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Research Article

New advances in the treatment of primary hepatocellular carcinoma

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Primary hepatocellular carcinoma (HCC) is one of the most common malignant tumors, Alpha-fetoprotein, B-ultrasound and other means of diagnosis are conducive to the early diagnosis of primary liver cancer ; however, most of the patients are diagnosed at the advanced stage. In the recent years, some progresses have been made in the treatment of primary hepatocellular carcinoma. The aim is to improve the prognosis of patients with HCC, such as new chemotherapeutics and molecular targeted agents, improvement of Transarterial Chemoembolization (TACE) and Radiofrequency ablation(RAF), the combination of different treatment methods, such as TACE combined with sorafenib, and Chinese medicine therapy, all bring new hope for the treatment of HCC. The purpose of this review is to summarize the latest advances in HCC regimens and their pros and cons and help clinical treatment.

Keywords: Hepatocellular Cancer Therapy; Transarterial Chemoembolization; Radiofrequency ablation; Chinese Medicine Therapy.

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Introduction

Hepatocellular carcinoma (HCC) is the sixth most common cancers, the third most common reason cancer caused death and the most common primary malignancy of the liver[1]. HCC has become the third most common cancer in Asia due to HBV and HCV infection in China, The incidence of HCC in China accounts for 55% of the global incidence of HCC[2]. Unfortunately, since HCC is often accompanied with liver disease, insidious onset, when the patient is diagnosed with HCC, usually in the advanced stage, and it results in poor prognosis. Although there are many comprehensive treatments, including surgery, local ablation, hepatic artery intervention, chemotherapy and radiotherapy, only 15% of the patients are treated with surgery. For advanced cases, the opportunity of radical surgical resection and liver transplantation are very limited, chemotherapy, molecular targeted therapy have become the main treatment to reduce the symptoms of patients, improve the quality of life and extend the survival period[3]. Therefore, the early diagnosis and discovery of HCC is particularly important. Increased surveillance of high-risk patients and surgical treatment of early-stage HCC can improve survival rate in HCC patients. Early treatment is the cornerstone of improving overall survival in patients with cirrhosis[4]. To achieve this goal, the first step is to identify "at-risk populations," primarily cirrhotic patients, which HCC screening will be cost-effective. The second step is to perform ultrasound every 6 months in cirrhotic patients[5]. So far, the prognosis of patients with liver cancer is still poor, life expectancy is difficult to predict[6], 80% of patients undergoing resection within 4 years of recurrence, 50% relapse within two years[7, 8]. In the treatment options, it is necessary to consider the tumor stage, but also pay attention to the impact of liver damage, therefore, the accurate assessment and classification of the disease is a very important part of the management of HCC patients[9]. Prognostic algorithms, such as Cancer of the Liver Italian Program (CLIP)[10] and the Barcelona Clinic Liver Cancer (BCLC), the advent of detection, radiographic techniques, and the emergence of novel therapeutic approaches have brought new hope for the prognosis of HCC patients[11].

Surgical Resection

Surgical treatment is the gold standard for resectable

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HCC. Surgical treatment needs to balance two contradictory goals : to remove the tumor and potential high-risk cancer based on reserving the liver parenchyma and to preserve liver function as much as possible[12]. More accurate liver function assessment and segmental liver imaging are important in reducing mortality[1]. Small solitary HCC patients with anatomic Liver Resection(LR) compared to limited resection have obvious advantages in overall and disease-free survival rates[13, 14],anatomic LR has the potential to eliminate undetected foci (portal vein metastases and satellite nodules) from primary tumors[12].

The size of the tumor and the extended of impaired liver function have a major impacts on the prognosis of hepatectomy. Patients with cirrhosis have a lower rate of recurrence after hepatectomy, a higher correlation with portal hypertension and a higher risk of tumor recurrence, and even if the degree of liver fibrosis is not high, steatosis and inflammation may produce significant postoperative liver regeneration influences[15, 16]. Due to changes in the structure of the liver parenchyma and impaired liver regeneration, there are also liver dysfunction, coagulation disorders, increased risk of infection and other risks after surgical resection[17]. Therefore, in addition to the tumor removal, the degree of surgical stress, and liver damage should also be considered for HCC patients with chronic liver disease. Patients with severe chronic liver disease may experience different postoperative complications such as (1) protein synthesis and metabolic deterioration; (2) gastrointestinal congestion, ascites, portal hypertension and hypersplenism causing pancytopenia; and 3) susceptibility to infectious diseases and hepatopulmonary syndrome (hypoxemia) due to increased shunting of blood vessels[18].

Liver residuals correlate with postoperative liver dysfunction. Although the safety limitation for normal liver residual volume is approximately 30% of the total liver volume (TLV), it is generally accepted that Chronic liver disease(CLD) patients should retain 40% -50% of the remaining liver volume[1]. Therefore, preoperative effective tumor volume, liver function evaluation and postoperative risk assessment is necessary. Schiano et al. [19] have confirmed that the liver volume was related to the liver function reserve. More accurate selection of liver resection site and residual liver volume calculation, play an important role in protect postoperative liver function and improve patient survival rate. At present, there are many ways to evaluate the function of liver reserve preoperatively, mainly from laboratory tests, comprehensive scoring system, quantitative liver function tests, imaging studies and liver volume measurement. However, none of them can be fully and effectively implemented assessment of liver reserve function. Wigmore et al[20] used computed tomography (CT) three-dimensional imaging technique to measure the volume of liver, calculate the remaining volume of liver and the proportion of resected liver, Department of Surgery at the University Hospital of Varna has developed techniques for assessing liver volume from computed tomography images, and encapsulated within a software tool[21].

The selective uptake of radioactive technetium by normal hepatocytes and the use of Single-Photon Emission Computed Tomography (SPECT) to estimate the reserve function of hepatocytes is a good assessment of liver function reserve, currently[22]. In addition to the remaining liver volume (RLV) calculation, indocyanine green (ICG) clearance test, dynamic test of galactose elimination and methacetin breath test (maximum liver capacity) are widely used[23];currently, ICG is a more accurate quantitative assessment of liver reserve function, but studies have found that the ICG clearance test does not meet our expectation of predicting post-hepatectomy liver failure (PHLF) in non-cirrhotic patients[23]. Although ICG is a sensitive index to evaluate the function of liver reserve, it can not be decided clinically whether to surgically remove the liver volume. Other quantitative detection: lidocaine test, aminopyrine clearance test, oral glucose tolerance test, arterial blood ketone body ratio, cytochrome CYP450 1A2 phenacetin metabolism and other quantitative detection methods[24], due to clinical evaluation of clinical liver reserve function failed to provide a unified opinion and cumbersome detection methods, are not routinely used in clinical practice.

For tumors with larger tumors or smaller tumors but located in the center, the indications for LR are limited[25]. In 1990, Makuuchi et al. [26] first proposed to minimize the preoperative liver dysfunction by embolizing one-sided portal vein to induce atrophy of the lobes of the embolized lobe, hypertrophy of the lateral lobe, preoperative liver volume adjustment, to minimize postoperative liver dysfunction. Transcatheter arterial chemoembolization (TACE) and preoperative portal vein embolization(PVE)

before operation increase the rate of hypertrophy of the future liver reserve (FLR) and leads to a high rate of complete tumor necrosis associated with longer recurrence-free survival[27]. Similarly, there are other strategies to improve the resectability of tumors in HCC patients, including (1) Tumor downstaging; (2) hepatectomy with revascularization; and (3) Heterotopic liver resection [28]. Tumor downstaging is a new concept of unresectable malignancy of tumors[29, 30]. Part of the embolization can achieve the purpose of tumor degradation, so as to achieve the tumor from unresectable to the resectable, the main method is to reduce the tumor volume by local therapy, satellite lesions disappear, main portal vein tumor thrombi regress and disappear, and future remnant part of the liver undergoes hypertrophy, Clinical studies have shown that 10.9% ~ 57.1% of unresectable HCC cases successfully cut down after tumor degradation[28]. It is noteworthy that the initial cause of tumor unresectable does not affect the prognosis after liver resection[31]. Laparoscopic LR is a less invasive procedure for treating liver disease than conventional LR[32], notably, laparoscopic surgery often takes longer, but there is no difference in tumor outcome from LR[33]. Prevention and early detection of liver cancer is an important foundation for the treatment of HCC. LR, as the primary means of early treatment of HCC, improving surgical techniques and related equipment, and accurately assessing liver function, applicating anatomic Liver Resection will help to improve patient prognosis and reduce tumor recurrence rate.

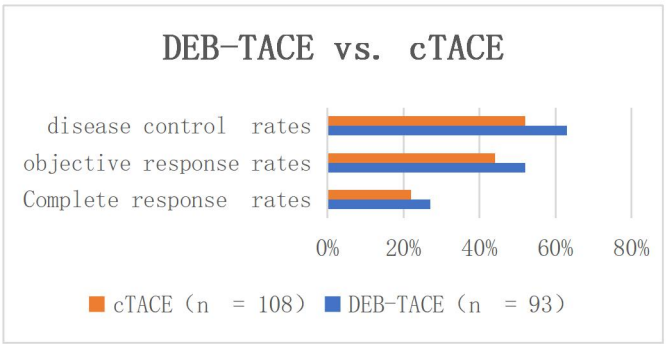

Fig 1. rates of complete response, objective response, and disease control.

Liver Transplantation

Liver Transplant(LT) is considered the most effective way to treat cancer and underlying liver disease. Because it removes detectable and undetectable tumor nodules as well as precancerous lesions present in cirrhotic liver[1]. In addition, it simultaneously treats potential cirrhosis and prevents postoperative or long-term complications associated with portal hypertension and liver failure, and LT is not limited by impairment of liver function[34]. The eligibility for transplantation depends on the size and number of tumors, selection criteria is Milan criteria （A single tumor ≤ 5cm or 3 tumors ≤ 3cm） , although liver transplantation is a good treatment for liver cancer, there is a serious shortage of liver transplant recipients,several strategies and surgical techniques have been applied to reduce this shortage, mainly including：living donor liver transplantation (LDLT), in which part of the liver is donated leaving the donor with enough liver remnant to have excellent long-term quality of life[35-37], LDLT is the primary method of liver transplantation in patients with liver cancer in Asia due to the low rate of donation[38, 39]. In one study, researchers found that patients with LDLT had a significantly higher rate of recurrence of HCC (29% vs 12%, P <0.05) than those who had died of donor liver transplantation (DDLT)[40]; donation after circulatory death (DCD)[41], which is different from the classic donation after brain death (DBD), DBD gains more severe ischemia-reperfusion injury and ischemia-reperfusion injury has been considered carcinogenic and promotes cancer growth. Therefore, the oncology treatment of HCC patients with DCD is underperformance[42, 43].

Transarterial Chemoembolization (TACE)

The basic principle of TACE is intra-arterial infusion of chemical drugs (such as cisplatin or doxorubicin), with or without viscous emulsion, and then embolization of blood vessels with gelatin sponge particles or other embolic agents to achieve strong local tumor tissue cytotoxicity role and ischemia[44]. TACE is the current standard of care for patients, primarily applicable to multisnodular HCC with no major vascular invasion or extrahepatic spread, absence of cancer-related symptoms and preservation of liver function[45-47]. Not all patients with HCC have similar benefits from TACE, and some patients may benefit from other therapies. TACE has been banned from patients with HCC who have portal vein infiltration or extrahepatic spread[48].

TACE is considered palliative as it is difficult to achieve complete tumor necrosis even after repeated treatments[46,

49]. In the meta-analysis of TACE, L lovet and Bruix reported that objective response rate was 35%, 2-year survival rate of 41%[50]. In a histological analysis, only 43% of 122 HCC nodules were found to be completely necrotic[51]. Therefore, the high rate of tumor recurrence after TACE is predictable, which explains a randomized study of 67% of deaths after TACE as a result of tumor progression[52].

The ideal TACE regimen should be to maximize the concentration of chemotherapeutic drug in the tumor for a longer period of time while minimizing the systemic toxicity of the drug combined with a precise tumor vasoconstriction[44]. Conventional transarterial chemoembolization (cTACE) uses a chemotherapeutic agent (e.g. doxorubicin or cisplatin) and a mixture of lipiodol as a standard treatment, in order to enhance the transport of chemotherapeutic agents in vivo to reduce systemic toxicity and increase the local drug concentration, TACE with drug eluting beads (DEB-TACE) was introduced, which is a embolic microsphere containing a chemotherapeutic agent(predominantly doxorubicin), and the ability to slow release of a drug, thereby creating a high local drug concentration and a low systemic drug concentration[53]. The positive effect of DEB-TACE was validated experimentally in patients treated with DEB-TACE compared with cTACE patients treated with lipiodol, DEB-TACE showed higher rates of tumor necrosis in the experiment which was pathologically confirmed in contrast with cTACE patients livers of HCC patients undergoing liver transplantation[54]. Randomized European Precision V phase-2 trial compared Efficacy and safety of DEB-TACE vs. cTACE (in 212 patients with predominately intermediate stage HCC), The drug-eluting bead group showed higher rates of complete response, objective response, and disease control compared with the cTACE group, DC Bead was associated with improved tolerance and severe hepatotoxicity was significantly reduced ($P < 0.001$), adriamycin-related side effects were significantly reduced ($P = 0.0001$). TACE in combination with DC Bead and doxorubicin in the treatment of HCC is safe and effective and provides benefits to patients with more severe diseases[55].

Tumor recurrence after TACE is characterized by increased VEGF production and angiogenesis. TACE-induced ischemic injury can up-regulated the vascular endothelial growth factor (VEGF), increase the expression of VEGF in residual cancer tissues and induce other pro-angiogenic factors such as hypoxia-inducible factor 1α alpha, which play an important role in the pathogenesis of HCC[56-58], the combination of TACE and anti-angiogenic agents seems to be a reasonable method. Similarly, the effect and theoretical basis of TACE combined with other therapies in the treatment of HCC deserve our further exploration.

Radioembolization

In patients with intermediate stage HCC who do not respond to TACE or are contraindicated, alternative care needs to be considered, such as radioembolization. Radioembolization refers to the injection of microspheres of radioactive microspheres into arteries as a means of internal radioactive sources. Radioactive materials mainly include microspheres containing yttrium-90 (Y^{90}), iodine-131, iodine-125 iodinated oil or the like[59]. The therapeutic effect of radioactive embolism is mainly due to the particle irradiation of the tumor, partly due to embolism-induced ischemia[60], the most obvious advantage of radioactive embolization compared to TACE is the safy for the patients with portal vein thrombosis due to the minimal embolic effect of 90Y microspheres[61, 62]. At the same time, radioembolization can be used as an alternative to TACE for large HCCs, which are beyond the Milan criteria, achieve tumor degradation, serving as a bridge to transplant[63].

HCC is a radiation-sensitive tumor[64]. Hepatotoxicity caused by *in vitro* radiation therapy depends on the dose delivered by radiation, the volume of liver tissue involved, the degree of cirrhosis, preoperative liver function, and current therapies[65], when more than 35 Gy of radiation are absorbed, severe hepatotoxicity appears, which limited the use of *in vitro* radiation therapy[66]. Internal radiation therapy, an attempt to solve this problem, provides radioactive particles that kill tumoricidal doses and limits the particle's sparing the non-tumoral liver by embolizing the hepatic artery. Y^{90}, mainly used, is a high-energy radiation source with short half-lives (2.67 days) and short tissue penetration (average 2.5 mm and maximum 11 mm). Over 2 weeks after injection, more than 95% of the radiation is delivered to the tissues surrounding the microspheres embolized vessels[60]. Iodine-125 is currently applied in liver cancer less, but it is widely used

in various tumors including prostate, pancreatic, lung and head and neck cancers[67]. The average photon energy emitted by I^{125} was very low at 28.5 keV with a specific gamma-ray constant of 1.32-1.45R·cm^2/mCi·h and a half-life of 59.4-60.2 days, a radiation diameter of 2 cm for tissue and 0.025 mm for lead, which makes shielding easier[68]. MR guided I-125 implanted HCC is technically feasible and effective[69], In the study by Lin J et al., 399 patients had 13,977 seeds in total, (1.07%) seeds migrated to the chest in (20.30%) patients. There were no patients with related symptoms due to seed migration[70]. Unfortunately, the difference between the validity of Y^{90} and I^{125} needs further study.

The arteries injected into the radioactive microspheres determine the volume of liver tissue exposed to radiation. The biological effects of radiotherapy are mainly dependent on the absorbed dose of the tumor tissue. Radiation dose of tumor tissue is an important factor for tumor response, which is mainly affected by the hemodynamics of the hepatic artery blood flow, and the vessel density inside the tumors[60]. Most HCC patients are often accompanied by cirrhosis, vascular changes caused by cirrhosis further affects the distribution of microspheres; on the other hand, reduced hepatic function reserves cirrhosis which leads to increased risk of liver failure after extensive resection or liver injury (including toxic or viral acute hepatitis, or external irradiation)[71]. Post-embolism syndrome (seen after TACE) has not been seen, but a large number of studies have reported that there may be some minor surgery-related symptoms after surgery, including fatigue (54-61%), abdominal pain (23-56%), Nausea and vomiting (20-32%) and low-grade fever (3-12%), usually only a few hours[60], Mild to moderate lymphopenia is common after radiation embolism but is not associated with increased susceptibility to infection[72].

Unlike other forms of brachytherapy, the precise dose of radioembolization can not be predicted[60] ; however, despite these uncertainties in tumor dosimetry, tumor growth is inhibited in more than 90% of patients[73]. The safety of radiation embolization has been confirmed in several Phase 1 and 2 clinical studies[73-75]. One study reported a correlation between radiologic and pathological findings in patients with hepatocellular carcinoma who received radiation embolization with Y^{90} microspheres prior to transplantation, with all of the target lesions exhibiting some degree of histological necrosis, of which 23 (61%) showed complete pathological necrosis[76]. The prognosis after radiation embolism depends largely on pre-treatment liver function and tumor burden (internal and external) and response to treatment[73, 77].

Radiofrequency Ablation (RFA)

Percutaneous treatment of hepatocellular carcinoma (HCC) includes numerous technologies including unipolar radiofrequency ablation (RFA), multi-polar RFA, microwave ablation, cryoablation, and irreversible electroporation. The classic unipolar percutaneous RFA generates current (375 to 500 KHz) based on the monopolar electrode tip inserted into the HCC, inducing a Joule effect by ion agitation and thus generating localized heat(60-100 ℃), resulting in coagulation necrosis[78]. Pathologically, tumor lesions after RFA can be classified into three regions: (a) a peripheral zone that undergoes sub-lethal hyperthermia; and (b) a peripheral zone that undergoes sub-lethal hyperthermia; and (C) The outermost organization not affected by RFA[79]. RAF is a treatment option for patients with early stage HCC and primarily suitable for tumors less than 2-3 cm[80]

In order to increase the efficacy and size of ablation, new ablation devices have been developed: expansible multi-tip devices, internally cooled electrodes, multipolar ablation using bipolar electrodes, microwave ablation[81]. Now RFA has replaced percutaneous ethanol injection as the most commonly used percutaneous HCC treatment;

Five RCTs showed the superiority of percutaneous radiofrequency ablation in local control, with fewer sessions required for tumor necrosis and fewer local tumor recurrences compared to percutaneous ethanol injection[82, 83]. The main treatments for hepatocellular carcinoma less than 5 cm in length with cirrhosis include surgical resection, liver transplantation and radiofrequency ablation. However, the respective roles of ablation and hepatectomy for liver cancers less than 3 to 5 cm in cirrhosis are controversial, in cases of HCC of less than 2-3 cm developing on cirrhosis, Classical monopolar RFAs seem to provide long-term results which are similar to surgical resections; ablation combined with TACE provides sustained local control over monopolar RFA in the treatment of tumors over 3 cm in diameter[81, 84].

The major complications of percutaneous ablation include pleural effusion, pneumothorax, hepatic hematoma

or ascites, transfusion ascites, liver failure, liver abscess, gallbladder injury, biliary stricture, colon or gastric perforation, diaphragmatic injury and tumor seeding[79],local tumor recurrence can be effectively and safely treated by repeated ablation[85]. The tumor recurrence rates ranged from 49% to 63%, 58% to 81% and 80% to 88% at 3, 5, and 10 years, respectively[86].

Cytotoxic chemotherapy

Since the diagnosis of HCC patients is usually in the advanced stage, some patients can only choose palliative treatment, such as chemotherapy, TACE, and targeted therapy, but only prolong survival[45]. Small molecule targeted therapies targeting various signal transduction pathways have also begun to be used after liver resection and after liver transplantation, especially for local treatment such as TACE failure[87, 88]. However, due to the dose-limiting toxicity and multidrug resistance (MDR) of chemotherapy during HCC treatment, the application of chemotherapy in HCC is limited. The main reason for the infrequent chemotherapy in advanced HCC is adverse events (AEs). Many studies have reported response rates of 10% -20% to chemotherapeutic agents in HCC. Anthracyclines, such as doxorubicin, show response rates ranging from 0% to 79%, but their limited utility in HCC treatment due to the toxicity of chemotherapeutic agents and the poor liver reserve in HCC patients[89].

Traditional chemotherapeutic drugs are mainly used in the later stage of the disease, especially after the progress of local treatment, however, the ideal effect is not obtained in the treatment of HCC. Monotherapy lack of obvious advantages, so the joint application of anti-cancer drugs is necessary. For example, PIAF, a combination of cisplatin, interferon, doxorubicin and 5-fluorouracil (5-FU), had a median survival of 8.9 months[90]. However, the PIAF regimen had no significant survival benefit compared with doxorubicin monotherapy[3]. Similarly, the FOLFOX4(fluorouracil, leucovorin, oxaliplatin) regimen did not show significant survival benefit over doxorubicin monotherapy. The FOLFOX4 regimen was compared to doxorubicin monotherapy. FOLFOX4 was more effective in progression free survival, effective rate (8.15% vs 2.67%, P = 0.002) and disease control rate (52.17% vs 31.55%, P <0.001).In addition to these positive results and safety, the primary end point of the observational study (overall survival of 6.40 months vs 4.97 months, P = 0.07) was not statistically different.[3, 60]

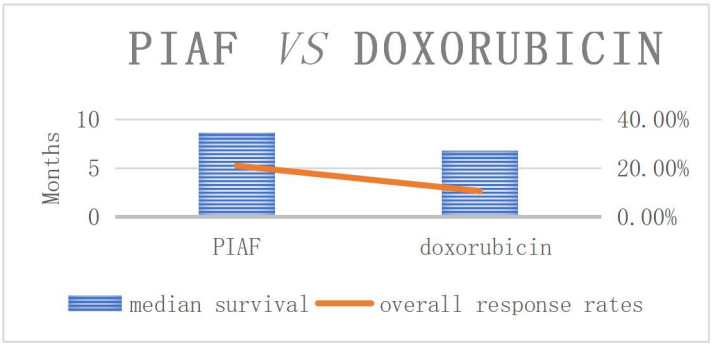

Fig 2. PIAF *vs* Doxorubicin, median overall survival (OS) is not statistically significant (P = 0.07), but the OS of FOLFOX4 group showed an improvement trend.

Fig 3. The overall effective rate of PIAF group was higher than that of doxorubicin group, but the difference was not statistically significant.

Recently, some new chemotherapeutic agents have been evaluated for the treatment of advanced HCC, such as capecitabine, mainly acting on DNA synthesis and slowing tumor growth. The current role in HCC therapy is based on a randomized, controlled trial[91], the median time to recurrence in capecitabine and control groups was 40.0 months (95% confidence interval[95% CI], 31.0-49.2 months) and 20.0 months (95% CI, 12.8-27.2 months) = 0.046). The 5-year overall survival rates in capecitabine and control groups were 62.5% and 39.8%, respectively (P = 0.216). Adverse reactions to capecitabine are usually mild, including nausea, vomiting, diarrhea and decreased white blood cell and / or platelet counts. Capecitabine postoperative adjuvant therapy is well tolerated, postponing the recurrence of HCC, reducing the risk of tumor recurrence. From a safety standpoint, the drug shows good tolerance.

With the advent of new chemotherapeutic drugs and the combination of therapies, HCC therapy brings new ideas. Although most experiments showed no significant

statistical difference between combination therapy and monotherapy, combination therapy has shown an improving trend in overall survival. To further improve the chemotherapy regimen and the synergy between the drugs, it is possible to improve the survival time of patients with advanced HCC.

Sorafenib

HCC is a highly vascularized tumor, vascular endothelial growth factor (VEGF) and angiopoietin-2 (Ang-2) are key factors in tumorigenesis and proliferation, VEGF in particular promotes the growth, migration and morphogenesis of endothelial cells and increases vascular permeability[92, 93]. Inhibition of angiogenesis is crucial in the treatment of HCC. Sorafenib, a tyrosine kinase inhibitor, by targeting multiple genes (EGFR-1, VEGFR-2, VEGFR-3, PDGFR-β, Raf, RET and FLT-3) to achieve the dual purpose of anti-angiogenesis and anti-proliferation[94, 95].

Among the various multi-kinase inhibitors used to treat HCC, sorafenib is the only drug approved for the treatment of advanced HCC[96]. Sorafenib monotherapy prolonged 3-month overall survival and delayed the progression of advanced HCC[97]. The benefits of sorafenib in the treatment of HCC were confirmed in two global Phase III trials, the SHARP trial[98] and the Child-Pugh A Advanced HCC Study in Asia Pacific[99].

Asia-Pacific Child-Pugh A Advanced HCC Study

226 patients were randomized to either experimental (n = 150) or placebo (n = 76). Median overall survival was 6.5 months (95% CI 5.56-7.56) in patients who received sorafenib vs. 4.2 months (3.75-5.46) in placebo (hazard ratio[HR] 0.68[95% CI 0.50 -0.93]; p = 0.014).

In adverse events, the incidence of diarrhea, weight loss, skin reactions in the hands and feet and hypophosphataemia were higher in the sorafenib group, and these adverse events rarely led to withdrawal. After the advent of sorafenib, there are still many targeted drugs(Linifanib, Sunitinib, Everolimus, Lenvatinib, Cabozantinib, Ramucirumab, Tivantinib, Regorafenib and Erlotinib, etc.) as potential first-line / second-line drugs for phase III clinical trials, however, no trial has proved that a drug has a clear advantage in the treatment effect compared to sorafenib[100]. In the SPACE trial, sorafenib or placebo combined with transarterial chemoembolization, the sorafenib group (compared with placebo) failed to show a longer time to progression(TTP)[101]. Similarly, as an adjunct to radical hepatectomy and radiofrequency ablation, sorafenib has not significant improve the prognosis[102]. The effect of sorafenib in combination with other therapies remains to be verified. Further investigation should be considered.

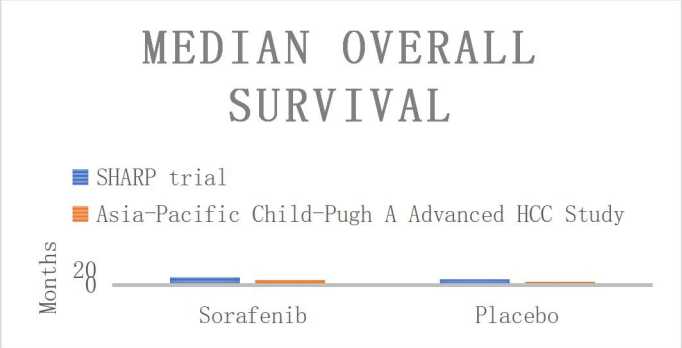

Fig 4. **SHARP trial:** 602 patients with advanced HCC. The median overall survival was 10.7 months in the sorafenib group and 7.9 months in the placebo group (hazard ratio 0.69 for the sorafenib group; 95% confidence interval 0.55-0.87; p <0.001).

Antiviral treatment

Theoretically, anti-virus therapy can reduce the incidence of HCC in patients with chronic hepatitis B (CHB), reduce the incidence of end-stage liver disease and improve the survival rate by inhibiting viral replication and controlling liver inflammation, in recent years, there is more evidence of evidence-based medicine[103, 104]. A retrospective cohort study showed that preoperative high viral load (> 104 copies/ml) was an independent risk factor for postoperative overall survival (OS) and recurrence-free survival (RFS)[105].

Studies have also shown that antiviral therapy can reduce long-term recurrence rates after surgery or intervention but have no significant effect on early relapse[106, 107]. Chronic hepatitis B virus (HBV) infection remains a major cause of HCC (especially in Asia). Among HCC patients with HBV infection, postoperatively high viral replication status, active inflammation, and post-injury hepatocyte regeneration associated with increased risk of recurrence and poor long-term survival outcomes[108-110].In addition, the

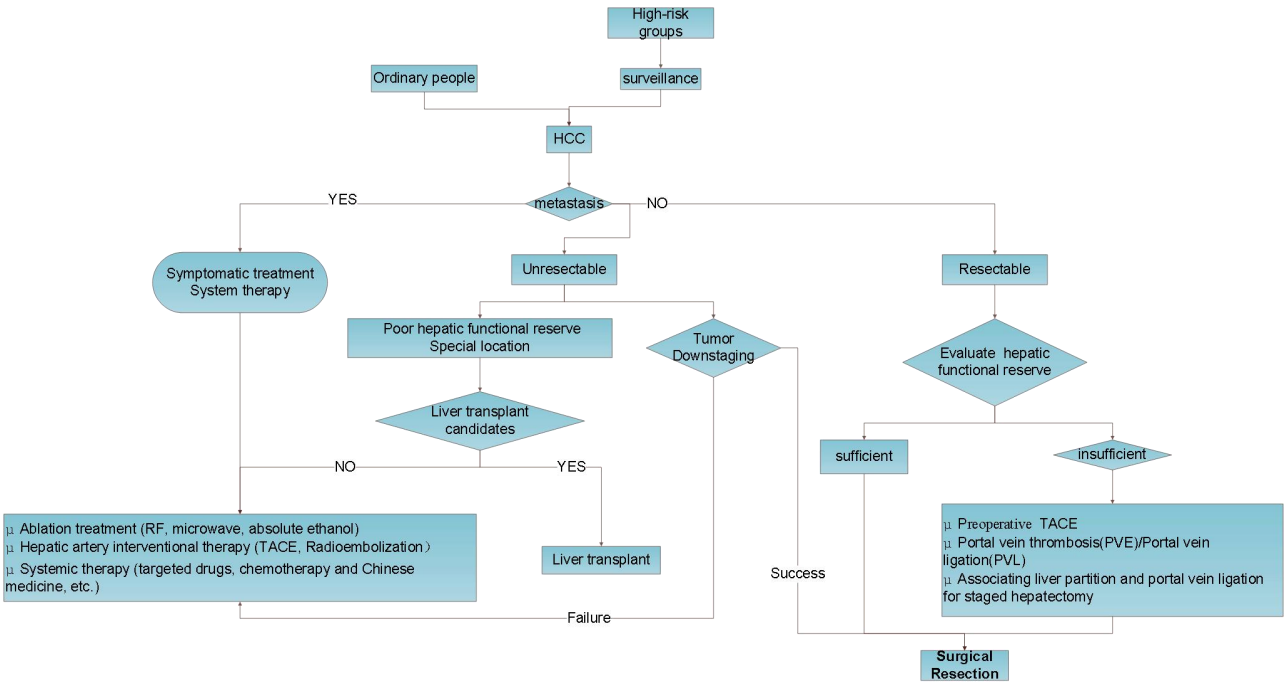

Fig 5. Treatment process

sustained low HBV load predicted good long-term recurrence-free survival (RFS) and overall survival (OS)[111], there is growing evidence that antiviral treatment with nucleoside analogs (NAs) can reduce the risk of HCC in patients with chronic HBV infection[112, 113]. A total of 9,009 patients were enrolled into the meta-analysis by Xu-Xiao Chen et al. The pooled analysis showed that antiretroviral treatment was associated with overall survival (OS) (hazard ratio[HR]: 0.58; 95% confidence interval[CI]: 0.51-0.67; P<0.00001) and recurrence-free survival (RFS) (HR: 0.68; 95% CI: 0.63 -0.74. Antiviral treatment of NAs has significant survival benefit in patients with HBV-associated HCC after radical resection, especially in patients with high baseline HBV DNA levels (> 20,000 IU / mL)[114]. Chronic hepatitis C (CHC) evolves slowly, with no specific symptoms until it progresses to liver fibrosis, so it is difficult to start antiviral therapy early in the disease. Antiviral treatment of chronic hepatitis C (CHC) aims to reduce (HCV) related morbidity and mortality, including the development of liver fibrosis or cirrhosis and hepatocellular carcinoma (HCC). Antiviral therapy reduces the extent of liver necrotizing inflammation and induces the regression of liver fibrosis[115]. Sustained virological response (SVR) is a surrogate marker of eradication of HCV and is considered "cure"[116]. In patients with chronic hepatitis C, antiviral therapy can reduce the development and mortality of HCC, especially when SVR is achieved[117].

However, postoperative antiviral therapy has not yet formed a diagnosis and treatment consensus for HBV-related HCC. Therefore, more evidence-based medical evidence is needed to confirm that antiviral therapy can bring survival benefit to patients with liver cancer. In conclusion, attention should be paid to closely monitoring the virus activity in patients with HBV-related HCC. Comprehensive treatment programs such as antiviral therapy minimize postoperative recurrence and improve prognosis.

Chinese medicine therapy

Recently, it has been reported that Chinese Herbal Medicines (CHM) (such as Scutellaria baicalensis, Berberine, Chrysanthemum indicum Linn, Tanshinone II A, Solanum nigrum L, Tetrandrine, Andrographolide, Gamboge[118])has gradually become the treatment of hepatocarcinoma due to its multi-level, coordination intervention and multi- targets for liver cancer[119].

CHM was used for the prevention of diseases long ago, with the development of modern technology, more and more Chinese herbal compounds were isolated and confirmed its role in the prevention of liver cancer. Ursolic

acid can effectively prevent diethylnitrosamine (DEN) -induced oxidative stress and hepatocellular carcinoma[120]. Similarly, Pentaacetyl geniposide, Curcumin, Berberine and Saikosaponin-d isolated from Chinese Herbal are used to prevent liver cancer[121].

<table>
<tr><td>Radical treatment</td><td colspan="4">Liver Transplantation</td></tr>
<tr><td rowspan="11">Non-radical treatment</td><td colspan="4">Liver Resection</td></tr>
<tr><td rowspan="8">Local therapy</td><td rowspan="5">Percutaneous treatment</td><td colspan="2">Anhydrous alcohol injection</td></tr>
<tr><td rowspan="2">Radiofrequency Ablation</td><td>unipolar radiofrequency ablation</td></tr>
<tr><td>multi-polar RFA</td></tr>
<tr><td colspan="2">microwave ablation</td></tr>
<tr><td colspan="2">cryoablation</td></tr>
<tr><td colspan="2">irreversible electroporation</td></tr>
<tr><td rowspan="5">Embolization</td><td rowspan="3">Radioembolization</td><td>iodine-125</td></tr>
<tr><td>iodine-131</td></tr>
<tr><td>yttrium-90</td></tr>
<tr><td rowspan="2">Transarterial Chemoembolization</td><td>cTACE</td></tr>
<tr><td>DEB-TACE</td></tr>
<tr><td rowspan="3">Systemic treatment</td><td colspan="3">Cytotoxic chemotherapy</td></tr>
<tr><td colspan="3">Sorafenib</td></tr>
<tr><td colspan="3">Chinese medicine therapy</td></tr>
<tr><td>Adjuvant therapy</td><td colspan="4">Antiviral treatment</td></tr>
</table>

Fig 6. Treatment options

Gao L et al[122]. Searched for putative active ingredients and targets of herbs by the Network pharmacology approach and found that some CHMs could activate ACSL1, ADH1C, ASS1, AURKA, CA1, CCNA2, CCT3, EGFR, ESR1, FTCD, GAPDH, GLUD1, GSTP1, KRAS, NME1, NOS2A, PTGS2, SRC, TOP2A and AKT2, MAPK and other genetic targets with anti-cancer effects, and gene enrichment analysis found that the phosphatidylinositol 3'kinase/Akt (PI3K/Akt) signaling pathway, nuclear SMAD2/3 signaling, and E-cadherin might be influenced by these herbs. Chinese herbal compounds mainly play an anti-cancer role in four fields (anti-angiogenesis, apoptosis induction, inhibition of proliferation and metastasis), and other effects include cell senescence and anoikis, cell cycle arrest, inhibition of EMT, metastasis and angiogenesis, regulation of immune function, reversal of drug resistance and enhancement of chemotherapeutic effects[121, 122].

CHM combined with TACE, LR and other treatment options is also a potential method of treatment of HCC. JDF particle preparation is a commonly used traditional Chinese medicine preparation in traditional Chinese herbal medicine theory, which is composed of anticancer and detoxification internal medicine. The current research shows that TACE combined with JDF granules can improve the prognosis of patients and prolong the survival of patients with advanced HCC[123]; Chinese medicine combined with chemotherapy compared with chemotherapy, 1 year, 2 years, 3-year survival rate increased, these studies have shown that CHM combined TACE, LR and other treatment options may benefit HCC patients, but because of the quality of these studies, there is a need for high-quality, tightly controlled trials to confirm[124].

The mechanism of action and pharmacological studies have shown that CHM is an important resource for the development of new anticancer drugs, CHM combined with existing therapies, also provide the possibility of improving the survival time of patients with HCC.

Conclusion

The treatment of HCC patients is particularly challenging, due to the tumor specificity (size, number, location and vascular involvement) of HCCs and the diminished capacity of the liver reserve. Risk stratification programs (such as: CLIP and BCLC), used to assess the risk for the patient to choose a more appropriate treatment options. Of course, these risk stratification programs need to be further improved. As the results of clinical trials of new drugs failed to achieve satisfactory results, we expect more research on CHM and the combination of different therapies, in order to exert the complementary effects of different treatment regimens and different drugs. In the meantime, clinical studies related to predictive biomarkers such as miRNAs and lncRNAs will help the surveillance of high-risk patients. So as to achieve the purpose of early detection and cure, improve the survival rate of HCC patients. We also need to continually deepen our understanding of HCC biology and learn from the

development of other solid tumor treatments.

Acknowledgemen

None

Conflict of Interest

None

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