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Review

Hong Kong Consensus Recommendations on the Management of Hepatocellular Carcinoma

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Abstract
Background: Hepatocellular carcinoma (HCC) is particularly prevalent in Hong Kong because of the high prevalence of chronic hepatitis B (CHB) infection; HCC is the fourth commonest cancer in men and the seventh commonest in women, and it is the third leading cause of cancer death in Hong Kong. The full spectrum of treatment modalities for HCC is available locally; however, there is currently no local consensus document detailing how these modalities should be used. ***Summary:*** In a series of meetings held between May and October 2013, a multidisciplinary group of Hong Kong clinicians – liver surgeons, medical oncologists, clinical oncologists, hepatologists, and interventional radiologists – convened to formulate

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local recommendations on HCC management. These recommendations consolidate the most current evidence pertaining to HCC treatment modalities, together with the latest thinking of practicing clinicians engaged in HCC management, and give detailed guidance on how to deploy these modalities effectively for patients in various disease stages. ***Key messages:*** Distinct from other regional guidelines, these recommendations provide guidance on the use of antiviral therapy to reduce the incidence of HCC in CHB patients with cirrhosis and to reduce recurrence of CHB-related HCC.

The sixth most common cancer worldwide [1], hepatocellular carcinoma (HCC) is particularly prevalent in Hong Kong because of the high prevalence of chronic hepatitis B (CHB) infection – it is the fourth commonest cancer in men and the seventh commonest in women, and it is the third leading cause of cancer death in Hong Kong [2].

The full spectrum of treatment modalities for HCC is available locally, including surgical resection, liver transplantation, local ablation, transcatheter arterial chemoembolization (TACE), transcatheter arterial radioembolization (TARE), external radiotherapy, and the multikinase inhibitor sorafenib. However, there is currently no local consensus document detailing how these modalities should be used. The Barcelona Clinic Liver Cancer (BCLC) staging system [3] – widely accepted in clinical practice in Western countries – does not recognize the evolving role of a number of modalities in various disease stages [4], and so is viewed as inadequate for use in Asia. The consensus recommendations developed by the Asian Pacific Association for the Study of the Liver (APASL) [5] more closely reflect local clinical practice, but even these are unable to provide nuanced guidance on specific scenarios encountered by Hong Kong clinicians treating HCC. Very recently, Yau *et al.* published the Hong Kong Liver Cancer (HKLC) staging system, a prognostic classification scheme with treatment guidance for Asian patients with HCC [6]. However, while the staging system provides a treatment algorithm together with the classification scheme, they do not expound on specific treatment strategies.

There is a need for treatment recommendations that take into account local circumstances, and which span indications and specific techniques, to ensure optimum patient outcomes.

Methods

In a series of three meetings held between May and October 2013, a multidisciplinary group of Hong Kong clinicians – liver surgeons (n=5), medical oncologists (n=2), clinical oncologists (n=2), hepatologists (n=4) and interventional radiologists (n=3) – convened to formulate recommendations on HCC management. Local clinicians known to have a special clinical and/or research interest in HCC management were invited from the two universities and eight main 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 were circulated among the members and modified according to feedback. At the meetings, each statement was assessed on a five-point Likert scale (1. Accept completely, 2. Accept with some reservations, 3. Accept with major reservations, 4. Reject with reservations, 5. Reject completely); voting was done via electronic keypads to encourage independent assessment. Agreement by 80% of the group to accept completely a statement was defined as consensus on that statement. A statement for which consensus was not achieved was modified, after which it was voted upon until consensus was reached. Many of the statements were developed with reference to other regional consensus guidelines, including those of the APASL [5] and of the Japan Society of Hepatology (JSH) [7], with modifications based on local practice. Finally, the group evaluated each statement's level of evidence as per the 2011 Oxford criteria [8]. Where applicable, the levels are given in parentheses at the end of the recommendations.

Consensus Recommendations

Surgical Resection

1. Liver resection is generally a first-line curative treatment for solitary or multifocal HCC confined to the liver, anatomically resectable, and with satisfactory liver function reserve [5]. (Level 4)

2. In Child-Pugh A/B patients with ≤3 tumors measuring ≤2 cm in diameter, without extrahepatic lesions or vascular invasion, either resection or ablation may be conducted. (Level 4)

Resection is the mainstay curative treatment for small tumors, although ablation is often considered a viable alternative in the local setting. Location of the lesion is important: for centrally located tumors, the common practice in Hong Kong is to perform ablation in lieu of resection in an effort to preserve liver function. Resection of multinodular HCC is associated with reasonable long-term survival outcomes [9]. For tumors >2 cm in diameter, resection is preferred to ablation.

3. Resection may be considered in patients with intrahepatic portal vein or hepatic vein branch invasion; the presence of main portal vein or inferior vena cava tumor thrombosis is generally a contraindication for resection [5]. (Level 4)

An aggressive surgical strategy targeting patients with tumor thrombosis limited to the intrahepatic portal branches can result in significant survival benefit [10, 11]. This is corroborated by results from the performance assessment of the HKLC staging system, which demonstrated the survival benefit of radical curative therapies, including resection, for BCLC-B and BCLC-C patients classified as HKLC-II – a subset which includes patients with small tumors with intrahepatic vascular invasion [6].

4. Resection of isolated extrahepatic metastasis after hepatic resection is justified in selected patients. (Level 4)

There is an expanding body of evidence indicating favorable survival outcomes in selected HCC patients after resection of pulmonary or abdominal metastases [12–15].

5. Patients with a predominant large mass in one lobe and one or two small tumor nodules in the other lobe may benefit from combined resection of the predominant tumor and resection or ablation of the contralateral nodules [5]. (Level 4)

Recent studies have shown that combined hepatectomy and radiofrequency ablation (RFA) is a safe, effective treatment for selected patients with multifocal HCC [16–18]. Of note, in Hong Kong, some clinicians may elect to perform TACE first-line, followed by combined resection-ablation if there is good response to therapy, even in the absence of published data.

6. In HCC patients with borderline liver function and liver remnant volume for major hepatectomy, preoperative portal vein embolization to induce hypertrophy of liver remnant can reduce the chance of liver failure. (Level 1)

A meta-analysis of 37 studies, involving a total of 1,088 patients, concluded that preoperative portal vein embolization is safe and effective in inducing liver hypertrophy to prevent post-resection liver failure resulting from insufficient liver remnant [19].

7. Laparoscopic hepatectomy in selected patients is associated with long-term outcomes similar to open hepatectomy, with fewer operative complications and shorter hospital stays. (Level 4)

There have been no randomized controlled trials (RCTs) to date comparing open and laparoscopic hepatectomy for HCC. However, numerous matched case-control studies have reported similar survival rates comparing these modalities [20–23]. The likelihood of a favorable outcome is increased when the laparoscopic procedure is performed on properly selected patients by an experienced surgical team [21].

8. The anterior approach is the preferred approach for large, right-lobe HCC. (Level 2)

Results of a 2006 RCT showed that the anterior approach was associated with less operative blood loss and significantly longer overall survival (OS) compared with the conventional approach for large right liver tumors [24]. A more recent retrospective review reported a lower recurrence rate and longer disease-free survival (DFS) with the anterior approach, although an OS benefit was not demonstrated [25].

9. There is, as yet, no well-proven effective adjuvant treatment to prevent recurrence of HCC after curative-intent resection [5]. (Level 2)

10. Aggressive treatment of intrahepatic tumor recurrence with surgical or locoregional therapy can prolong patient survival [5]. (Level 4)

11. In selected patients with recurrent HCC within transplant criteria, salvage liver transplantation can be considered when repeated hepatic resection or ablation is not feasible. (Level 3)

Several approaches, including adjuvant interferon [26] and adoptive immunotherapy [27], have been reported to reduce HCC recurrence rates in small-sample RCTs, but their potential benefits have not been validated by subsequent studies. A recently completed trial of adjuvant sorafenib after surgical resection or local ablation did not meet its primary endpoint of improving recurrence-free survival [28]. To date, there have been no RCTs comparing survival outcomes of the various surgical and locoregional modalities in the treatment of recurrent HCC. Similar survival outcomes have been reported for repeated resection and RFA, although the greater repeatability of RFA, and that it can be delivered percutaneously, makes it an attractive option for selected patients [29]. Of note, a recently published retrospective analysis of data from a single center showed that salvage transplantation and repeated resection led to comparable survival outcomes, and that both treatments resulted in significantly better survival outcomes than repeated RFA [30]. In Hong Kong, it is the usual practice to attempt surgical resection to treat a first recurrence then perform RFA or TACE for subsequent recurrences.

Liver Transplantation

12. For patients aged ≤65 years with Child-Pugh C cirrhosis, liver transplantation provides the best curative treatment of early HCC within transplant criteria [5, 7]. (Level 4)

13. Transplantation can be considered for Child-Pugh A/B patients with unresectable HCC who meet transplant criteria. (Level 4)

14. In centers where graft shortage is a severe problem, resection or ablation as first-line treatment for Child-Pugh A patients, followed by salvage transplantation for recurrent tumors or liver failure, is a reasonable strategy [5]. (Level 4)

We adopted the position of the APASL and the JSH on orthotopic liver transplantation being the ideal first-line treatment for Child-Pugh C patients meeting the Milan criteria. The main barrier to implementation of this recommendation is donor availability – as in the rest of the region, there is a severe shortage of grafts in Hong Kong.

Liver transplantation for patients with small HCC and compensated cirrhosis remains controversial. While advocates point to the excellent disease-free survival outcomes associated with transplantation in this group [31, 32], critics argue that resection should be first-line instead, given that OS results of the two modalities are largely similar and that adding these patients to the transplant recipient pool will lengthen transplant waiting times, compounding the existing graft shortage. In Hong Kong, transplantation is occasionally considered for Child-Pugh A/B patients meeting the Milan criteria.

15. The University of California, San Francisco (UCSF) criteria may be used as an alternative to the Milan criteria, with acceptable long-term survival results; the survival benefits associated with other expanded criteria have yet to be validated. (Level 4)

Hong Kong transplant surgeons utilize the UCSF criteria, which expand the indication of transplantation to solitary tumors ≤6.5 cm, or three or fewer nodules with the largest lesion ≤4.5 cm and a total tumor diameter of ≤8.0 cm [33]. A growing number of cohort studies have shown that survival outcomes of transplant patients chosen under the UCSF criteria are comparable to that for Milan-qualified patients [34–36]. Other groups have proposed their own versions of expanded criteria [37–41], but the survival outcomes reported for patients chosen under these have yet to be validated in larger cohorts.

16. Living-donor liver transplantation is an acceptable option for HCC within transplant criteria when deceased-donor graft is not available, but the potential risk of donor mortality and complications need to be considered in offering such treatment [5]. (Level 1)

A 2012 meta-analysis covering seven studies and 1,310 patients [42], and a Canadian cohort study of 345 patients [43], found no differences in OS and recurrence rates between living-donor and deceased-donor transplantation. That there exists a small chance of donor mortality from complications of surgery [44], as well as the likelihood of recipient complications [45], mandates rigorous post-procedure follow-up of both recipients and donors of living-donor transplantation.

17. Bridge therapy using chemoembolization or local ablation may reduce dropout due to tumor progression with long waiting times of >6 months [5], but there is no proven benefit in long-term survival. (Level 4)

Bridge therapy refers to pre-transplant resection, local ablation or TACE to prevent tumor progression while the patient waits for transplantation. Importantly, tumor progression during this waiting period may be associated with vascular invasion, a strong determinant of postoperative recurrence [46]. The benefit of TACE is seen largely with mean waiting time in the transplant list of >6 months [47]. There is currently no evidence that bridge therapy in patients transplanted within 6 months of being listed reduces the risk of tumor progression or improves survival after transplantation.

18. The role of liver transplantation for HCC initially beyond transplant criteria downstaged to within criteria after locoregional therapy is still controversial. (Level 1)

Downstaging refers to reducing the size of a tumor via resection, local ablation or TACE, specifically to meet the criteria for transplantation [48]. A recent systematic review reported that downstaging is feasible in up to 69% of patients, with OS and DFS rates comparable to those in patients within transplant criteria [49]. Nonetheless, given the severe shortage of grafts in Hong Kong, we agreed that priority for transplantation should be given to patients *within transplant criteria*, whose chances for a good survival outcome are likely to be high. Adding downstaged patients to the transplant recipient pool will lengthen transplant waiting times, compounding the existing graft shortage.

Local Ablation

19. Local ablation is an acceptable alternative to resection for small HCC (<2 cm) in Child-Pugh A/B patients [5]. (Level 4)

20. Local ablation is the treatment of choice for unresectable, solitary HCC <5 cm or 2–3 nodules <3 cm in Child-Pugh A/B patients when transplantation is not feasible. (Level 4)

Image-guided percutaneous ablation therapies are frequently utilized in Hong Kong, with RFA the most widely used technique. It is generally accepted that local ablation is for patients with small HCC (<5 cm) confined to the liver that is unresectable due to limited liver reserve or compromised liver function [50]. Tumor size is a risk factor for both local recurrence [51, 52] and incomplete ablation [53]. A local study reported technical feasibility of complete ablation for tumors up to 8 cm in diameter [54], but the long-term survival benefit of RFA for such large tumors has yet to be established.

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

22. For >3 nodules, ablation combined with TACE may be beneficial in selected patients. (Level 4)

23. For solitary tumors 5–7 cm in diameter, ablation combined with TACE may be beneficial in selected patients. (Level 2)

A recently published meta-analysis of seven RCTs reported 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 [55]. Moreover, there is emerging evidence that the ablation-TACE combination provides a survival benefit over ablation alone in patients with multiple tumors [56] and in those with larger solitary tumors up to 7 cm [56, 57].

24. For resectable tumors 2–5 cm in diameter, whether RFA can replace resection as the treatment of choice remains controversial. (Level 1)

Surgical resection is associated with greater OS and DFS rates than RFA, according to the results of a 2013 systematic review and meta-analysis covering two RCTs and 10 non-RCTs; however, ablation is associated with fewer post-treatment complications and shorter hospital stays [58]. Conversely, there are data from other RCTs showing comparable long-term survival outcomes with resection and RFA [59, 60].

25. RFA via the surgical approach is preferred when tumor location incurs a high risk of biliary or visceral injury by the percutaneous approach, and may offer a survival benefit for patients with large HCC >3 cm. (Level 4)

The incidence of postoperative complications and local tumor progression is lower after surgical than after percutaneous ablation [61]. While complete ablation rates are similar when performing the percutaneous approach versus the surgical approach for medium-sized HCC (3.1–5 cm), 1- and 3-year survival rates are significantly higher in patients managed via the surgical approach [62].

26. RFA is superior to ethanol injection in the treatment of small HCCs in terms of treatment response, recurrence, and OS [5]. (Level 1)

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

Statement 26 is based on the results of a meta-analysis of five RCTs [63]. Nonetheless, not all lesions are suitable for RFA (e.g., tumors near the biliary tree); for these, percutaneous ethanol injection may be reasonably attempted.

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

29. Microwave ablation may be more effective than RFA for tumors adjacent to big vessels owing to less heat-sink effect; more clinical studies are needed to confirm this benefit. (Level 4)

In some Asian centers, microwave ablation is utilized as an alternative to RFA, with several studies reporting similar survival outcomes [64–67]. The heat-sink effect is defined as tissue cooling by adjacent visible vessels that causes deflection of the ablation zone away from the vessel [68]; this protective effect of blood flow in the liver may help explain the high rate of local recurrence seen in some clinical series of RFA [69]. In animal models, pathological examination of lesions that had been subjected to microwave ablation showed significantly less blood vessel-mediated cooling than lesions post-RFA [69, 70], suggesting that microwave ablation may lead to fewer tumor recurrences in the long term. However, prospective studies comparing microwave ablation to RFA are needed to show its clinical benefit for tumors close to major vessels.

30. 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 for patients with cirrhosis. (Level 4)

31. 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)

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

HIFU is now in use at one Hong Kong center [71], where similar survival outcomes compared with RFA for patients with HCC <3 cm [72] and for those with recurrent HCC [73] have been observed. HIFU can be performed safely in patients with gross ascites, which both serves as a medium for energy transfer and protects subcutaneous tissue from being damaged by the focused ultrasound energy [74]. Finally, data from a retrospective study showed that significantly more HIFU-bridged patients had a complete response to treatment compared with TACE-treated patients [75].

33. Irreversible electroporation should be considered an investigational modality in HCC. (Level 4)

We reviewed the promising data from preliminary studies of irreversible electroporation [76–78], but agreed that they are insufficient to develop a recommendation for (or against) its use in Hong Kong.

Transarterial Chemoembolization

34. 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/B) [5]. (Level 1)

35. Selective or superselective TACE should be attempted in order to preserve nontumorous liver parenchyma, maximize treatment effect, and minimize complications [5]. (Level 5)

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

TACE is the mainstay of therapy in Hong Kong for patients with large (>5 cm), unresectable HCC and Child-Pugh A/B cirrhosis, providing a significant survival benefit in this population [79–81]. That optimal TACE is premised on the highly selective embolization of tumor-feeding arteries makes it ideal even for small tumors, for which thermal ablative therapies are contraindicated.

37. TACE may offer survival benefit in HCC patients with minimal portal vein invasion [7]. (Level 1)

Portal vein thrombosis is generally considered a contraindication to TACE, but an ever increasing number of studies are reporting favorable survival outcomes with TACE in patients with minimal portal vein invasion [82–84]. Indeed, a recent meta-analysis of eight controlled trials reported survival benefits with TACE compared with conservative treatment in HCC patients with portal vein tumor thrombus, even in those with main portal vein obstruction; however, temporary liver decompensation and postembolization syndrome were noted to occur frequently [85].

38. TACE can be used as a bridge therapy for HCC patients awaiting transplantation. (Level 4)

There is evidence from small-sample, retrospective studies that bridge therapy with TACE is associated with good survival outcomes after liver transplantation [86, 87]. Furthermore, TACE may lower the HCC recurrence rate in patients meeting the Milan and UCSF criteria, and the response to TACE is likely a good indicator of low recurrence [88].

39. There is insufficient evidence to specify the most effective chemotherapeutic agent or combination regimen for TACE. (Level 1)

This was the conclusion of a 2007 systematic review of cohort and randomized studies of transarterial therapies [89]. Of note, cisplatin is the most widely used chemotherapeutic agent for conventional TACE procedures in Hong Kong, whereas doxorubicin is the preferred agent for TACE with drug-eluting beads (DEB).

40. TACE with DEB is a safe and effective treatment for HCC, but there is no clear evidence of survival benefit over lipiodol-based conventional TACE. (Level 1)

41. TACE-DEB may offer better tumor control in patients with advanced tumors, or in those who have failed conventional TACE. (Level 2)

The PRECISION V study randomized 212 patients with Child-Pugh A/B cirrhosis and large and/or multinodular, unresectable HCC to treatment with either TACE with doxorubicin-loaded beads or conventional TACE with doxorubicin [90]. Although TACE-DEB was associated with higher rates of complete response, objective response and disease control compared with conventional TACE, superiority was not demonstrated. A 2013 meta-analysis of seven studies concluded that the techniques yield comparable treatment response rates [91]. In PRECISION V, patients with Child-Pugh B cirrhosis, Eastern Cooperative Oncology Group (ECOG) 1 performance status, bilobar disease and recurrent disease displayed a significantly better response with TACE-DEB than with conventional TACE [90]; these findings validate the current practice of Hong Kong clinicians who reserve TACE-DEB for patients with more advanced tumors or for those in whom conventional TACE failed.

42. TACE should be repeated at intervals of 2–3 months based on assessment of tumor status and liver function. (Level 4)

In Hong Kong, the usual practice is to perform repeat-TACE when viable residual tumor or new tumor growth is observed in a patient with good liver function. Assessment of tumor status via computed tomography or magnetic resonance imaging is crucial: the efficacy and tolerability of TACE has been found to be greater when used only when tumor growth is detected [92]. Moreover, results of a recent retrospective study of 116 patients with unresectable HCC showed that, after a second chemoembolization procedure, up to 47% of initial TACE nonresponders showed a significant response [93]. Therefore, a reasonable approach would be to perform at least two TACE procedures on the same targeted lesion, after which further treatment with another modality should be considered if TACE fails.

43. TACE should be stopped when liver impairment develops or there are other serious complications. (Level 5)

44. TACE should be stopped when there is radiologic tumor progression (e.g., extrahepatic spread, development of vascular invasion, increase in tumor size) despite adequate drug administration. (Level 5)

45. For patients with post-TACE tumor progression confined to the liver, other locoregional therapies, such as Y-90 radioembolization, can be considered. Patients with extrahepatic spread should be treated with systemic therapy. (Level 5)

Currently, there is no consensus on what constitutes "TACE failure." Raoul *et al.* proposed that no response after at least two sessions of TACE signifies TACE failure [94]. More recently, a panel of Asian experts defined TACE failure as no response after three or more TACE procedures to the same area within a 6-month period [95]. With statements 43 and 44, we specified two scenarios for which further TACE treatment is no longer warranted.

In general, TACE does not induce significant long-term worsening of liver function in patients with Child-Pugh A/B cirrhosis [96]; however, should hepatic decompensation occur after a TACE procedure, a repeat TACE is contraindicated because the ischemic damage associated with embolization can lead to a rapid decline in liver function and, potentially, death. Likewise, development of other serious post-TACE complications – including hepatic

artery injury, non-target embolization, liver abscess, and variceal bleeding [97] – should preclude further TACE procedures. We agreed that radiologic progression after at least two TACE procedures warrants consideration of alternate therapy: TARE for patients with intrahepatic tumor progression, and sorafenib for patients with extrahepatic tumor spread.

46. Patients with liver-dominant tumor and limited extrahepatic spread may benefit from TACE. (Level 1)

Notwithstanding our recommendation of systemic therapy for patients with advanced HCC, there is growing evidence that this group may also derive benefit from TACE: a systematic review of 15 studies of TACE in HCC patients with vascular invasion or extrahepatic metastasis concluded that TACE can be safely performed in these patients [98]. Notably, four studies included in the review reported that TACE prolonged OS compared with conservative management, with patients with portal vein branch invasion and well-preserved liver function having more favorable survival outcomes. Of note, some Hong Kong clinicians will occasionally perform TACE in patients with small lymph node metastases or isolated lung metastasis, putting them at the leading edge of worldwide TACE practice.

Transarterial Radioembolization

47. TARE with yttrium-90-loaded resin/glass beads may be used as an alternative locoregional treatment for unresectable HCC. (Level 4)

48. TARE with yttrium-90 may offer benefit over TACE in HCC patients with large tumors, or tumors with portal vein invasion. (Level 4)

Three large-scale retrospective series have shown that TARE is a safe and effective treatment for patients with unresectable HCC [99–101]. International treatment guidelines acknowledge its role in the locoregional treatment of unresectable HCC [102, 103]. In Hong Kong, TARE is regarded mainly as an alternative to TACE, which is still preferred by most clinicians as the former requires substantially more time, cost and effort.

Whereas a compromised portal circulation is usually considered a contraindication to TACE, it is not considered a contraindication to radioembolization – the injected microspheres are unlikely to have a significant macroembolic effect that could lead to liver decompensation [104]. Regrettably, survival outcomes in radioembolized patients with main portal vein thrombosis have not been favorable (e.g., 3–6 months) [105, 106]. Patients with lobar or segmental portal vein thrombosis have fared better in studies, with median survival times of 10–14 months post-TARE [104, 105].

49. Lobar or segmental TARE can be used to induce lobar shrinkage and contralateral lobar hypertrophy, downstaging tumor for potential subsequent resection. (Level 4)

Subsequent resection after successful downstaging with TARE has been described in the literature [107, 108]; in selected patients, this approach provides the possibility of long-term survival [109]. Resection is usually carried out around 6–8 months after downstaging to allow time for the target tumor to shrink, the non-tumorous liver to hypertrophy, and remaining radiation to dissipate.

50. There is no evidence of clinical benefit of TARE over conventional TACE for patients with multinodular tumors without vascular invasion. (Level 4)

Retrospective analyses have shown that TARE and TACE result in similar survival and safety outcomes in patients with unresectable HCC [110, 111]. Very recently, however, the open-label, multicenter, pilot SIRTACE study showed that, after patients received a mean of 3.4 TACE interventions or one TARE treatment (yttrium-90 loaded resin microspheres), median progression-free survival (PFS) and OS were not significantly different between the two groups, suggesting that a single session of TARE may be as safe and effective as multiple TACE sessions; however, the study was not designed to measure differences in survival outcome [112]. Greater clarity on this issue will be derived from the results of the phase II, multicenter,

randomized, controlled TRACE trial, which will directly compare TACE-DEB with TARE (yttrium-90 loaded glass microspheres) [113].

External Radiotherapy

51. High-precision radiotherapy offers effective local control to selected HCC confined to the liver, with an acceptable toxicity profile in patients with Child-Pugh A cirrhosis. (Level 4)

52. High-precision radiotherapy is a viable option for unresectable HCC that is ineligible for or refractory to TACE or other locoregional therapies. (Level 4)

Recent advancements in radiotherapy technique now allow the delivery of a radiation dose that tightly conforms to tumor outline while sparing normal liver tissue [114]. High-dose, three-dimensional conformal radiotherapy (3-DCRT) has been shown to be well tolerated in the treatment of HCC patients with Child-Pugh A/B cirrhosis, with favorable response rates [115]. A local retrospective study of HCC patients treated with stereotactic radiotherapy showed a median survival of 23 months, and 1-year and 3-year OS rates of 62% and 28%, respectively [116]; similarly, a median survival of 17.2 months and a 1-year OS rate of 71.7% were reported by a local study assessing image-guided, highly-conformal radiotherapy [117].

In Hong Kong centers where TARE is not available, HCC patients have been shown to respond well to external radiotherapy. Results of a Korean series of 158 patients with unresectable HCC – including 51 patients undergoing salvage therapy after failure of repeated TACE – showed that external radiotherapy is associated with a median survival of 16 months, and 2-year and 5-year OS rates of 30.5% and 9%, respectively [118]. In a recently published Canadian prospective trial of stereotactic body radiation therapy (SBRT) in patients with predominately large, advanced-stage HCC not eligible for surgery, RFA or TACE, the authors reported a median OS of 17 months and a local control rate of 87% at 1 year [119].

53. High-precision radiotherapy may be combined with TACE for unresectable HCC, but the optimal sequencing and timing is not known, and the survival benefit is uncertain. (Level 4)

Patients with small, solitary, primary HCC treated with TACE followed by SBRT have been found to have greater complete response rates and longer DFS than patients treated with TACE alone [120]. Similarly, advanced HCC patients treated with TACE followed by 3-DCRT achieved favorable response rates and 1-, 3- and 5-year OS rates in a retrospective, non-comparative analysis [121]. A retrospective analysis of data from 412 registry patients concluded that the combination of TACE and 3-DCRT is a safe, effective option for relieving and/or stabilizing portal vein tumor thrombosis associated with advanced HCC [122]. More recently, Tang *et al.* retrospectively compared 3-DCRT followed by TACE versus surgical resection followed by TACE, and found that patients treated with the 3-DCRT-TACE combination had significantly greater OS rates than patients treated with the resection-TACE combination [123].

Systemic Treatments

54. Sorafenib is the first-line treatment for advanced-stage patients with Child-Pugh A cirrhosis who are not suitable for locoregional therapy [5]. (Level 2)

55. Sorafenib may possibly impart a survival benefit in selected patients with compensated Child-Pugh B cirrhosis. (Level 4)

In Hong Kong, sorafenib is the standard of care for patients with advanced HCC (i.e., extrahepatic spread or portal vein invasion) and Child-Pugh A cirrhosis. In two RCTs, sorafenib treatment was shown to prolong survival in patients with advanced disease which was not amenable to, or had progressed after, surgery or locoregional therapy [124, 125].

A retrospective analysis of data from 172 Hong Kong Chinese patients with advanced HCC treated with sorafenib showed similar clinical benefit rates and PFS comparing Child-

Pugh A patients and Child-Pugh B patients [126]. Conversely, PFS, time to progression (TTP) and OS were markedly longer in Child-Pugh A patients compared to Child-Pugh B patients in a prospective study of 300 Italian patients; nonetheless, the authors concluded that their data suggest that patients with Child-Pugh B cirrhosis may still benefit from sorafenib [127].

Importantly, worsening cirrhosis was associated with worsening outcomes – whereas Child-Pugh B patients with a cirrhosis score of 7 had a median OS similar to those with Child-Pugh A cirrhosis (5.4 versus 6.1 months), those with a score of 8 or 9 had a significantly less favorable survival outcome (2.3 months) in the local study [126]. Similar findings were observed in a retrospective study of 267 Korean patients [128].

In terms of safety, whereas the incidence of side effects was similar comparing Child-Pugh A patients and Child-Pugh B patients, Child-Pugh B patients developed more cirrhotic complications, including anemia, gastrointestinal bleeding and hepatic encephalopathy [126]. Therefore, the option for sorafenib treatment should be extended only to Child-Pugh B patients with "compensated cirrhosis," i.e., patients who have not developed cirrhotic complications; these patients should then be closely monitored for the development of such complications. The results of the global, non-interventional GIDEON study, aimed at evaluating the safety of sorafenib in all patients with unresectable HCC under real-life practice conditions, particularly for Child-Pugh B patients, are eagerly awaited [129].

56. Patients with extrahepatic tumor progression after locoregional therapy and with compensated liver function should be treated with sorafenib. (Level 2)

57. Sorafenib may also be used in patients with intrahepatic tumor progression after locoregional therapy and with compensated liver function. (Level 5)

A subanalysis of the pivotal SHARP trial showed that patients with macroscopic vascular invasion and/or extrahepatic spread treated with sorafenib had longer OS (8.9 versus 6.7 months) and TTP (4.1 versus 2.7 months) than patients treated with placebo; this is comparable to the outcomes in patients without macroscopic vascular invasion and/or extrahepatic spread, with those given sorafenib having an OS of 14.5 months versus 10.2 months for patients given placebo [130].

We recommend TARE (see statement 45) or external radiotherapy (see statement 52) for patients with intrahepatic tumor progression after TACE. However, given that sorafenib benefits patients with extrahepatic spread post-locoregional therapy, sorafenib may be a reasonable option even for those with intrahepatic spread.

58. There is evidence of safety for the combination of TACE and sorafenib in patients with intermediate/advanced-stage HCC; however, more evidence from phase III randomized clinical trials is needed to show survival benefit. (Level 2)

The phase II, single-arm, open-label START trial showed that conventional TACE followed by sorafenib is safe and effective, with no unexpected side effects [131]. The few RCTs that have been published have corroborated these safety findings but have not reported an OS benefit [132–134].

59. The combination of sorafenib and chemotherapy may provide a survival benefit in selected patients with advanced HCC. (Level 2)

Data from a phase II, multinational RCT of 96 patients with advanced HCC and Child-Pugh A cirrhosis showed that treatment with sorafenib plus doxorubicin resulted in greater median TTP, OS and PFS compared with doxorubicin monotherapy [135]. More recently, Yau *et al.* reported the results of a phase II, multicenter, single-arm study evaluating the efficacy and tolerability of the combination of sorafenib, oxaliplatin and capecitabine (SECOX) in the treatment of 51 Asian patients with advanced HCC mostly from Hong Kong: median TTP was 5.29 months, median PFS was 5.26 months, and median OS was 11.73 months [136]. The authors concluded that their data support the conduct of an RCT comparing SECOX and sorafenib monotherapy in the treatment of advanced HCC.

Antiviral Therapy

60. Nucleoside/nucleotide analogue treatment may reduce the incidence of HCC in CHB patients with cirrhosis. (Level 4)

Recently published cohort studies support this approach; for instance, data from two studies showed that long-term treatment with the nucleoside analogue entecavir reduced the risk of HCC in patients with CHB [137, 138]. However, we noted that most trials examining this issue have been observational in nature. Furthermore, pooled data from 49 studies showed that HCC still developed at a rate of 1.3 per 100 patient years in CHB patients already receiving oral antiviral therapy [139], underscoring the need for continued HCC surveillance even in this treated population.

61. Nucleoside/nucleotide analogues have been shown to reduce recurrence and prolong survival after resection of hepatitis B virus (HBV)-related HCC and are recommended after curative hepatectomy. (Level 1)

62. Interferon-based antiviral treatment may reduce recurrence and prolong survival after complete removal or ablation of HCV-related HCC but is associated with significant side effects. (Level 1)

Results of a meta-analysis of nine studies, involving a total of 551 patients who had undergone either resection or ablation for HBV-related HCC, showed that post-treatment antiviral therapy was associated with a 41% reduction in risk of recurrence, as well as significant reductions in liver-related and overall mortality, compared with no therapy [140]. Antiviral therapy is particularly important for patients with a high viral load, for whom it is recommended before and/or after curative therapy of HCC [141].

Similarly, a meta-analysis of five studies, involving a total of 355 patients who had undergone curative treatment for HCV-related HCC, showed that interferon-alpha was associated with a 67% reduction in risk of recurrence, particularly in populations achieving high rates of sustained virologic response (SVR) [142]. However, interferon-alpha is associated with a wide spectrum of side effects (especially hematological toxicity) [143], the occurrence of which, especially in cirrhotic patients, can prevent reaching and maintaining the dose needed for maximal SVR. The use of new direct-acting antivirals for HCV is associated with SVR rates as high as 90% after only 12 weeks of treatment [144]; however, current data are insufficient to make a recommendation for their use in preventing HCC recurrence.

63. Anti-HBV therapy may reduce the risk of reactivation and liver failure in patients undergoing TACE and is recommended. (Level 4)

In a retrospective study examining 590 hepatitis B surface antigen-positive HCC patients who had undergone either surgical resection or TACE, the HBV-reactivation rate in the group of TACE-treated patients who had received anti-HBV therapy was 1.5% versus 17.5% in those who had not received anti-HBV therapy, and the rates of deterioration of liver function were 1.5% and 8.1%, respectively [145].

Conclusion

These recommendations consolidate the most current evidence pertaining to HCC treatment modalities, together with the latest thinking of practicing clinicians engaged in HCC management, resulting in detailed guidance on how to deploy these modalities effectively for patients in various disease stages.

Distinct from other guidelines, such as those developed by the European Association for the Study of the Liver [146] and the American Association for the Study of Liver Diseases [147, 148], these recommendations eschew traditionally imposed restrictions on the use of

certain modalities for specific stages only; emerging evidence from new studies, coupled with our experience of positive outcomes in our patients, is substantiating the benefit associated with the use of these modalities beyond the established indications (e.g., transplantation for Child-Pugh A/B patients with unresectable HCC who meet transplant criteria; TACE for patients with minimal portal vein invasion or extrahepatic spread). Moreover, the recommendations cover treatments not reviewed or endorsed by previous guidelines (e.g., HIFU for small HCCs; TARE for patients with unresectable HCC; the combination of sorafenib and chemotherapy for advanced HCC).

Notably, these recommendations provide guidance on the use of antiviral therapy to reduce the incidence of HCC in CHB patients with cirrhosis, and to reduce recurrence of CHB-related HCC.

Conflict of Interest

None declared.

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