

23. Selective TACE can be performed in patients with small tumors in whom ablation is difficult to perform because of tumor location or medical comorbidities (Level 5).

    In Hong Kong, TACE has emerged as the "standard" therapy for patients with unresectable HCC and Child-Pugh A/B cirrhosis, and its safety and efficacy in this population is supported by 2 RCTs [36, 37] and 3 out of 4 meta-analyses [38–41].

24. TACE can be considered in patients with unresectable HCC with segmental portal vein invasion (Level 4).

Although TACE has been contraindicated in HCC patients with portal vein thrombosis, several groups have reported that selective TACE can be used in these patients to improve OS [42]. However, a prospective controlled study found that the survival benefit of TACE is minimal for patients with major PVT, with a greater benefit evident for patients with segmental PVT [43].

25. TACE with drug-eluting beads (TACE-DEB) is an alternative treatment for HCC after conventional TACE fails, but there is no evidence of survival benefit over conventional TACE (Level 2).

Conventional TACE and TACE-DEB with doxorubicin-loaded beads have been compared in the PRECISION V randomized trial [44]. TACE-DEB was associated with higher rates of complete response, objective response and disease control compared with conventional TACE, but superiority was not demonstrated [44]. Based on data so far, conventional cisplatin-lipiodol TACE is the standard regimen in Hong Kong, with TACE-DEB reserved for patients who fail conventional TACE or have more advanced disease.

26. TACE should be repeated at intervals of 2–3 months based on assessment of tumor status and liver function (Level 4).
27. TACE should be stopped when there is liver impairment or other serious complications; or radiologic tumor progression, despite adequate drug administration (Level 5).
28. TACE should be stopped when there is absence of viable tumor (Level 5).

In Hong Kong, the usual practice is to repeat TACE when viable residual tumor or new tumor growth is observed in a patient with good liver function. The efficacy of TACE has been found to be greater when used only when tumor growth is detected [45]; therefore, computed tomography or magnetic resonance imaging should be used to monitor therapy. Other Asian guidelines have defined TACE failure as 2–3 rounds of treatment with no response [45–47], but the specific factors that guide when to stop TACE vary among centers, and a pragmatic approach is recommended including assessments of liver function, tumor status, and the detection of events such as extrahepatic spread or venous invasion.

29. The clinical benefit of additional sorafenib to TACE is minimal. Routine combination of sorafenib and TACE is not recommended (Level 1).

Several trials have evaluated the combination of sorafenib added to TACE or TACE-DEB, but no improvements in progression or survival from the addition of sorafenib were observed [48–50].

Role of TARE

30. TARE is useful as a bridge therapy to liver transplantation in suitable candidates (Level 4).
31. TARE is useful for Child-Pugh A patients with multifocal or large burden HCC (Level 5).
32. For unresectable or unablatable HCC >5 cm, TARE can be considered (Level 5).
33. TARE is useful for Child-Pugh A and selected Child-Pugh B patients with small burden HCC but fail to respond to conventional TACE (Level 5).

A recent publication from a Singaporean expert group is generally representative of other guidelines for use of Y-90 TARE to treat HCC. Y-90 TARE is an option as a bridging therapy in patients with early HCC awaiting transplant, in intermediate HCC patients who have failed conventional TACE, or in advanced HCC with vascular invasion [51]. A meta-analysis of 10 studies comparing Y-90 TARE and TACE, including 2 RCTs, concluded these 2 treatments have similar effects in terms of survival, response rate and safety profile, although tumor progression is delayed after TARE [52]. A retrospective case series has found similar major and minor complication rates between TACE and TARE, but greater hospitalization for both initial procedure and readmission, and worse postembolization syndrome, with TACE [53]. There is no published cost-effectiveness study on use of Y-90 TARE for HCC; a small

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randomized trial that evaluated health-related quality of life of patients with unresectable HCC did not find a significant difference between TACE and Y-90 TARE [54].

34. TARE is useful for HCC with vascular invasion, and disease is liver-dominant, and patients have bilirubin <2 mg/dL and Child-Pugh score ≤7 (Level 4).

While survival outcomes in radioembolized patients with main portal thrombosis are poor (3–6 months), more encouraging results are seen in patients with lobar or segmental portal vein thrombosis, with median survival times of 10–14 months after TARE [55, 56].

35. After unilobar TARE, it is advised to follow up the patient for at least 6 months, for possible disease downstaging and curative resection (Level 5).

Although Y-90 TARE is usually given with a palliative intent in Hong Kong, this treatment can induce tumor shrinkage or control, while promoting contralateral hypertrophy, which may permit future resection. While a systematic review of 7 studies examining contralateral hypertrophy after Y-90 TARE for diverse liver cancers found 26–47% contralateral lobe hypertrophy at 44 days to 9 months, this review is limited by the heterogeneity of the diseases treated, dose and delivery of Y-90 TARE, and time to measurement of hypertrophy. An analysis compared hypertrophy induced by PVE or Y-90 TARE in 52 patients with liver malignancies, pair-matched for criteria known to influence liver growth, finding that FLR volume increase was significant in both groups (PVE, 61.5%; Y-90 TARE, 29%; $p < 0.001$) [57]. Y-90 TARE may be useful for large, bulky tumors abutting essential vascular and/or biliary structures, or when the ability to achieve adequate oncological margins is a concern. Given the dynamic nature of tumor response, ipsilateral lobe atrophy, contralateral lobe hypertrophy, disease progression (e.g., formation of new lesions in untreated lobe, extrahepatic metastases), and potential complications such as portal hypertension and hypersplenism, we recommend patients are followed-up after Y-90 TARE clinically and with imaging to investigate possible disease downstaging and curative resection.

Two recent phase III trials have compared Y-90 TARE with sorafenib with consistent results in patients with advanced HCC, a population with poor prognosis. In both trials, Y-90 TARE showed a higher tumor response rate in the initial phase and a better adverse event profile than sorafenib, but neither trial showed a statistically significant difference in survival between treatment arms [58, 59].

Role of External Radiotherapy

36. SBRT is an acceptable option for unresectable HCC (up to 5 lesions) (Level 4).

37. SBRT can be considered for patients with limited liver reserve (up to Child-Pugh Grade B8 and platelet count ≥50 × 10^9/L).

38. SBRT can be an alternative to ablation for tumors close to major blood vessels or biliary duct (Level 5).

39. Local control can be achieved by SBRT with limited toxicities (Level 4).

40. SBRT can be considered as a bridging therapy before liver transplantation (Level 4).

In Hong Kong, the majority of HCC patients are inoperable (for resection or transplantation) at the time of diagnosis, and some tumor factors such as size (>5 cm), location, or portal vein invasion may preclude use of nonsurgical RFA. Historically, radiation therapy for liver metastases has been limited by the risk of radiation-induced liver disease, but new developments in SBRT reduce these limitations by using real-time stereotactic 3D tracking of organ and tumor position to deliver high-dose radiation to the tumor while minimizing excessive irradiation of the remaining liver and surrounding tissues. SBRT is typically delivered as several fractions (range, 1–6) over 1–2 weeks.

A review of published data on liver-directed SBRT including numerous retrospective and prospective phase I and phase II studies has demonstrated the safety and efficacy of SBRT [60]. SBRT for hepatic malignancies has been evaluated in a phase I/II study including 26

patients which reported a median survival of 11.1 months, and 1-year OS rate of 45%, with adverse events including a decline in Child-Pugh score in 9 patients and 2 grade 5 hepatic failures [61]. A small study has also evaluated SBRT as a bridge to transplantation, concluding it is a feasible and well-tolerated bridging therapy which may prolong a patient's candidacy for a curative liver transplant [62].

Patient selection criteria for SBRT in Hong Kong centers typically includes: Child-Pugh score of B8 or below; up to 5 lesions; uninvolved liver volume ≥700 mL (not compulsory); and platelet count ≥50 × 10^9/L. Repeated SBRT can be considered for new lesions in the liver not previously irradiated (time interval from last SBRT should be preferably 6 months or longer). Radiation is usually delivered in an individualized dose according to tumor volume, liver reserve, and technique. The dose may be up to 5 × 10 Gy, if dose constraints to the rest of liver or other normal organs can be met.

Data on SBRT in HCC patients with a Child-Pugh score of B8 and above are scarce due to the poor prognosis of this population. While some studies have suggested avoiding SBRT in patients with Child-Pugh score of B8 and above except as a bridge to transplant [63, 64], other studies of SBRT have included small numbers of such patients with encouraging results [65, 66]. A recent consensus statement recommends that SBRT be used with caution in all Child-Pugh B patients and only at low-dose volumes [67]. Clinical practice in Hong Kong is to treat selected Child-Pugh B8 patients with SBRT at the discretion of the treating physicians.

Role of Chemotherapy
41. There are inadequate data to establish chemotherapy as a standard treatment for advanced HCC.
42. FOLFOX and SECOX regimens are feasible options in selected fit patients with advanced, unresectable HCC (Level 5).

In a randomized trial comparing doxorubicin to no antitumor therapy in inoperable HCC, patients receiving doxorubicin had a survival benefit versus those receiving no antitumor therapy (10.6 vs. 7.5 weeks, respectively) but with fatal complications in 25% of patients [68]. Several trials have evaluated recombinant alpha-interferon (α-IFN) for HCC in Asian and Western patients. A randomized trial comparing doxorubicin with α-IFN in Asian patients found α-IFN induced better tumor regression and fewer serious or fatal complications [69], and a trial comparing α-IFN with no antitumor therapy found α-IFN improved survival and induced tumor regression [70]. α-IFN was compared with symptomatic treatment in a randomized trial in a Western population with HCC [71]; α-IFN did not modify the probability of progression and was not well tolerated in patients with cirrhosis.

Cisplatin/α-IFN/doxorubicin/fluorouracil (PIAF) combination therapy was compared with doxorubicin in HCC, with PIAF-treated patients having a nonsignificantly higher response rate and better survival than doxorubicin-treated patients [72]. However, PIAF was associated with higher treatment-related toxicity [72].

A randomized phase III trial compared sorafenib plus doxorubicin with doxorubicin alone in HCC, with sorafenib plus doxorubicin resulting in improvements to median time to progression, OS and progression-free survival (PFS) compared with doxorubicin [73]. Sorafenib has been compared with sorafenib plus doxorubicin in HCC in a recent phase III study, which found that the addition of doxorubicin resulted in higher toxicity, but did not improve OS or PFS [74].

Modified infusional fluorouracil, leucovorin, and oxaliplatin (FOLFOX4) has been compared with doxorubicin as palliative chemotherapy for HCC [75]. No significant differences in toxicities were observed, and although the trial did not meet its primary endpoint, a trend toward improved OS with FOLFOX4 was observed [75], and Chinese treatment guidelines for HCC recommend FOLFOX4 for advanced HCC patients [76].

Despite numerous trials, there are insufficient data to routinely recommend any chemotherapy regimen in HCC, and no such agent has been approved. Chemotherapy can be considered for patients who have failed to respond to sorafenib, providing performance status and organ functions are sufficient to tolerate it. A sorafenib, oxaliplatin, capecitabine (SECOX) regimen was evaluated in phase II study of 51 HCC patients with promising results [77], and a phase III study is ongoing [78]. Although the evidence base is limited, in Hong Kong FOLFOX4 or SECOX regimens have been adopted in some centers for advanced HCC patients with good results, especially in patients with lung metastases.

Role of Targeted Therapy
43. Sorafenib is currently the standard first-line systemic treatment for HCC with Child-Pugh A liver function who are not suitable for surgery, locoregional therapy or transarterial therapy (Level 2).
44. Regorafenib is an option for second-line treatment for patients who developed progressive disease to sorafenib treatment (Level 2).
Sorafenib has become a standard treatment for HCC in Asia and elsewhere, based on large RCTs which demonstrated a modest survival advantage [79, 80], although subgroup analyses of these data show the survival benefit is reduced in the presence of HBV infection [81, 82]. A phase III placebo-controlled trial has found regorafenib can improve survival of sorafenib-refractory patients by 2 months compared with placebo, with the commonly-reported adverse events including grade 3 diarrhea, hypertension, increased bilirubin, and hand-foot skin reactions (3,16,11, and 11% of patients, respectively) [83]. Additional phase III trials in this population are ongoing, and while results of second-line therapy trials are encouraging, the patients enrolled in these trials are often selected for better liver function and patient performance, and thus may not be representative of sorafenib-refractory patients encountered in clinical practice. The clinical experience with sorafenib in Hong Kong is consistent with the modest benefits seen in the studies.

A recent phase III trial has compared the multikinase inhibitors lenvatinib and sorafenib as a first-line treatment in patients with unresectable HCC [84]. Lenvatinib was noninferior to sorafenib for OS, and similar numbers of patients in both arms experienced treatment-emergent adverse events [84]. Patients in the lenvatinib arm had statistically significant improvements in PFS [84], time to progression, and objective response rate, suggesting lenvatinib may be a treatment option for advanced HCC.

Role of Immunotherapy
45. Anti-PD1 therapy is potentially a second-line or subsequent line of treatment in patients with sorafenib-refractory disease (Level 3).
In recent years, there has been considerable interest in therapeutically targeting immunoregulatory checkpoints to stimulate the immune system to attack tumors. HCC is an inflammation associated cancer and can be immunogenic [85], and HBV and HCV infection are associated with upregulation of circulating T-cell inhibitory receptor programmed cell death protein 1 (PD1) [86, 87]. In a study of HBV-associated HCC patients, upregulation of PD1 and its ligand (PD-L1) are associated with poor outcomes [88], and higher intratumoral expression of PD-L1 is associated with poorer disease-free survival and OS after hepatectomy [89]. Preclinical and clinical studies have shown that blockade of the PD1 pathway can induce tumor regression in various tumor types [90], and PD1 blockade with monoclonal antibodies has extended survival in mouse models of HCC [91, 92].

A phase I/II open-label dose-escalation trial has evaluated nivolumab, a humanized monoclonal antibody to PD1, in unresectable HCC patients who have good liver function, and have had disease progression on sorafenib [93]. Safety profile was similar to what has been

observed in other tumor types without any new safety signals [93]. Nivolumab maintained a manageable tolerability profile during escalation with common adverse events including fatigue, pruritus, rash, and diarrhea [93]. Objective responses were durable irrespective of HBV/HCV status, prior sorafenib treatment, or PD-L1 expression on tumor cells, and OS rate was encouraging [93]. Based on durable objective responses observed in a 154-patient subgroup of this trial, nivolumab was recently approved by the US Food and Drug Administration for HCC patients who have been previously treated with sorafenib [94]. A phase III study of nivolumab in patients with advanced HCC is ongoing [95], and future studies may identify biomarkers that predict response to anti-PD1/PD-L1 therapy.

Conclusions

These treatment guidelines integrate the latest evidence and expert opinion from physicians with a high level of experience in the management of HCC patients. Compared to other guidelines, we advocate a broader use of surgical resection, and distinct from other groups, our guidelines incorporate the HKLC staging system, which has shown favorable results in prognosis and guiding treatment in both Asian and non-Asian populations.

Our statements offer detailed guidance on assessing patient suitability for resection and techniques for increasing FLR; use of transplantation and guidance for antiviral therapy to reduce HCC incidence are summarized in the 2015 recommendations. Our recommendations for local ablation, TACE and TARE represent an evolution of the statements from the 2015 document. The emergence of sorafenib as a standard therapy and regorafenib as an emerging treatment for HCC is recognized, and the potential for immunotherapy is noted.
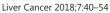
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