

An overview in management of hepatocellular carcinoma in Hong Kong using the Hong Kong Liver Cancer (HKLC) staging system

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Abstract: In Hong Kong, liver cancer is the fifth most common cancer and the third most common cause of cancer deaths. The prevalence of hepatitis B is high in Hong Kong because of the high rate of hepatitis B virus infection, and chronic hepatitis B has remained the leading cause of hepatocellular carcinoma in the city, accounting for 80% of all cases in the period from 1992 to 2016. In view of the different etiologies of hepatocellular carcinoma around the world, a group of liver experts in Hong Kong developed the Hong Kong Liver Cancer staging system in order to provide more aggressive treatment guidance (predominantly a wider use of surgical resection) for Asian patients of hepatocellular carcinoma. In this article focussing on the Hong Kong Liver Cancer staging system, we briefly reviewed the screening criteria adopted in Hong Kong for liver resection, local ablation, transcatheter arterial chemoembolization, transcatheter arterial radioembolization, stereotactic body radiation therapy, and systemic therapy.

Keywords: HKLC, HCC, SBRT, liver cancer staging, cirrhosis, hepatectomy, ablation, systemic therapy, laparoscopic

Introduction

Globally, liver cancer shows a remarkable distribution in which more than 80% of hepatocellular carcinoma (HCC) cases occur in the East-Asian region (1). In Hong Kong, liver cancer is the fifth most common cancer (with a total of 1,834 registered cases) and the third most common cause of cancer deaths (10.8%) (2). According to data from the cancer registry, the incidence and mortality of liver cancer are higher in men (fourth and third respectively among all cancers) than in women (eleventh and fourth respectively among all cancers). The prevalence of hepatitis B is high in Hong Kong because of the high rate of hepatitis B virus infection, and chronic hepatitis B has remained the leading cause of HCC in the city, accounting for 80% of all cases in the period from 1992 to 2016 (3).

The mechanism of hepatitis B carcinogenesis includes a combination of gradual liver cell necrosis, inflammation, massive fibrosis, and eventual cirrhosis. Overall, the duration between hepatitis B virus infection and development of HCC may take as long as 50-60 years (4). Therefore, depending on the degree of malignancy, the severity of neighboring invasion and the adequacy of remnant liver function, treating HCC could be extremely challenging and long in duration. Treatment plans are personalized for maximum benefits

for patients. Currently, surgical (liver resection, liver transplantation, local ablation, *etc.*) and non-surgical modalities (transcatheter arterial chemoembolization (TACE), stereotactic body radiation therapy (SBRT), chemotherapy, targeted therapy, *etc.*) are available for HCC treatment in Hong Kong.

In view of the different etiologies of HCC around the world, a group of liver experts in Hong Kong developed the Hong Kong Liver Cancer (HKLC) staging system (Figure 1) in order to provide more aggressive treatment guidance (predominantly a wider use of surgical resection) for Asian HCC patients (5). In most Western regions, where the Barcelona Clinic Liver Cancer staging system is widely used, the main risk factors for HCC development are chronic hepatitis C, alcohol-related cirrhosis and non-alcoholic fatty liver disease instead of chronic hepatitis B as in Asia. The HKLC staging system, supported by data from 3,856 patients treated in Hong Kong, has successfully identified patients who are suitable for more aggressive treatment (6).

Screening

Alpha-fetoprotein (AFP) is the most widely used biomarker for HCC detection. However, an elevation of AFP level can also be seen in conditions like germ

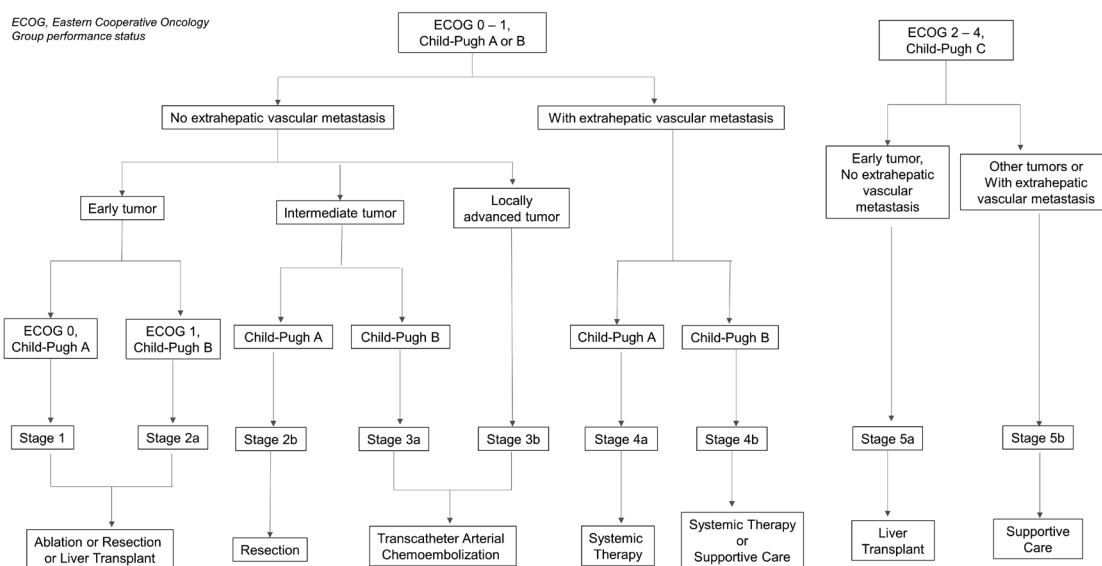


Figure 1. Summary of the Hong Kong Liver Cancer (HKLC) staging system.

cell tumors, liver inflammation (*e.g.* chronic hepatitis), regenerating nodules, and pregnancy. Furthermore, up to 40-50% of HCCs are non-AFP-secreting, further lowering the sensitivity of AFP alone for detection. It was reported that the sensitivity of AFP for detecting early HCC ranged from 39 to 65%, whereas the specificity ranged from 76 to 97% (7). Ultrasound can be used in conjunction with AFP for more reliable clinical surveillance. A meta-analysis reported that ultrasound alone had a sensitivity of only 47% in detecting early-stage HCC in cirrhotic patients, while another study reported that the addition of AFP to ultrasound imaging remarkably increased the sensitivity of early HCC detection (8). To date, the Cancer Expert Working Group on Cancer Prevention and Screening has made the following screening guidelines after reviewing scientific evidence and local epidemiology (9). For persons at average risk, routine screening with AFP and ultrasound is not recommended. Patients with chronic hepatitis B or C or liver cirrhosis are categorized as a high-risk group for HCC development. Routine cancer surveillance (*e.g.* every 6-12 months) with AFP and ultrasound is recommended depending on patients' age, family history, presence of cirrhosis, and other clinical conditions.

The role of surgery

Liver resection

According to the HKLC staging system, liver resection should be considered the first-line treatment for patients with intermediate-stage HCC who have desirable liver function reserve. Indications for liver resection include unilobar disease and absence of invasion of the portal vein and inferior vena cava (5). While imaging

techniques such as computed tomography and magnetic resonance imaging provide evidence of liver size and tumor position, liver function must be assessed before resection so as to formulate the best surgical procedures. The volume of functional liver reserve should be measured by multiple qualitative and quantitative tests to establish a reliable preoperative assessment. Hence, a tumor larger than 10 cm should not be considered to be a contraindication to liver resection if the liver reserve is satisfactory and a curative resection is expected. This has been supported by a retrospective study comparing surgical outcomes in patients with different tumor sizes. In the study, the median survival of patients with curative resection of solitary HCC larger than 10 cm without macroscopic venous invasion was 38.0 months (10). To study the actual functional liver capacity, biochemical parameters are measured and scoring systems (*e.g.* Child-Pugh score and Model for End-stage Liver Disease score) are used to grade the extent of disease. The indocyanine green (ICG) clearance test should be performed and used together with Child-Pugh classification for better assessment of liver function reserve. The cut-off values for a safe major hepatectomy and minor hepatectomy are 14% and 22% respectively (11). These values could be pushed higher in relatively young patients and those with a sufficient remnant liver volume. A study of 68 patients in Hong Kong revealed a significant correlation between liver stiffness measurement and ICG retention rate at 15 minutes after injection (ICG-R15). The combination of ICG-R15 and liver stiffness measurement may be used for better prediction of outcomes in potential liver resection candidates (12). Aspartate transferase level and alanine transferase level are markers of liver damage and correlate with the extent of hepatocellular necrosis rather than the actual liver function. Albumin

and clotting factors are exclusively synthesized by the liver, and therefore their plasma concentrations can indicate liver function. While plasma bilirubin concentration provides indirect information on the uptake, conjugation and excretion functions of the liver, non-hepatic factors may also influence the plasma bilirubin level. As a result, plasma bilirubin concentration is often used in combination with other laboratory findings and clinical grading systems. Minimally invasive liver surgery initially benefitted patients who had liver metastasis but relatively normal liver function. However, minimally invasive surgical techniques have become much more advanced. Nowadays, it is a common practice to remove HCCs in cirrhotic patients by minimally invasive surgery. It was reported that minimally invasive liver resection resulted in fewer short-term complications but similar long-term oncological outcomes when compared with open liver resection (13,14).

Local ablation

In general, liver resection remains the "gold standard" treatment for HCC in Hong Kong if the tumor is operable and satisfactory liver remnant function is expected. Local ablation can be considered an alternative approach to resection for small HCCs (< 3 cm) in Child-Pugh A/B patients. Surgical resection remains the preferable option for resectable tumors (3-5 cm) in patients with good functional liver reserve.

Radiofrequency ablation (RFA) utilizes high-frequency radio waves delivered *via* a needle electrode to cause destruction of tumor by local heating. A local randomized clinical trial comparing treatment outcomes of hepatic resection and radiofrequency ablation in early-stage HCC (solitary tumor no larger than 5 cm; or no more than 3 tumors, each 3 cm or smaller) revealed that they both shared similar clinical data in terms of tumor reoccurrence, overall survival and disease-free survival. In addition, RFA was associated with shorter hospital stay, less blood loss and shorter treatment duration due to its less invasive procedure (15). However, another study found that RFA is more likely to result in incomplete clearance of tumor at specific sites of the liver, in which surgical resection may be the more suitable option (16). Nevertheless, RFA alone has a tendency to achieve good tumor growth control in small HCC tumours and is recommended for such patients (17). RFA has also proved to be safe and effective when adopted in combination with other interventions. This was supported by a retrospective study in which the prognosis and treatment outcomes of patients with multifocal HCC and similar tumors characteristics were reviewed. The group receiving both surgical resection and RFA had fewer major resections (32% vs. 62%), less blood loss (400 vs. 657 mL), shorter operation time (270 vs. 400 min) and shorter

hospital stay (7 vs. 8.5 d) than that receiving only surgical resection (18). For HCC larger than 3 cm, RFA was found to be safe and effective. The study suggested that an overall ablation rate of 91% was achieved for HCCs 3.1-8.0 cm in size with a treatment mortality rate of 3% (19). A systematic review and meta-analysis showed that RFA plus TACE was associated with a more significant advantage in recurrence-free survival and overall survival than a stand-alone treatment with RFA (20).

Microwave ablation is used as an alternative to RFA. Multiple studies have reported a similar efficacy and safety profile to RFA, with microwave ablation being superior in larger HCC nodules (21-23).

High-intensity focused ultrasound (HIFU) ablation is a truly non-invasive tumor ablation technique, which requires an extracorporeal source of ultrasound beams targeting lesions *via* intact skin without surgical technique (24). In Hong Kong, HIFU ablation is one of the treatment options adopted as a bridging therapy for HCC patients awaiting deceased donor liver transplantation. HIFU ablation is generally well tolerated in HCC patients with advanced cirrhosis and gross ascites (25). This modality is also safe for Child-Pugh A and B patients and even for selected Child-Pugh C patients, offering them a good alternative before transplantation (26). Figures from a retrospective study showed that patients with unresectable HCC receiving HIFU ablation had a significantly better rate of complete response and long-term survival rates compared to that receiving TACE as primary treatment (27).

Non-surgical treatments

Transcatheter arterial chemoembolization (TACE)

TACE involves the intra-arterial administration of chemotherapeutic drugs carried by iodized poppy seed oil, Lipidol, through the feeding artery of the tumor to achieve cytotoxic effects. This effect is potentiated by simultaneous delivery of an embolic agent such as Gelfoam, achieving tumor ischaemia, which delays the wash out rate by blood flow from the tumor vascular bed (28). In Hong Kong, TACE has emerged as a recommended treatment for unresectable HCC with a good liver reserve, no vascular invasion and absence of extrahepatic spread. A local randomized controlled trial gave evidence of its safety and effectiveness, in which TACE has shown an excellent tumor response with one-year survival rate of 57% compared to 32% when conservative management was given (29). Furthermore, advanced age is not a contraindication of TACE treatment. Another study has confirmed the comparable efficacy and tolerance to TACE treatment for advanced HCC in both young (≤ 70 years) and elderly (> 70 years) patients, indicating a reliable palliative treatment

for unresectable HCC (30). In addition, a recent retrospective study suggested that preoperative TACE was associated with an improved overall survival and recurrence free survival after resection of huge HCC (≥ 10 cm) (31).

TACE with drug-eluting beads is an option when conventional TACE has failed but evidence of its superiority over conventional TACE is still lacking. In TACE with drug-eluting beads, exertion of drug function and embolization occur simultaneously, whereas in conventional TACE, the embolic agent is applied after drug injection (32). A recent retrospective study in Taiwan reported that TACE with drug-eluting beads provided better long-term benefits than conventional TACE did (33). Although several studies showed the benefits of this new TACE option over conventional TACE, the method is still very controversial in clinical practice.

Current guidelines in Hong Kong state that TACE should be repeated every 2-3 months based on tumor status and liver function closely monitored by computed tomography or magnetic resonance imaging. TACE should be stopped when there is liver impairment or other serious complications. When there is no viable tumor, TACE should also be discontinued and only repeated when residual tumor or new tumor growth has been detected.

Transcatheter arterial radioembolization (TARE)

TARE is a useful bridging therapy as a tumor downstaging treatment for suitable liver transplantation candidates. It also offers a second chance for intermediate HCC patients who have failed to respond to conventional TACE. Radioembolization with yttrium-90 (^{90}Y) mainly induces tumor death by local close-distance radiation instead of embolization in TACE. This treatment has gradually gained support as more studies have provided robust evidence to prove its efficacy and ability to prolong unresectable HCC patients' survival (34-38).

A single center study in Hong Kong has found that patients were able to enjoy a longer progression-free survival and overall survival, which was supported by the duration of AFP response ≥ 6 months after radioembolization. Besides, this study also found that radioembolization had positive effects when presented with portal vein thrombosis in their HCC, which is usually regarded as a contraindication to hepatectomy or liver transplantation (35). A retrospective study at the same center and a publication from an expert panel also echoed that TARE is a good choice for treatment in patients diagnosed with HCC plus portal vein thrombosis. Encouraging results were seen in this study because patients with major vascular invasion undergoing TARE had a median survival duration of 12 months and a 2-year survival rate of 15.6% (36,37).

Stereotactic body radiation therapy (SBRT)

In Hong Kong, most HCC patients are inoperable at the time of diagnosis. Treatment options may become limited due to unfavorable factors including tumor size, location and complications such as portal vein thrombosis. The development of SBRT has lowered the risk of radiation-induced liver disease, a long-time barrier of traditional radiation therapy that results in limited use for treating HCC. This is achieved by the delivery of high-dose radiation localized to only the diseased portion of the liver guided by real-time stereotactic 3D tracking of tumor position. This minimizes excessive radiation to normal liver parenchyma and surrounding healthy tissues.

Currently, the typical patient criteria for SBRT in Hong Kong includes Child-Pugh score of B8 or below, up to 5 lesions, uninvolved liver volume ≥ 700 mL and platelet count $\geq 50 \times 10^9/\text{L}$. A consensus made by a board of Asian experts confirms that SBRT is a safe and effective therapeutic option for patients with small-sized HCC, and offers substantial local control, improved overall survival, and low toxicity (38). Another study comparing outcomes following SBRT for Child-Pugh B and C patients with HCC also found that SBRT is suitable for patients with small HCCs and modestly impaired (Child-Pugh B7) liver function (39). SBRT can also be used as an alternative to HCC treatment in close proximity to major blood vessels and biliary duct, which is usually a contraindication to ablation techniques. While a retrospective study suggested that a combination of TACE and SBRT provides a survival benefit in patients with HCC tumors of ≥ 3 cm (40), and another study found no significant differences in the survival and adverse effects in patients with small HCCs who underwent SBRT with or without TACE (41). SBRT can also be used as a bridging therapy before liver transplantation thanks to its effective function of downsizing and stabilizing tumors prior to liver transplantation with minimal side effects (42). Another retrospective study on long-term outcomes of SBRT as a bridging therapy showed that 27% of the patients had achieved complete tumor necrosis according to explant pathology (43). Not only did all patients remain on the transplant wait list, no post-transplant recurrences were reported. All these encouraging findings suggested that SBRT could enable patients to remain on the transplant wait list longer especially in Hong Kong, where organ donation rates are low.

Systemic therapy

Sorafenib is used as a first-line treatment for advanced HCC with Child-Pugh A liver function patients who are not suitable for resection, locoregional ablation therapy and transarterial therapy. The Sorafenib HCC Assessment Randomized Protocol trial (SHARP) was a

multicenter, phase-3, double-blind, placebo-controlled trial in advanced HCC patients with Child-Pugh class A liver function (44). SHARP concluded that median survival was approximately 3 months longer for patients in the Sorafenib group than those in placebo group.

Regarding the Asia-Pacific region, a few studies have supported the use of Sorafenib as an effective treatment (45-47). A randomized controlled trial including 271 Asian patients indicates a 2-month prolongation in terms of median overall survival when Sorafenib was given, comparable to the results of SHARP. It was also found to be well tolerated, with common adverse effects being hand-foot skin reaction, diarrhea and fatigue (46). The subset analyses of this study suggested that Sorafenib consistently demonstrates a desirable efficacy and safety profile, irrespective of disease etiology, baseline tumor burden and prior therapy (47). In the SHARP trial, treatment was continued until both radiological and symptomatic progression or unacceptable toxicity occurred (48). Regorafenib is a second option when patients have developed progressive disease to Sorafenib treatment. In a phase-3 placebo-controlled trial (RESORCE), Regorafenib displayed a survival benefit in Sorafenib-refractory HCC patients; median survival was 10.6 months for Regorafenib compared with 7.8 months for placebo. The improvement in overall survival was consistent in all subgroup analyses (49). A retrospective analysis in Korean patients has illustrated results that are consistent with RESORCE; confirming the efficacy and safety outcomes for advanced HCC patients after disease progression on Sorafenib (50).

Conclusion

Management of HCC has evolved in the past decades because of pioneering research and innovative medical advances. In Hong Kong, where the prevalence of hepatitis-B-related HCC is relatively high, surgical resection is the first-line treatment for suitable HCC patients, as evidence has shown that more aggressive treatment is effective and safe in the Asia-Pacific region. The "left shift" of HCC treatment is to ensure maximum survival benefits, and careful patient selection for the most appropriate treatment should be enforced.

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