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Review article

Treatments of Hepatocellular Carcinoma Patients with Hepatitis B Virus Infection: Treat HBV-related HCC

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Abstract: There have been major advances recently on the therapeutic approaches of hepatitis B virus (HBV)-related hepatocellular carcinoma (HCC). Surgical treatments are the key curative treatments of HCC, whereas local ablative treatments may also achieve clinical remission in selected cases. Trans-arterial locoregional therapies are regarded as palliative but still lead to improved survival. There have been major breakthroughs in the systemic therapies for HCC. The first marketed targeted therapy, sorafenib, was shown to improve survival in patients with advanced HCC. Studies on other targeted therapies also showed promising results. Suppressing HBV with effective antiviral treatment would also benefit HCC patients by reducing recurrence and improving liver function.

Keywords: hepatitis B; HBV DNA; hepatocellular carcinoma; cirrhosis; lamivudine; entecavir; tenofovir; interferon; sorafenib; sirolimus

Abbreviations: HBeAg, hepatitis B e antigen; HBsAg, hepatitis B surface antigen; HBV, hepatitis B virus; HCC, hepatocellular carcinoma; mTOR, mammalian target of rapamycin; NA, nucleos(t)ide analog; OLT, orthotopic liver transplantation; RFA, radiofrequency ablation

1. Introduction

Chronic hepatitis B virus (HBV) infection is the leading cause of cirrhosis and hepatocellular carcinoma (HCC) in Asia [1]. The burden of HBV-related HCC is believed to be the highest in Eastern Asia, sub-Saharan Africa because of HBV endemicity [2]. Worldwide, HCC is the fifth most common cancer in men (523,000 new cases per year, 7.9% of all cancers) and the seventh in women (226,000 new cases per year, 6.5% of all cancers) [3].

The outcome of patients suffering from HBV-related HCC has been steadily improved over the last two decades because of the expansion and advances in treatment options. The treatments are not only for the tumor but also for the virus. The new therapeutic approaches for HBV-related HCC are reviewed together with the conventional ones in this article.

Table 1. Applicability and survival data of various treatment options for hepatocellular carcinoma.

Treatments	Applicability	Post-treatment survival
Surgical treatments		
Liver Resection	Resectable tumor, good liver reserve	5-year overall survival: 27% to 81% [4,5]
Liver Transplantation	Resectable tumor, poor liver reserve	4-year overall survival: 83% 4-year disease-free survival: 75% [17]
Local ablative treatments		
Radiofrequency ablation (RFA)	Resectable tumor, poor liver reserve	5-year overall survival: 33% to 55% [17]
Microwave ablation	Unresectable tumor but amendable for local ablation, poor liver reserve	1-, 2-, 3-, and 4-year overall survival: 81.6%, 61.2%, 50.5%, and 36.8% [87]
Percutaneous ethanol injection	Use alone or in combinations with other modalities	1-, 3-, 5-year overall survival (HCC < 3 cm): 93%, 65% and 28% [46]
High-intensity focused ultrasound (HIFU) Ablation		1- and 3-year overall survival: 87.7% and 62.4% [47]
Cryotherapy		5- and 10-year overall survival: 25.7% and 9.2% [55]
Trans-arterial locoregional therapies		

Transarterial chemoembolization (TACE)	Unresectable tumor, not amendable for local ablation, poor liver reserve, no portal vein thrombosis	1-, 2-, 3-year overall survival 57%, 31%, 26% [58]
Transarterial radioemoblization (TARE)	Unresectable tumor, not amendable for local ablation, poor liver reserve, presence of portal vein thrombosis	Median survival - Child-Pugh A: 17.2 months Child-Pugh B: 7.7 months [66]
Stereotactic body radiation therapy (SBRT)	Failed or contraindicated for TACE Huge HCC unsuitable for other local treatment modalities	As primary treatment: 5-year overall survival: 100% [72] For recurrent HCC: 2-year overall survival: 64% [71]
Systemic therapies		
Sorafenib	Unresectable tumor, extrahepatic spread	Median survival: 6.5 to 10.7 months [78,79]
Anti-angiogenic agents (*e.g.* sunitinib, brivanib, linifanib)	To be defined	Median survival - Sunitinib: 7.9 months [81] Brivanib: 9.5 months [82] Linifanib: 9.1 months [80]
Anti-proliferative agents (*e.g.* erlotinib)	To be defined	Median survival: 9.5 months [83]
Antiviral therapy	To all patients with detectable HBV DNA or above 2,000 IU/mlL	N.A.

2. Surgical Treatments

2.1. Liver Resection

Liver resection remains the mainstay of cure for hepatocellular carcinoma in patients with good liver reserve. The reported 5-year overall survival after liver resection for early hepatocellular carcinoma ranged from 27 to 81% [4,5]. In major institutions worldwide, the reported morbidities ranged from 11% to 45% and the operative mortality rate ranged from 0% to 5% [4,5]. There was a trend towards improved overall survival in recent years. Nevertheless, liver resection remains challenging in the patients with HBV infection due to the co-existing liver cirrhosis.

2.2. Pre-operative liver function assessment

Various methods have been reported to investigate the functional hepatic reserve. Indocyanine green retention rate at 15 min (ICG R15) has been widely used in Eastern countries [6]. However, it is expensive and time consuming; and is not popular in Western countries. Child-Pugh classification does not provide precise estimation of postoperative hepatic functional recovery [7,8]. Liver biopsy and quantify portal hypertension might provide more accurate result but they are all invasive. Liver stiffness measurement (LSM) by transient elastography (Fibroscan®, Echosens, Paris, France), as a non-invasive, rapid and reproducible method for LSM, is increasingly explored as a pre-operative assessment tool for hepatectomy. Initial results demonstrated reasonable correlations between LSM and post-hepatectomy outcomes [6,9,10]. CT volumetry can be used to calculate the volume of the Future Liver Remnant (FLR) volume. For cirrhotic patients undergoing resection for HCC, FLR of at least 40% is recommended [11].

2.3. Portal Vein Embolization

Portal vein embolization (PVE) can be considered in if FLR is less than 40% [12,13]. PVE induces hypertrophy of the expected FLR by blood flow redistribution. Various techniques have been reported for PVE and percutaneous transhepatic technique is the standard technique for PVE. In a recent meta-analysis, PVE had a mortality of 0.1% and major complication rate of less than 1% [12]. Only 80% of the originally planned liver resections were finally performed due to insufficient hypertrophy or local tumor progression. In order to halt HCC progression while liver remnant is undergoing hypertrophy, sequential use of transarterial chemoembolization (TACE) and PVE is being employed.

2.4. Minimally Invasive Liver Resection in HCC

Recently, liver resection with minimally invasive approach has gained popularity especially for peripherally located tumor [14,15]. Minimally invasive approach can achieve comparable long-term oncological outcome even in patients with liver cirrhosis [14,15]. Report from the second international consensus conference confirmed that minor laparoscopic liver resection is a standard practice and is adopted by an increasing proportion of surgeons while major laparoscopic liver resection remains an innovative procedure in exploratory or learning phase [16].

2.5. Liver Transplantation

Liver transplantation is the most effective treatment option for patient with HBV-related HCC because it treats both the cancer and the underlying liver cirrhosis at the same time. The Milan

criteria (single tumor ≤ 5 cm, up to 3 tumors each≤ 3 cm in diameter) are the gold standard for selection of deceased donor liver transplantation [17]. Mazzaferro *et al*. studied 48 patients within the Milan criteria and reported an overall mortality rate of 17% after 4 years and the actual survival rate and recurrence-free survival rate were 75% and 83% respectively [17]. Patients transplanted within Milan criteria have a 5-year survival similar to patients transplanted for non-HCC indications [18].

The criteria for liver transplantation have improved over many years [19,20]. However, the organ donation rate in Asia remains low [21]. Living-donor liver transplantation is an excellent alternative and is a mainstay of treatment of HCC in cirrhotic patients in many Asian countries [22–24]. Studies comparing outcomes of deceased-donor liver transplantation and living donor liver transplantation showed similar overall survival rates [25–27].

3. Local ablative Treatments

Local ablative treatment is a form of local treatment for malignant liver tumors including HCC. It involves the introduction of chemicals like alcohol or heat energy like laser, radiofrequency and microwave into tumor to cause necrosis of tumor. Initially it is regarded as a form of palliative treatment for HCC, but now it is believed to have a curative potential especially for small size HCC (i.e. < 3 cm).

3.1. Radiofrequency ablation (RFA)

RFA is the most commonly used local ablative treatment for HCC nowadays [28–31]. It has largely replaced percutaneous ethanol injection because of the better recurrence-free survival and less treatment sessions [32]. The RFA needle can be placed into the tumor via percutaneous route, laparoscopic route or during open operation. The heat energy generated causes coagulative necrosis of tumor according to the size of needle used and the duration of treatment applied. The procedure is usually well tolerated with mortality < 1% and morbidity less than 10%. Complete ablation could be achieved in more than 90% of patients with small HCC [33]. The reported overall 5-year survival rates were between 33% and 55% [34]. The therapeutic efficacy of RFA for HCC less than 3 cm is comparable to surgical resection [33]. Nevertheless, RFA had limited success in treating large or multifocal HCC, as well as juxta-vascular tumor [35].

3.2. Microwave ablation

Microwave is another type of local ablative treatment that has been used for more than 20 years [36]. It receives attention in recent years again because of the tremendous progress in the technology of microwave. Currently, frequencies of 915 and 2,450 MHz are being used for microwave tissue ablation. Heating by microwave is primarily active and the transmission of microwaves in the living tissue is not limited by tissue desiccation and charring [36,37]. Therefore it has advantages over RFA

including reduced “heat-sink” effect, achieve higher temperature with a shorter ablation time, maintenance of higher intra-tumoral temperatures, deeper penetration and greater ablative zone [38,39]. Furthermore, there is no need to apply earth plates on patient as in RFA. Therefore it can avoid the potential complication of earth plate burn injury. The complete ablation can be achieved in > 90% of patients [39–41]. When compared with RFA, microwave ablation produced equivalent local tumor control, complications and long-term survival [38,42,43]. It may be more effective in treating larger tumors when compared with RFA.

3.3. Percutaneous ethanol injection

Percutaneous ethanol injection (PEI) is a safe, inexpensive and effective ablative treatment for small HCC [44,45]. Absolute ethanol is injected into the tumor under ultrasound or CT guidance to cause tumor coagulation necrosis [45]. The reported 1-, 3-, 5-year survival rates of PEI for HCC smaller than 3 cm were 93%, 65% and 28% respectively [46]. PEI is a common treatment option in patients with HBV-related HCC for two reasons. First, it can be considered in patients with Child’s C cirrhosis, although the survival rates of patients with Child’s A or B cirrhosis was higher than those in Child’s C patients [46]. Second, PEI could be easily repeated in cases of recurrence, which is very common in patients with underlying HBV infection [46]. Limitations of PEI include higher rate of tumor recurrence and the need for multiple treatment sessions.

3.4. HIFU Ablation

High-intensity focused ultrasound (HIFU) ablation is an extracorporeal non-invasive ablation using focused ultrasound energy with a unique frequency of 0.8–3.5 MHz to induce coagulative necrosis of the targeted HCC. Initial reports on HIFU have shown that it is safe and effective for patients with HCC [47,48]. For patients with HBV-related HCC, they usually have co-existing liver cirrhosis and ascites. The presence of ascites in patients with HBV-HCC actually facilitates energy propagation to the target HCC as ultrasound energy travels better in water than in air.

Cheung et al. reported the experience of 100 patients who received HIFU ablation for their HCC. Among these 100 patients, 80% were hepatitis B carrier [48]. Thirteen (13%) patients developed a total of 18 complications; 14 of them were Clavien-Dindo grade 2 or below. The complete ablation rate with single treatment was 87% for tumor < 3 cm. Moreover, HIFU ablation is also safe in treating juxta-vascular lesions. Zhang et al enrolled 39 patients with HCC located within 1 cm from main blood vessels (inferior vena cava, main hepatic vein branches, portal vein) for HIFU ablation [49]. No major blood vessel injury was reported in any subject. More extensive clinical trials are needed to determine the role of HIFU ablation in patients with HBV-related HCC.

3.5. Cryotherapy

Cryotherapy or cryoablation is a less commonly used local ablative treatment, which is effect not only just due to local effect but also as the consequences of stimulation of cryo-immunity [50], production of pro-inflammatory cytokines [51] and natural killer cell function [52]. Cryotherapy or cryoablation can be either used alone or in combination with other treatment modalities in patients with advanced HCC [53,54]. A recently published single center experience of 1,595 cases showed favorable safety and efficacy, particularly when a large zone of ablation is required [55].

4. Trans-arterial Locoregional Therapies

4.1. Transarterial chemoembolization (TACE)

TACE is the most commonly used treatment for HCCs that are unresectable or not suitable for local ablative treatment [56–58]. TACE takes the advantage of dual blood supply of liver and involves intra-arterial injection of chemotherapeutic agents (usually doxorubicin and cisplatin) suspended in lipiodol into the hepatic artery, followed by embolization with agents (most commonly Gelform) [59]. Tumor cells selectively uptake the chemotherapy/lipiodol mixture can remain active inside the cell from weeks to months. TACE results in survival benefit when compared with conservative management [58]. A meta-analysis of six studies observed a survival benefit for TACE over conservative treatment.56 The combination of TACE with RFA also provides better overall survival compared with RFA alone [60,61].

The use of drug eluting bead in TACE (DEB-TACE) aimed at preloading the embolic particles with drug, followed by controlled drug elution in target tissue [62]. Based on the currently available evidence, DEB-TACE offered no survival benefit over traditional TACE. However, results from randomized controlled trial and systemic review reported improved tumor response rate and slightly lower incidence of adverse events for DEB-TACE when compared with traditional TACE [63,64]. Patients with HCC which are not amendable for liver resection or local ablation can be considered for TACE if they have preserved liver function, no portal vein thrombosis and extrahepatic spread.

4.2. Transarterial radioemoblization (TARE)

Yttrium-90 (Y90), a β-emitting isotope, is the agent that most commonly used to deliver selective internal radiation to the tumor via transarterial administration in TARE [65,66]. TARE can be performed in patients in patients with portal vein thrombosis because it does not cause ischemia. Patients with unresectable HCC that are not amendable to ablation or transplantation are the major indications for TARE if there is absence of extrahepatic metastasis. TARE can be used as a bridge to transplantation or for downstaging tumor outside the Milan criteria [67]. Studies comparing outcomes after TACE and TARE reported comparable efficacy for TACE and TARE in terms of

tumor response and overall survival [66,68].

5. Stereotactic Body Radiation Therapy (SBRT)

SBRT for advanced HCC has been recently reported in several studies [69–72]. SBRT allows real-time tracking of a tumor which allows delivery of radiation beams with high precision and rapid fall-off doses when the target is away. The reported responses rate are 37–90% with a 2-year survival ranged from 43–82% 73 SBRT is regarded as a salvage treatment for unresectable HBV-related HCC patients who failed or contraindicated for TACE or for patients with huge HCC unsuitable for other local treatment modalities [74,75]. It provides good local tumor control and high overall survival rates when compared with best supportive care or sorafenib therapy [69]. The on-going randomized phase III study of sorafenib versus SBRT followed by sorafenib in hepatocellular carcinoma will likely clarify the efficacy of SBRT in advanced HCC. (Clinicaltrials.gov NCT01730937) Recently, SBRT is also used as a bridge therapy in patients with HCC awaiting liver transplant [73]. The risks associated with SBRT include radiation induced liver disease, progression of liver cirrhosis, chest wall toxicity and biliary toxicity. The reported grade 3 or higher toxicity is 0–40% [76].

6. Systemic therapies

The response to the conventional cytotoxic chemotherapies in advanced HBV-related HCC is known to be poor because of the inherent chemo-resistance of HCC and the high toxicity associated with the altered drug metabolism in cirrhotic liver [77]. With better understanding of hepatocarcinogenesis, the development in target therapy for advanced HCC is evolving. Sorafenib is an oral multi-kinase inhibitor that has activity against several serine/threonine kinases and tyrosine kinases. It is the first oral multi-kinase inhibitor approved by FDA for the treatment of “unresectable” HCC in 2007 based on the results of two landmark randomized controlled trials [78,79].

The landmark Sorafenib HCC Assessment Randomized Protocol (SHARP) trial is multicenter phase III double-blinded randomized controlled study involving 602 patients with advanced HCC from 121 centers [79]. Patients were randomized to receive 400mg sorafenib twice daily verses placebo. The overall median survival was 10.7 months (95% CI: 9.4–13.3) in the sorafenib group compared to 7.9 months (95% CI: 6.8–9.1) in the placebo group ($p < 0.001$). Cheng et al. in another phase III double-blinded randomized controlled study involving 271 patients with advanced HCC from 23 centers in the Asia-Pacific region, also demonstrated a 2 months survival benefit in the sorafenib group [78].

Subsequently several phase III randomized trials had compared other targeted therapies to sorafenib [80–83]. Anti-angiogenic agents (like sunitinib, brivanib, linifanib) or combinations of sorafenib with anti-proliferative agents (erlotinib) have failed to show superiority to sorafenib in improving the overall survival [80–83]. At the moment, Sorafenib is the only target therapy that has demonstrated the effect of providing significant survival benefit. Common side effects of sorafenib

include hand-foot skin reactions, diarrhea and fatigue.

7. Controversies in HCC Treatments

7.1. Small HCC: resect, ablate or transplant?

Small HCC is generally defined as those small than 2 cm in very early stage or Barcelona clinic liver cancer (BCLC) Stage 0, or those than 3 cm in early stage or BCLC Stage A [84]. Surgical resection is generally the first line treatment option if patients have good liver reserve. Local ablative treatments with either RFA or PEI in fact achieved similar overall survival rates and lower rate of complications, in the expenses of lower disease-free survival rate in patients with HCC of sizes 3 cm to 5 cm [85–87]. But if only confined to those with tumor smaller than 2 cm, RFA achieved excellent sustained complete response rate of 97% at 2.5 years [33].

The modality of local ablative treatments also matters. RFA worked better than PEI in terms of better overall survival and lower rate of treatment failure [88–90]. Therefore the latest treatment guidelines recommended surgical resection for patients with compensated cirrhosis and good liver reserve; local ablative treatments, preferably RFA, may be offered to patients with small HCC (< 2–3 cm), decompensated cirrhosis or non-surgical candidates. Liver transplantation is often reserved in patients with decompensated cirrhosis [91].

7.2. Liver transplantation: deceased or living donor liver transplantation?

Higher risk of HCC recurrence has been a concern after living donor liver transplantation (LDLT) when compared with deceased LT, however these data have not been confirmed [27]. In regions with shortage of deceased donors, LDLT is considered to be cost–effective and can be offered to patients with HCC if the waiting list exceeds 7 months [24].

8. Antiviral Therapy

There is evolving evidence showing the potential beneficial effects of antiviral therapy in reducing the risk of HCC recurrence after curative treatment and improving survival of patients with HBV-related HCC [92,93]. Three meta-analyses regarding the efficacy of antiviral therapy in prevention of recurrence after curative liver resection have been published [93–95]. Nucleos(t)ide analogue treatment could reduce the risk of HCC recurrence after curative treatment by 41% [93].

Remnant liver function is a major determining factor in selecting subsequent treatment for HCC recurrence and is a key prognostic factor for the overall survival. Antiviral treatment, in addition to the possible prevention of HCC recurrence after curative resection, may also render patients with HBV-related HCC able to tolerate aggressive treatments for their recurrence better and hence, improve prognosis. We studied the effect of antiviral therapy on post-hepatectomy survival in 404

patients with HBV-related HCC and found that use of antiviral therapy was associated with better liver function reserve at the time of recurrence and a greater proportion of patients could receive curative treatment for recurrence (38.5% vs. 24.3%, $p = 0.041$) [92].

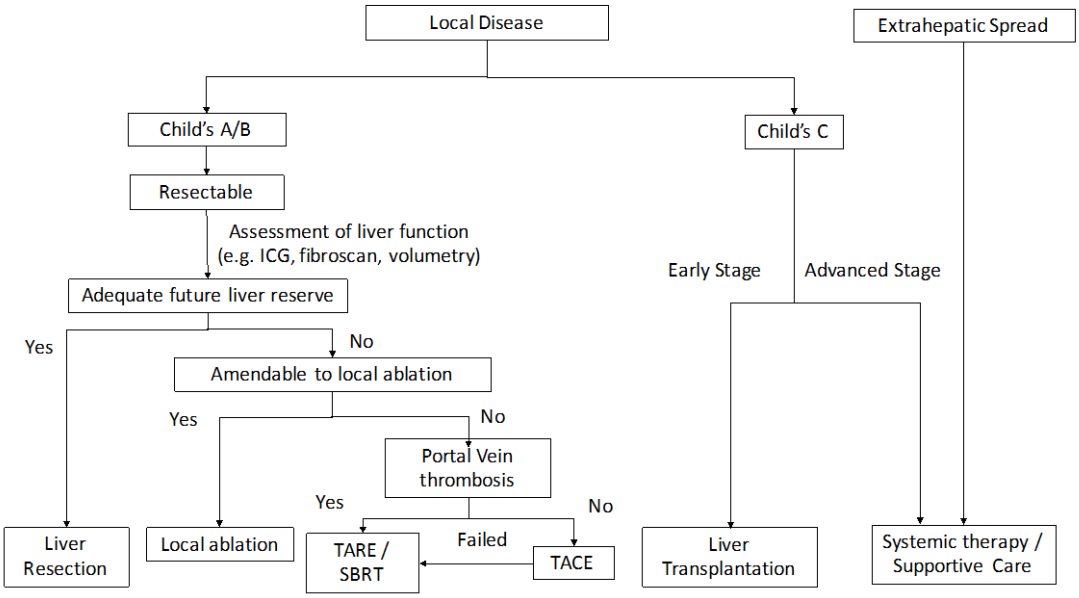

Figure 1. Treatment algorithm for hepatocellular carcinoma. Abbreviations: ICG = Indocyanine green; TARE = Transarterial radioemoblization; SBRT = Stereotactic body radiation therapy; TACE = Transarterial chemoembolization.

Use of antiviral therapy also improved the long-term post-hepatectomy survival in patients with HBV-related HCC. In a recent non-randomized study, which compared the impact of antiviral treatment in 79 patients underwent curative hepatectomy for HCC, the authors showed that antiviral treatment promoted postoperative viral clearance and increased residual liver volume, which significantly enhanced tolerance to subsequent therapy for disease recurrence [96]. Although antiviral treatment did not reduce short-term recurrence rate, there was a significant better 1- and 2-year overall survival rates in the treatment group. This echoed the results from the previously mentioned meta-analysis by Wong et al [93]. Higher chance of receiving aggressive salvage therapy during HCC recurrence could be observed among patients receiving antiviral therapy due to better liver reserve, and resulting in a better survival.

The impact of HCC treatment modalities on the beneficial effect of antiviral therapy was evaluated in a large-scaled real-life cohort study of more than 2,000 HCC patients [97]. While antiviral therapy reduced the risk of HCC recurrence most obviously in those received surgical resection (adjusted sub-hazard ratio 0.58), the benefits in those received local ablative treatments just fell short of statistical significance (adjusted sub-hazard ratio 0.68, 95% CI 0.46 to 1.01) [97]. Antiviral therapy helps in patients of all ages; whereas male patients benefit more from the antiviral

therapy than female patients. Despite the difference in resistance profile,98 both lamivudine and entecavir reduces HCC recurrence equally well [97].

9. Conclusions

With better understanding the carcinogenic mechanisms of HBV-related HCC, we can improve the management of patients suffering from this life-threatening disease at both diagnostic and therapeutic levels. Some biomarkers and targeted therapies have been made available clinically, whereas even more are currently on the pipeline. Yet the heterogeneity of this disease is the key challenge to bring all these laboratory discoveries to bedside. While removal and killing of cancerous tissue remains the key of curative treatments, suppressing the virus helps further by reducing de novo recurrence. We are looking forward to the accurate HCC biomarkers and effective targeted therapies to further improve the prognosis of these patients.

Author Contributions

Charing Chong and Grace Wong were responsible for the drafting of the manuscript, critical revision of the manuscript for important intellectual content.

Conflict of Interests

Charing Chong declared that she has no competing interests. Grace Wong has served as an advisory committee member for Otsuka and Gilead as well as a speaker for Abbvie, Bristol-Myers Squibb, Echosens, Furui, Gilead, Janssen Otsuka and Roche.

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