**Name of journal: World Journal of Gastroenterology**

**ESPS Manuscript NO: 11219**

**Columns: Topic Highlights**

**WJG 20th Anniversary Special Issues (20): Gastrointestinal surgery**

**Advances in non-surgical management of primary liver cancer**

Chen X *et al*. Non-surgical management of liver cancer

Xiao Chen,Hai-Peng Liu, Mei Li, Liang Qiao

**Xiao Chen,Hai-Peng Liu, Mei Li,** Department of General Surgery, Lanzhou University Second Hospital, Lanzhou 730030, Gansu Province, China

**Xiao Chen,Hai-Peng Liu, Mei Li,** Key Laboratory of Digestive System Tumors of Gansu Province, Lanzhou 730030, Gansu Province, China

**Liang Qiao,** Storr Liver Unit, Westmead Millennium Institute, Department of Medicine and Western Clinical School, The University of Sydney, NSW 2145, Australia

**Author contributions:** Chen X contributed to conception, design, and generation of the first draft; Liu HP and Li M assisted in the writing the manuscript, reference search, and table generation; Qiao L made considerable language editing and revision of the manuscript, and has approved the final version of this manuscript.

**Correspondence to: Liang Qiao, MD, PhD,** Storr Liver Unit, Westmead Millennium Institute, Department of Medicine and Western Clinical School, The University of Sydney, Westmead, NSW 2145, Australia. liang.qiao@sydney.edu.au

**Telephone:** +61-2-98459132 **Fax**: +61-2-98459103

**Received:** May 9, 2014 **Revised:** June 17, 2014

**Accepted:** July 22, 2014

**Published online:**

**Abstract**

Hepatocellular carcinoma (HCC) is the fifth most common cancer and the third most common cause of cancer-related death worldwide. There have been great improvements in the diagnosis and treatment of HCC in recent years, but the problems, including difficult diagnosis at early stage, quick progression, and poor prognosis remain unsolved. Surgical resection is the mainstay of the treatment for HCC. However, 70%-80% of HCC patients are diagnosed at an advanced stage when most patients are ineligible to the potentially curative therapies such as surgical resection and liver transplantation. In recent years, non-surgical management for unrespectable HCC, such as percutaneous ethanol injection, percutaneous microwave coagulation therapy, percutaneous radiofrequency ablation, transcatheter arterial chemoembolization, radiotherapy, chemotherapy, biotherapy, and hormonal therapy have been developed. These therapeutic options, either alone or in combination, have been shown to control tumor growth, prolong survival time and improve quality of life to some extent. This review covers the current status and progresses of non-surgical management for HCC.

© 2014 Baishideng Publishing Group Inc. All rights reserved.

**Key words**: Ablation therapy; Biotherapy; Hepatocellular carcinoma; Hormonal therapy; Percutaneous ethanol injection; Percutaneous microwave coagulation therapy; Radiofrequency ablation; Radiotherapy; Transcatheter arterial chemoembolization; Chemotherapy

**Core tip:** In recent years, there has been a considerable progress in the development of non-surgical management for unrespectable hepatocellular carcinoma. These therapeutic options, either alone or in combination, have been shown to control tumor growth, prolong patient survival, and improve the quality of life to some extent. Some of these strategies have been extensively used in the clinical practice as the preferred approaches for the advanced primary liver cancer.

Chen X,Liu HP, Li M, Qiao L. Advances in non-surgical management of primary liver cancer. *World J Gastroenterol* 2014; In press

**Introduction**

Primary liver cancer, with the hepatocellular carcinoma (HCC) being the most common form, is the fifth most common cancer and the third most common cause of cancer-related death worldwide[1]. It was predicted that the incidence of liver cancer in China would increase over the next few years[2]. Thus, liver cancer poses a heavy burden for our community. In the United States, it was reported that the number of new HCC cases has increased over the past several years, and the incidence rate increased significantly from 2.7/100000 in 2001 to 3.2/100000 in 2006[3].

At present, surgery-based comprehensive therapy plays a dominant role in the treatment of HCC. However, the majority of patients had lost their opportunities of surgical treatment when diagnosis was confirmed. Moreover, only 15% patients may benefit from surgical excision.

# In clinical practice, the type of treatment for HCC is largely dependent on how advanced the tumors have developed. Thus, tumor staging is a crucial basis for the selection of surgical and non-surgical therapeutic interventions and it thus has a significant impact on the therapeutic outcomes. Many different staging systems have been developed including the American Joint Committee on Cancer tumor-node-metastasis staging system (Table 1), the Okuda staging system (Table 2)[4], Cancer of the Liver Italian Program Scoring System (Table 3)[5,6], the Barcelona Clinic Liver Cancer (BCLC) System (Table 4)[7,8], the Chinese University Prognostic Index (Table 5)[9], Japan Integrated Staging Score, and Groupe d’ Etude et de Traitement du Carcinoma Heatocellulaire. However, each of these systems have their advantages and disadvantages, and no worldwide consensus as to which is the more preferred prognostic staging system for HCC has been established.

Regardless of which staging system is used in clinical practice, non-surgical approaches have shown great promise in the management of primary hepatic carcinoma. Among all non-surgical approaches, percutaneous ethanol injection (PEI), percutaneous microwave coagulation therapy (PMCT), and percutaneous radiofrequency ablation (RFA) have become the three most widely used techniques for the treatment of HCC that are less than 5 cm in diameter and/or have a tumor number less than 3. In this review article, we aim to summarize the recent advances in the non-surgical therapeutic approaches for HCC.

**Ablation therapy**

Ablation therapy is considered the best treatment choice for patients with early but unresectable liver cancer[10]. Most commonly used ablation therapies include PEI, RFA, microwave coagulation therapy (MCT), high intensity focused ultrasound (HIFU), interstitial laser photo-coagulation and freezing treatment.

***PEI***

In this procedure, 95% alcohol is slowly injected into the tumor mass *via* a puncture needle previously inserted into the tumor mass under the guidance of ultrasound. The high concentration of ethanol infiltrates the tumor tissue where it dehydrates the tumor cells, and causes protein degradation and coagulative necrosis of the tumor and surrounding tissues. This procedure is simple, convenient and less costly. PEI is an effective treatment for small HCC. The efficacy of PEI for HCC tumors smaller than 3 cm in diameter is significantly better than for the tumors larger than 5 cm in diameter. It has been reported that in HCC patients whose tumor mass was less than 3 cm, a complete response rate of 70%-80% and a 5-year survival of 40%-60% have been achieved[11].

The therapeutic efficacy of PEI for HCC has been adversely linked to the tumor size, Child-Pugh score, BCLC staging, and serum alpha fetoprotein levels[12]. PEI is strongly recommended to HCC patients in whom the tumors are located near major bile ducts, gallbladder, and diaphragm, or in whom the tumor size is < 1.5 cm in diameter[13].

The biggest drawback of PEI is the high recurrence rate, usually around the tumor margin[14]. Multiple injection and large amounts of alcohol are sometimes required to achieve a better therapeutic effect, but this may cause cumulative damage even cirrhosis in hepatic parenchyma.

***Rfa***

RFA is a minimally invasive treatment for solid tumors such as HCC. In RFA, the heat generated by high frequency alternating current (in the range of 350–500 kHz) is transduced into the tumor tissues through an electrode probe. The transduced heat will cause necrosis and then scarring in the tumor tissues. RFA is usually conducted in the outpatient setting, using either local anesthetics or conscious sedation anesthesia. Insertion of radiofrequency probes is usually done through percutaneous, laparoscopic, or open intraoperative ultrasound guidance.

RFA is commonly indicated for: (1) small HCC but patients are not suitable for resection; (2) single tumor with the maximum diameter ≤ 5 cm; or multiple but less than 3 tumors with the maximum diameter ≤ 3 cm; (3) HCC patients with no lymphovascular invasion or neighboring organ invasion; and (4) patients with Child-Pugh Class A or B liver function[15]. In a report involving 88 cases of small HCC treated with RFA[16], the 3-year local recurrence rate was 4.8%, 3- and 5-year survival rates were 83.0% and 70.0% respectively, and the 3- and 5-year disease-free survival rates were 34.0% and 24.0%, respectively.

The major disadvantages of RFA include: (1) dissipation of the RF heat through nearby major blood vessels, therefore, the curative effect may be reduced and the adjacent organs may be damaged; and (2) in large tumors, the rate of necrosis is low. The following are independent risk factors of recurrence after RFA treatment: (1) tumor diameter is > 3 cm; (2) tumor is located near the intrahepatic vasculature; (3) subcapsular tumors; and (4) PT extends over 3 s. The effect of RFA can be improved if these risk factors are taken into account in the clinical practice[17].

Ultrasound-guided RFA is a relatively safe, well-tolerated, and versatile treatment option that offers excellent local control of primary and metastatic liver tumors. The appropriate use of percutaneous, laparoscopic, and open surgical RFA is beneficial in the management of patients with liver tumors in a variety of situations[18]. Randomized controlled trials have shown that RFA offers a higher complete response at fewer treatment sessions and a better survival compared to ethanol injection[11].

***PMCT***

MCT is a relatively new type of ablative approach for the treatment of liver cancer. MCT can efficiently induce coagulative necrosis in tumor tissues, and tumors with unfavorable location or those larger than 3 cm in diameters are also suitable for MCT without having further risk of local tumor recurrence[19,20].

In a recent study, a novel 915 MHz system was used to treat 47 patients with 80 tumor nodules (average tumor size 2.6 ± 0.9 cm) in 51 treatment sessions[20]. The treatment was delivered laparoscopically in 20 cases or percutaneously in 31 cases. High-risk conditions (defined as unfavorable tumor location such as those invisible by native transabdominal ultrasound, superficial tumors, or risk of heat sink phenomena) were found in 28 cases (53%). Local recurrence rate was 17% on a per-patient basis and 12% on a per-tumor basis (*n* = 9). One patient died of uncontrollable upper gastrointestinal bleeding during the postoperative hospital stay. No MCT-associated complications occurred. Median follow-up period was 20 mo.

By a univariate logistic Cox regression, it was revealed that the tumor size, procedure access, and high-risk location were significant prognostic factors for local tumor recurrence. However, by a multivariate reiteration, only the chosen access to MCT and tumor size were significantly correlated with local recurrence.

The commonly encountered complications of MCT include skin burns, liver capsule bleeding, and severe pain. In case the tumor size is > 5 cm in diameter, cancer cells may become thermoresistant and active proliferation may occur, favoring tumor metastasis and recurrence. Nevertheless, MCT may be superior to other therapeutic approaches for HCC.

***HIFU***

HIFU is a highly precise procedure that applies high-intensity focused ultrasound energy to locally heat and destroy [diseased](http://en.wikipedia.org/wiki/Disease) or damaged [tissue](http://en.wikipedia.org/wiki/Tissue_(biology)) through ablation. Thus, HIFU belongs to hyperthermia therapy, a class of clinical therapies that use temperature to treat diseases. This minimally invasive therapeutic procedure directs acoustic energy into the diseases tissues[21]. Although the application of HIFU technology in the management of patients with hepatocellular carcinoma is still in its early stages, several studies concerning HIFU treatment of liver tumors have been reported. In a published study[22], 39 patients with cirrhosis Child A or B and unresectable HCC adjacent to major hepatic veins were treated with HIFU. These patient/tumor characteristics would be ineligible for other ablation treatments such as RFA or PEI. Following one session of HIFU treatment, more than 50% of the patients developed complete tumor necrosis, indicating that HIFU can achieve complete tumor necrosis even when the lesion is located adjacent to the major hepatic blood vessels. No major complications were observed and the overall survival rates at 1, 3, and 5 years were 75.8%, 49.8% and 31.8 %, respectively. In a similar study[23], Orsi et al showed that in six HCC patients whose tumors were located in difficult locations (i.e., tumors adjacent to a main hepatic blood vessel, heart, bowel, stomach, gall bladder, and bile ducts), treatment with HIFU achieved complete response in all patients without any complications[23].

***Targeted cryoablation therapy***

Helium cryoablation is minimally-invasive freezing equipment used to treat the solid tumor through extremely low temperature. Within a few seconds, the tip temperature of therapeutic device could drop to -140 °C, and then quickly rise to 20-45 °C. The unique freeze-thaw cycles of the temperature could more completely destroy the tumor tissues, regulate the presentation of tumor antigens, and activate the body’s anti-tumor immune response. Cryoablation kills tumor cells and induces necrosis in tumor tissues primarily through two mechanisms, namely cellular damage and vascular injury[24]. Cell damage occurs immediately in the freeze-thaw process, whereas vascular injury is the result of blood stagnation and further microcirculation failure.

The therapeutic effect of the cryoablation on target tissue could be influenced by many factors, including freezing temperature, freezing rate, thawing rate, and the frequency freeze-thaw cycle is applied. Cryogenic treatment not only effectively kills all tumor cells in the frozen region, but also maximally preserves the normal liver tissues. Based on a long-term follow-up study, cryosurgery could achieve a survival rate comparable to that of liver resection, and it also reduces the overall mortality and improves quality of life[25].

**Transcatheter arterial chemoembolization**

Normal liver has a dual blood supply system: 25%-30% of blood supply comes from the hepatic artery, and 70%-75% from portal vein system. In case of HCC, 90%-99% of tumor blood supply comes from the hepatic artery, whereas only a small portion of the tumor tissue is nourished by the portal vein. Transcatheter arterial chemoembolization (TACE) causes tumor necrosis by blocking the tumor blood supply with the emulsion of chemotherapy drugs and lipiodol while exerts minimal impact on the normal liver. TACE is the first choice for unresectable advanced liver cancer, and is one of the preferred therapies for small HCC.

Major indications of TACE include: (1) HCC patients with good liver function reserve but their tumors can not be radically resected; (2) no thrombosis in the portal vein trunk; (3) tumor occupies less than 70% of the whole liver; (4) to de-bulk the size of huge liver cancer for later resection; (5) palliative control of pain, bleeding and arteriovenous fistula caused by the tumor; and (6) as a preventive therapy after tumor resection[26]. In a study involving 8510 cases of unresectable HCC, the median survival time following TACE treatment was approximately 34 mo, and 1-, 3-, 5-, and 7-year survival rates were 82%, 47%, 26% and 16%, respectively[27]. In patients with portal vein thrombosis, the average survival time can still be extended by appropriate TACE therapy[28,29]. Overall, TACE shows satisfactory results on small HCC (< 5 cm in diameter)[30].

Incomplete necrosis of tumor tissues is the major drawback of TACE. Therefore, multiple treatments are needed. Pathological examination of surgical specimens after TACE showed live cancer cells around most tumors. This is mainly due to drug resistance of tumor cells, incomplete tumor embolization, and re-established collateral blood supply.

According to 2013 NCCN guidelines on HCC, all tumors irrespective of location may be amenable to arterially directed therapies provided that the arterial blood supply to the tumor may be isolated without excessive non-target treatment. Arterially-directed therapies include transarterial blood embolization (TAE), chemoembolization (TACE plus drug-eluting beads), and radioembolization with Yttrium-90 microspheres. All arterially-directed therapies are relatively contraindicated in patients with bilirubin > 3 mg/dL unless segmental injections can be performed. Radioembolization with Yttrium-90 microspheres has an increased risk of radiation-induced liver disease in patients with bilirubin over 2 mg/dL.

Arterially-directed therapies are relatively contraindicated in patients with main portal vein thrombosis and patients with liver function classified as Child-Pugh Class C. In HCC patients, if there is evidence of residual/recurrent tumor not amenable to other local therapies, and provided that the patients have adequate liver function, or their bilirubin return to baseline level, sorafenib may be an appropriate choice following arterially-directed therapies. The safety and efficacy of using sorafenib concomitantly with arterially-directed therapies and/or ablation is being investigated in ongoing clinical trials. Arterially-directed or systemic therapy should be considered in patients with unresectable/inoperable lesions > 5 cm[31-33].

**Radiotherapy**

It was previously believed that liver cancer is generally insensitive to radiotherapy. In addition, liver tissue is sensitive to radiation; therefore, when used to treat liver tumors derived from chronic viral hepatitis, radiotherapy may cause radiation-induced liver injury.

Studies over the past few years have shown that radiation therapy may find its potential therapeutic benefits in patients with advanced HCC. It has been verified that HCC is almost equally sensitive to radiation therapy as the poorly-differentiated nasopharyngeal squamous cell carcinoma[34]. Some of the recently developed stereotactic radiotherapy techniques including gamma knife, X knife, three-dimensional conformal radiotherapy (3DCRT), and intensity modulated radiation therapy may improve the irradiation capacity whereas the damage of X-ray to the normal liver tissue may be minimized. Image guided radiotherapy techniques shows even more enhanced therapeutic effect, as this technique takes account into the displacement error caused by the breathing movement of the target organ and uses the concept of 4D radiation therapy.

In a study of 70 cases of primary liver cancer treated with 3DCRT, 54.3% of the cases had reduction in their primary tumor lesions, and 39% had portal vein tumor thrombus cleared or shrunk, and the median survival period was extended to 11.2 mo[35]. Radiation therapy can also be applied to the palliative treatment of the large HCC and very late HCC, either alone or in combination with other treatment modalities[36,37]. For the palliative therapy for larger tumors or metastatic tumors, radiotherapy can help release major symptoms such as pain. For HCC complicated with local (*e.g.*, hepatic hila) or distant lymph node metastasis, radiotherapy can be applied to palliatively treat the tumor thrombus of the portal vein and inferior vena cava, as well as the lymph node and distant metastasis, provided that the primary tumors are well under control[38-40]. However, the cirrhotic liver may have reduced tolerance to radiation therapy. Thus, the correct safe dosage and partition of the radiation have not yet been standardized. At present, in order to improve the efficacy and reduce the adverse reaction, the radiation is usually given in a small and extended course, on a presumption that the accumulated total dose is therapeutically sufficient.

Monoclonal antibodies carrying radioactive material have been shown to achieve some therapeutic effect. For example, intraoperative injection of Yttrium-spherical particles via hepatic artery has been shown to shrink the tumor, relieve the symptoms and prolong the patient survival, and in a minority of patients tumor resection was possible after the therapy[41,42].

**Chemotherapy**

Liver cancer is a chemoresistant tumor, but the underlying molecular mechanisms are unclear. Altered biological characteristics of the cancer cells and the perturbed pharmacokinetic properties of the liver, as well as the inherent resistant nature of the cancer cells may all play a role.

P53 is an important tumor suppressor gene and is a critical regulator for chemotherapeutic drug-induced apoptosis. Inactivation of p53 pathway has been causally linked to primary drug resistance of the cancer cells[43]. P53 mutation occurs frequently in liver cancer. Hepatitis B virus (HBV) infection and chemical drugs have been shown to induce p53 mutation. Over-expression of DNA topoisomerase II alpha in HCC is likely responsible for the observed resistance of liver cancer cells to Adriamycin[44].

Reduced number of functional liver cells, impaired liver microcirculation, and compromized detoxifying capacity of the liver (*e.g.*, due to reduced activity of CYP450 system) all contribute to the poor absorption, distribution, and bioavailability of the conventional chemotherapeutic drugs. As a result, it can be difficult for the chemotherapeutic drugs to achieve the therapeutically relevant level, and the diseased liver may have an increased susceptibility to develop liver dysfunction and patients are vulnerable to develop complications such as infection, jaundice, ascites and gastrointestinal bleeding. The innate resistance of cancer cells particularly cancer stem cells may be related to the increased expression of drug efflux genes such as multidrug resistance gene[45].

So far, there is no convincing evidence that chemotherapy can improve overall survival of patients with advanced HCC[46]. For example, single agent doxorubicin may be effective in 10%-15% of cases, but it does not improve the overall survival and serious adverse reactions such as neutropenia is a hurdle for more aggressive treatment[47]. Other chemotherapeutic drugs such as cisplatin, etoposide, epirubicin, 5-FU, gemcitabine, irinotecan and liposomal doxorubicin also showed no significant effect, and adverse effects can also be severe[48-50]. Combinatorial chemotherapies have also failed to improve the overall survival in HCC patients[51,52].

**Biotherapy**

***Immunotherapy***

In recent years, tremendous progress has been made on the immunotherapy for HCC. Interferon is the cornerstone of the treatment for viral hepatitis, but its application in the management of advanced HCC is still controversial. High dose of interferon (2.5 × 107-50 × 107 IU/m2, 3 times per week) has been found to improve the overall survival of HCC patients in 30% of cases[53]. The main drawback of interferon treatment is its adverse reactions, but they can be minimized when interferon is used at a lower dose (3 × 106IU/m2, 3 times per week). Combination of monoclonal antibody and single chain antibody variable region gene (scFv) derived from tumor tissues has shown some anti-tumor effect[54]. Likewise, lymphoid immune therapy could improve the survival of the patients with primary liver cancer[55,56].

***Targeted molecular therapy***

With the enhanced understanding of the molecular mechanisms governing the development of HCC and treatment resistance, many molecular drugs have been developed. These agents may target one or more key signaling pathways that are important for cancer development and progression, such as cell proliferation, apoptosis, and angiogenesis[57]. Of most relevance to clinical practice, the multikinase angiogenesis inhibitor Sorafenib, a FDA approved agent for the treatment of advanced HCC, has shown promising results[58,59]. However, large clinical trials have revealed that less than 50% of the patients respond to Sorafenib treatment and in the responders this agent only increases the mean patient survival by 4.2-6.5 mo and the long-term response is lacking[59]. More importantly, rapid resistance will develop after the termination of drug administration[60,61]. Expansion of liver cancer stem cells in the hypoxic environment may be partially responsible for Sorafenib resistance in clinical practice, tumor aggressiveness and patient survival were correlated with the proportion of cancer stem cells[62].

Other molecular agents such as bevacizumab (monoclonal antibody against vascular endothelial growth factor), erlotinib and cetuximab (epidermal growth factor receptor blocking agents) have all been tested in various stages of clinical trials but the therapeutic effects remain to be further determined[63-65].

**Hormonal therapies**

Sex steroid hormones can interact with the growth receptors and promote the growth of cancer cells. As such, hormonal therapy has been explored as a potential treatment option for many types of solid tumors such as breast cancer, endometrial cancer, and prostate cancer. In HCC, sex hormone receptors, such as estrogen receptor, progesterone receptor and androgen receptor are all expressed[66]. Liver is sensitive to sex hormone stimulation, and this might play an important role in the development of liver cancer[67]. Consequently, hormone receptor blockers have been attempted in the treatment of advanced HCC. Unfortunately, prospective randomized controlled trials have failed to demonstrate an improved overall survival in patients with advanced HCC who were treated with hormone receptor blockers[68]. Meta-analysis of the published data on the use of hormonal therapy also failed to demonstrate a survival advantage for patients with advanced HCC[69]. Thus, there is no sufficient evidence to prove the therapeutic advantage of hormonal therapy for liver cancer.

**Combined modality therapies**

Since the single agent treatment only have limited therapeutic benefits, it is reasonable that combination of more than one treatment options may produce better therapeutic outcomes. However, no standard combinatorial protocols are available. It is generally believed that the combinatorial treatment for liver cancer should be individualized[10].

**Conclusion**

Although a definite non-surgical therapy for HCC is not available, many treatment modalities have been developed. Which therapeutic approach is most appropriate to a given patient is dependent on several factors mainly including tumor staging, patients’ age, co-morbidities, and the availability of the treatment modalities. The reasonable selection of the available treatment options is the key to improving the therapeutic outcome and patient survival.

**References**

1 **Parkin DM**, Bray F, Ferlay J, Pisani P. Global cancer statistics, 2002. *CA Cancer J Clin* 2005; **55**: 74-108 [PMID: 15761078 DOI: 10.3322/canjclin.55.2.74]

2 **Chen WQ**, Zheng RS, Zeng HM, Zhang SW, Li N, Zou XN, He J. [Trend analysis and prediction of cancer incidence in China]. *Zhonghua Yu Fang Yi Xue Za Zhi* 2012; **46**: 581-586 [PMID: 22943910]

3 **Centers for Disease Control and Prevention (CDC)**. Hepatocellular carcinoma - United States, 2001-2006. *MMWR Morb Mortal Wkly Rep* 2010; **59**: 517-520 [PMID: 20448528]

4 **Okuda K**, Ohtsuki T, Obata H, Tomimatsu M, Okazaki N, Hasegawa H, Nakajima Y, Ohnishi K. Natural history of hepatocellular carcinoma and prognosis in relation to treatment. Study of 850 patients. *Cancer* 1985; **56**: 918-928 [PMID: 2990661 DOI: 10.1002/1097-0142(19850815)56: 4<918:AID-CNCR2820560437>3.0.CO;2-E]

5 A new prognostic system for hepatocellular carcinoma: a retrospective study of 435 patients: the Cancer of the Liver Italian Program (CLIP) investigators. *Hepatology* 1998; **28**: 751-755 [PMID: 9731568 DOI: 10.1002/hep.510280322]

6 Prospective validation of the CLIP score: a new prognostic system for patients with cirrhosis and hepatocellular carcinoma. The Cancer of the Liver Italian Program (CLIP) Investigators. *Hepatology* 2000; **31**: 840-845 [PMID: 10733537 DOI: 10.1053/he.2000.5628]

7 **Llovet JM**, Fuster J, Bruix J; Barcelona-Clínic Liver Cancer Group. The Barcelona approach: diagnosis, staging, and treatment of hepatocellular carcinoma. *Liver Transpl* 2004; **10**: S115-S120 [PMID: 14762851 DOI: 10.1002/lt.20034]

8 **Llovet JM**, Brú C, Bruix J. Prognosis of hepatocellular carcinoma: the BCLC staging classification. *Semin Liver Dis* 1999; **19**: 329-338 [PMID: 10518312 DOI: 10.1055/s-2007-1007122]

9 **Leung TW**, Tang AM, Zee B, Lau WY, Lai PB, Leung KL, Lau JT, Yu SC, Johnson PJ. Construction of the Chinese University Prognostic Index for hepatocellular carcinoma and comparison with the TNM staging system, the Okuda staging system, and the Cancer of the Liver Italian Program staging system: a study based on 926 patients. *Cancer* 2002; **94**: 1760-1769 [PMID: 11920539 DOI: 10.1002/cncr.10384]

10 **Bruix J**, Sherman M; Practice Guidelines Committee, American Association for the Study of Liver Diseases. Management of hepatocellular carcinoma. *Hepatology* 2005; **42**: 1208-1236 [PMID: 16250051 DOI: 10.1002/hep.20933]

11 **Yin XY**, Lu MD. Percutaneous ablation for small hepatocellular carcinoma. *Expert Rev Gastroenterol Hepatol* 2009; **3**: 121-130 [PMID: 19351283 DOI: 10.1586/egh.09.7]

12 **Danila M**, Sporea I, Sirli R, Popescu A. Percutaneous ethanol injection therapy in the treatment of hepatocarcinoma--results obtained from a series of 88 cases. *J Gastrointestin Liver Dis* 2009; **18**: 317-322 [PMID: 19795026]

13 **Kim SR**, Imoto S, Nakajima T, Ando K, Mita K, Taniguchi M, Sasase N, Matsuoka T, Kudo M, Hayashi Y. Well-differentiated hepatocellular carcinoma smaller than 15 mm in diameter totally eradicated with percutaneous ethanol injection instead of radiofrequency ablation. *Hepatol Int* 2009; **3**: 411-415 [PMID: 19669368 DOI: 10.1007/s12072-009-9128-z]

14 **Khan KN**, Yatsuhashi H, Yamasaki K, Yamasaki M, Inoue O, Koga M, Yano M. Prospective analysis of risk factors for early intrahepatic recurrence of hepatocellular carcinoma following ethanol injection. *J Hepatol* 2000; **32**: 269-278 [PMID: 10707867 DOI: 10.1016/S0168-8278]

15 **Zhang YJ**, Chen MS. The indications and application about radiofrequency ablation of liver cancer. *J Hepatobiliary Surg* 2010; **18**: 9-10

16 **Waki K**, Aikata H, Katamura Y, Kawaoka T, Takaki S, Hiramatsu A, Takahashi S, Toyota N, Ito K, Chayama K. Percutaneous radiofrequency ablation as first-line treatment for small hepatocellular carcinoma: results and prognostic factors on long-term follow up. *J Gastroenterol Hepatol* 2010; **25**: 597-604 [PMID: 20074153 DOI: 10.1111/j.1440-1746.2009.06125.x]

17 **Yang B**, Zou J, Xia J, Ren Z, Gan Y, Wang Y, Zhang B, Ge N, Wang D, Chen Y, Chen R, Li L, Ye S, Wang X. Risk factors for recurrence of small hepatocellular carcinoma after long-term follow-up of percutaneous radiofrequency ablation. *Eur J Radiol* 2011; **79**: 196-200 [PMID: 20303686 DOI: 10.1016/j.ejrad.2010.02.010]

18 **Machi J**, Uchida S, Sumida K, Limm WM, Hundahl SA, Oishi AJ, Furumoto NL, Oishi RH. Ultrasound-guided radiofrequency thermal ablation of liver tumors: percutaneous, laparoscopic, and open surgical approaches. *J Gastrointest Surg* 2001; **5**: 477-489 [PMID: 11985998 DOI: 10.1016/S1091-255X(01)80085-8]

19 **Eisele RM**, Denecke T, Glanemann M, Chopra SS. [Minimal-invasive microwave coagulation therapy for liver tumours: laparoscopic and percutaneous access]. *Zentralbl Chir* 2014; **139**: 235-243 [PMID: 24241949 DOI: 10.1055/s-0033-1350931]

20 **Tang Y**, Zhou XD. Research progress of ultrasound interventional therapy for primary liver carcinoma. *Disi Junyi Daxue Xuebao* 2008; **29**: 89-92

21 **Kennedy JE**. High-intensity focused ultrasound in the treatment of solid tumours. *Nat Rev Cancer* 2005; **5**: 321-327 [PMID: 15776004 DOI: 10.1038/nrc1591]

22 **Zhang L**, Zhu H, Jin C, Zhou K, Li K, Su H, Chen W, Bai J, Wang Z. High-intensity focused ultrasound (HIFU): effective and safe therapy for hepatocellular carcinoma adjacent to major hepatic veins. *Eur Radiol* 2009; **19**: 437-445 [PMID: 18795303 DOI: 10.1007/s00330-008-1137-0]

23 **Orsi F**, Zhang L, Arnone P, Orgera G, Bonomo G, Vigna PD, Monfardini L, Zhou K, Chen W, Wang Z, Veronesi U. High-intensity focused ultrasound ablation: effective and safe therapy for solid tumors in difficult locations. *AJR Am J Roentgenol* 2010; **195**: W245-W252 [PMID: 20729423 DOI: 10.2214/AJR.09.3321]

24 **Cormier JN**, Thomas KT, Chari RS, Pinson CW. Management of hepatocellular carcinoma. *J Gastrointest Surg* 2006; **10**: 761-780 [PMID: 16713550 DOI: 10.1016/j.gassur.2005.10.006]

25 **Kerkar S**, Carlin AM, Sohn RL, Steffes C, Tyburski J, Littrup P, Weaver D. Long-term follow up and prognostic factors for cryotherapy of malignant liver tumors. *Surgery* 2004; **136**: 770-779 [PMID: 15467661 DOI: 10.1016/j.surg.2004.07.001]

26 **Vogl TJ**, Naguib NN, Nour-Eldin NE, Rao P, Emami AH, Zangos S, Nabil M, Abdelkader A. Review on transarterial chemoembolization in hepatocellular carcinoma: palliative, combined, neoadjuvant, bridging, and symptomatic indications. *Eur J Radiol* 2009; **72**: 505-516 [PMID: 18835117 DOI: 10.1016/j.ejrad.2008.08.007]

27 **Takayasu K**, Arii S, Ikai I, Omata M, Okita K, Ichida T, Matsuyama Y, Nakanuma Y, Kojiro M, Makuuchi M, Yamaoka Y; Liver Cancer Study Group of Japan. Prospective cohort study of transarterial chemoembolization for unresectable hepatocellular carcinoma in 8510 patients. *Gastroenterology* 2006; **131**: 461-469 [PMID: 16890600 DOI: 10.1053/j.gastro.2006.05.021]

28 **Tezuka M**, Hayashi K, Kubota K, Sekine S, Okada Y, Ina H, Irie T. Growth rate of locally recurrent hepatocellular carcinoma after transcatheter arterial chemoembolization: comparing the growth rate of locally recurrent tumor with that of primary hepatocellular carcinoma. *Dig Dis Sci* 2007; **52**: 783-788 [PMID: 17268830 DOI: 10.1007/s10620-006-9537-y]

29 **Georgiades CS**, Hong K, D'Angelo M, Geschwind JF. Safety and efficacy of transarterial chemoembolization in patients with unresectable hepatocellular carcinoma and portal vein thrombosis. *J Vasc Interv Radiol* 2005; **16**: 1653-1659 [PMID: 16371532 DOI: 10.1097/01.RVI.0000182185.47500.7A]

30 **Maluccio MA**, Covey AM, Porat LB, Schubert J, Brody LA, Sofocleous CT, Getrajdman GI, Jarnagin W, Dematteo R, Blumgart LH, Fong Y, Brown KT. Transcatheter arterial embolization with only particles for the treatment of unresectable hepatocellular carcinoma. *J Vasc Interv Radiol* 2008; **19**: 862-869 [PMID: 18503900 DOI: 10.1016/j.jvir.2008.02.013]

31 **Fattovich G**, Stroffolini T, Zagni I, Donato F. Hepatocellular carcinoma in cirrhosis: incidence and risk factors. *Gastroenterology* 2004; **127**: S35-S50 [PMID: 15508101 DOI: 10.1053/j.gastro.2004.09.014]

32 **Bosch FX**, Ribes J, Borràs J. Epidemiology of primary liver cancer. *Semin Liver Dis* 1999; **19**: 271-285 [PMID: 10518307 DOI: 10.1055/s-2007-1007117]

33 **Bruix J**, Sherman M; American Association for the Study of Liver Diseases. Management of hepatocellular carcinoma: an update. *Hepatology* 2011; **53**: 1020-1022 [PMID: 21374666 DOI: 10.1002/hep.24199]

34 **Zeng ZC**, Jiang GL, Wang GM, Tang ZY, Curran WJ, Iliakis G. DNA-PKcs subunits in radiosensitization by hyperthermia on hepatocellular carcinoma hepG2 cell line. *World J Gastroenterol* 2002; **8**: 797-803 [PMID: 12378618]

35 **Kim TH**, Kim DY, Park JW, Kim YI, Kim SH, Park HS, Lee WJ, Park SJ, Hong EK, Kim CM. Three-dimensional conformal radiotherapy of unresectable hepatocellular carcinoma patients for whom transcatheter arterial chemoembolization was ineffective or unsuitable. *Am J Clin Oncol* 2006; **29**: 568-575 [PMID: 17148993 DOI: 10.1097/01.coc.0000239147.60196.11]

36 **Dawson LA**, McGinn CJ, Normolle D, Ten Haken RK, Walker S, Ensminger W, Lawrence TS. Escalated focal liver radiation and concurrent hepatic artery fluorodeoxyuridine for unresectable intrahepatic malignancies. *J Clin Oncol* 2000; **18**: 2210-2218 [PMID: 10829040]

37 **Meng MB**, Cui YL, Lu Y, She B, Chen Y, Guan YS, Zhang RM. Transcatheter arterial chemoembolization in combination with radiotherapy for unresectable hepatocellular carcinoma: a systematic review and meta-analysis. *Radiother Oncol* 2009; **92**: 184-194 [PMID: 19042048 DOI: 10.1016/j.radonc.2008.11.002]

38 **You CR**, Jang JW, Kang SH, Bae SH, Choi JY, Yoon SK, Choi IB, Lee DH, Chun HJ, Choi BG. [Efficacy of transarterial chemolipiodolization with or without 3-dimensional conformal radiotherapy for huge HCC with portal vein tumor thrombosis]. *Korean J Hepatol* 2007; **13**: 378-386 [PMID: 17898554 DOI: 10.3350/kjhep.2007.13.3.378]

39 **Kim DY**, Park W, Lim DH, Lee JH, Yoo BC, Paik SW, Kho KC, Kim TH, Ahn YC, Huh SJ. Three-dimensional conformal radiotherapy for portal vein thrombosis of hepatocellular carcinoma. *Cancer* 2005; **103**: 2419-2426 [PMID: 15822130 DOI: 10.1002/cncr.21043]

40 **Nakagawa K**, Yamashita H, Shiraishi K, Nakamura N, Tago M, Igaki H, Hosoi Y, Shiina S, Omata M, Makuuchi M, Ohtomo K. Radiation therapy for portal venous invasion by hepatocellular carcinoma. *World J Gastroenterol* 2005; **11**: 7237-7241 [PMID: 16437621]

41 **Geschwind JF**, Salem R, Carr BI, Soulen MC, Thurston KG, Goin KA, Van Buskirk M, Roberts CA, Goin JE. Yttrium-90 microspheres for the treatment of hepatocellular carcinoma. *Gastroenterology* 2004; **127**: S194-S205 [PMID: 15508085 DOI: 10.1053/j.gastro.2004.09.034]

42 **Dancey JE**, Shepherd FA, Paul K, Sniderman KW, Houle S, Gabrys J, Hendler AL, Goin JE. Treatment of nonresectable hepatocellular carcinoma with intrahepatic 90Y-microspheres. *J Nucl Med* 2000; **41**: 1673-1681 [PMID: 11037997]

43 **Hussain SP**, Schwank J, Staib F, Wang XW, Harris CC. TP53 mutations and hepatocellular carcinoma: insights into the etiology and pathogenesis of liver cancer. *Oncogene* 2007; **26**: 2166-2176 [PMID: 17401425 DOI: 10.1038/sj.onc.1210279]

44 **Watanuki A**, Ohwada S, Fukusato T, Makita F, Yamada T, Kikuchi A, Morishita Y. Prognostic significance of DNA topoisomerase IIalpha expression in human hepatocellular carcinoma. . *Anticancer Res* 2002; **22**: 1113-1119 [PMID: 12168909]

45 **Ng IO**, Liu CL, Fan ST, Ng M. Expression of P-glycoprotein in hepatocellular carcinoma. A determinant of chemotherapy response. *Am J Clin Pathol* 2000; **113**: 355-363 [PMID: 10705815 DOI: 10.1309/AC1M-4TY4-U0TN-EN7T]

46 **Palmer DH**, Hussain SA, Johnson PJ. Systemic therapies for hepatocellular carcinoma. *Expert Opin Investig Drugs* 2004; **13**: 1555-1568 [PMID: 15566313 DOI: 10.1517/13543784.13.12.1555]

47 **Gish RG**, Porta C, Lazar L, Ruff P, Feld R, Croitoru A, Feun L, Jeziorski K, Leighton J, Gallo J, Kennealey GT. Phase III randomized controlled trial comparing the survival of patients with unresectable hepatocellular carcinoma treated with nolatrexed or doxorubicin. *J Clin Oncol* 2007; **25**: 3069-3075 [PMID: 17634485 DOI: 10.1200/JCO.2006.08.4046]

48 **Zhu AX**. Systemic therapy of advanced hepatocellular carcinoma: how hopeful should we be? *Oncologist* 2006; **11**: 790-800 [PMID: 16880238 DOI: 10.1634/theoncologist.11-7-790]

49 **O'Reilly EM**, Stuart KE, Sanz-Altamira PM, Schwartz GK, Steger CM, Raeburn L, Kemeny NE, Kelsen DP, Saltz LB. A phase II study of irinotecan in patients with advanced hepatocellular carcinoma. *Cancer* 2001; **91**: 101-105 [PMID: 11148565 DOI: 10.1002/1097-0142(20010101)91: 1<101:AID-CNCR13>3.0.CO;2-K]

50 **Halm U**, Etzrodt G, Schiefke I, Schmidt F, Witzigmann H, Mössner J, Berr F. A phase II study of pegylated liposomal doxorubicin for treatment of advanced hepatocellular carcinoma. *Ann Oncol* 2000; **11**: 113-114 [PMID: 10690399 DOI: 10.1023/A: 1008386822906]

51 **Ikeda M**, Okusaka T, Ueno H, Takezako Y, Morizane C. A phase II trial of continuous infusion of 5-fluorouracil, mitoxantrone, and cisplatin for metastatic hepatocellular carcinoma. *Cancer* 2005; **103**: 756-762 [PMID: 15637692 DOI: 10.1002/cncr.20841]

52 **Lee J**, Park JO, Kim WS, Park SH, Park KW, Choi MS, Lee JH, Koh KC, Paik SW, Yoo BC, Joh J, Kim K, Jung CW, Park YS, Im YH, Kang WK, Lee MH, Park K. Phase II study of doxorubicin and cisplatin in patients with metastatic hepatocellular carcinoma. *Cancer Chemother Pharmacol* 2004; **54**: 385-390 [PMID: 15248028 DOI: 10.1007/s00280-004-0837-7]

53 **Lai CL**, Lau JY, Wu PC, Ngan H, Chung HT, Mitchell SJ, Corbett TJ, Chow AW, Lin HJ. Recombinant interferon-alpha in inoperable hepatocellular carcinoma: a randomized controlled trial. *Hepatology* 1993; **17**: 389-394 [PMID: 8383088 DOI: 10.1002/hep.1840170307]

54 **Tungpradabkul S**, Sandee D, Puthong S, Laohathai K. Construction of scFv derived from a tumor-associated monoclonal antibody having tumoricidal activity on human hepatocellular carcinoma. *Mol Immunol* 2005; **42**: 713-719 [PMID: 15781115 DOI: 10.1016/j.molimm.2004.09.023]

55 **Bertelli R**, Neri F, Tsivian M, Ruhrman N, Cavallari G, Beltempo P, Puviani L, DeVinci C, Pizza G, Nardo B. Endolymphatic immunotherapy in inoperable hepatocellular carcinoma. *Transplant Proc* 2008; **40**: 1913-1915 [PMID: 18675087 DOI: 10.1016/j.transproceed.2008.05.049]

56 **Peng BG**, Liang LJ, He Q, Kuang M, Lia JM, Lu MD, Huang JF. Tumor vaccine against recurrence of hepatocellular carcinoma. *World J Gastroenterol* 2005; **11**: 700-704 [PMID: 15655825]

57 **Villanueva A**, Newell P, Chiang DY, Friedman SL, Llovet JM. Genomics and signaling pathways in hepatocellular carcinoma. *Semin Liver Dis* 2007; **27**: 55-76 [PMID: 17295177 DOI: 10.1055/s-2006-960171]

58 **Llovet JM**, Bruix J. Molecular targeted therapies in hepatocellular carcinoma. *Hepatology* 2008; **48**: 1312-1327 [PMID: 18821591 DOI: 10.1002/hep.22506]

59 **Llovet JM**, Ricci S, Mazzaferro V, Hilgard P, Gane E, Blanc JF, de Oliveira AC, Santoro A, Raoul JL, Forner A, Schwartz M, Porta C, Zeuzem S, Bolondi L, Greten TF, Galle PR, Seitz JF, Borbath I, Häussinger D, Giannaris T, Shan M, Moscovici M, Voliotis D, Bruix J; SHARP Investigators Study Group. Sorafenib in advanced hepatocellular carcinoma. *N Engl J Med* 2008; **359**: 378-390 [PMID: 18650514 DOI: 10.1056/NEJMoa0708857]

60 **Bergers G**, Hanahan D. Modes of resistance to anti-angiogenic therapy. *Nat Rev Cancer* 2008; **8**: 592-603 [PMID: 18650835 DOI: 10.1038/nrc2442]

61 **van Malenstein H**, Dekervel J, Verslype C, Van Cutsem E, Windmolders P, Nevens F, van Pelt J. Long-term exposure to sorafenib of liver cancer cells induces resistance with epithelial-to-mesenchymal transition, increased invasion and risk of rebound growth. *Cancer Lett* 2013; **329**: 74-83 [PMID: 23111106 DOI: 10.1016/j.canlet.2012.10.021]

62 **Diehn M**, Clarke MF. Cancer stem cells and radiotherapy: new insights into tumor radioresistance. *J Natl Cancer Inst* 2006; **98**: 1755-1757 [PMID: 17179471 DOI: 10.1093/jnci/djj505]

63 **Philip PA**, Mahoney MR, Allmer C, Thomas J, Pitot HC, Kim G, Donehower RC, Fitch T, Picus J, Erlichman C. Phase II study of Erlotinib (OSI-774) in patients with advanced hepatocellular cancer. *J Clin Oncol* 2005; **23**: 6657-6663 [PMID: 16170173 DOI: 10.1200/JCO.2005.14.696]

64 **Huether A**, Höpfner M, Baradari V, Schuppan D, Scherübl H. EGFR blockade by cetuximab alone or as combination therapy for growth control of hepatocellular cancer. *Biochem Pharmacol* 2005; **70**: 1568-1578 [PMID: 16226226 DOI: 10.1016/j.bcp.2005.09.007]

65 **Ramanathan RK**, Belani CP, Singh DA, Tanaka M, Lenz HJ, Yen Y, Kindler HL, Iqbal S, Longmate J, Mack PC, Lurje G, Gandour-Edwards R, Dancey J, Gandara DR. A phase II study of lapatinib in patients with advanced biliary tree and hepatocellular cancer. *Cancer Chemother Pharmacol* 2009; **64**: 777-783 [PMID: 19169683 DOI: 10.1007/s00280-009-0927-7]

66 **Boonyaratanakornkit V**, Edwards DP. Receptor mechanisms mediating non-genomic actions of sex steroids. *Semin Reprod Med* 2007; **25**: 139-153 [PMID: 17447204 DOI: 10.1055/s-2007-973427]

67 **Shimizu I**, Ito S. Protection of estrogens against the progression of chronic liver disease. *Hepatol Res* 2007; **37**: 239-247 [PMID: 17397511 DOI: 10.1111/j.1872-034X.2007.00032.x]

68 **Chow PK**, Tai BC, Tan CK, Machin D, Win KM, Johnson PJ, Soo KC; Asian-Pacific Hepatocellular Carcinoma Trials Group. High-dose tamoxifen in the treatment of inoperable hepatocellular carcinoma: A multicenter randomized controlled trial. *Hepatology* 2002; **36**: 1221-1226 [PMID: 12395333 DOI: 10.1053/jhep.2002.36824]

69 **Nowak A**, Findlay M, Culjak G, Stockler M. Tamoxifen for hepatocellular carcinoma. *Cochrane Database Syst Rev* 2004; **(3)**: CD001024 [PMID: 15266436]

**P-Reviewer:** Augustin G, Hamid SS, Kanda T, Tamori A **S-Editor:** Ma YJ **L-Editor:** **E-Editor:**

**Table American Joint Committee on Cancer tumor-node-metastasis staging system**

|  |  |  |  |
| --- | --- | --- | --- |
| **Stage** | **Tumor** | **Node** | **Metastasis** |
| Stage I | T1: solitary tumor without vascular invasion | N0: no regional lymph | M0: no distant metastasis |
| Stage II | T2: solitary tumor with vascular invasion or multiple tumors, size < 5 cm | Node metastasis |  |
| Stage IIIA | T3: multiple tumors with size > 5 cm or tumor involving a major branch of the portal or hepatic vein(s) |  |  |
| Stage IIIB | T4: tumor that invades adjacent organs other than the gallbladder or perforates visceral peritoneum |  |  |
| Stage IIIC | Any T | N1: regional lymph node metastasis |  |
| Stage IV | Any T | Any N | M1: distant metastasis |

**Table 2 Okuda staging system1**

|  |  |  |
| --- | --- | --- |
| **Criteria** | **Positive** | **Negative** |
| Tumor size2 | > 50% | < 50% |
| Ascites | Clinically detectable | Clinically absent |
| Albumin | < 3 mg/dl | > 3 mg/dl |
| Bilirubin | > 3 mg/dl | < 3 mg/dl |

1Stage 1: no positive criteria; Stage 2: 1-2 positive criteria; Stage 3: 3-4 positive criteria; 2Measured from the largest cross-sectional area of tumor to the largest cross-sectional area of the liver.

**Table 3 Cancer of the Liver Italian Program staging system**

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **Criteria** | | | **Points** | | |
| Child-Pugh stage | | |  | | |
| A | 0 | |
| B | 1 | |
| C | 2 | |
| Tumor morphology | | |  | | |
| Uninodular and extension ≤ 50% | | | 0 | | |
| Multinodular and extension ≤ 50% | | | 1 | | |
| Massive or extension > 50% | | | 2 | | |
| Alpha-fetoprotein level | | |  | | |
| < 400 ng/mL | | | 0 | | |
| ≥ 400 ng/mL | | | 1 | | |
| Portal vein thrombosis | | |  | | |
| No | | | 0 | | |
| Yes | | | 1 | | |

**Table 4 Barcelona Clinic Liver Cancer staging system**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| Stage | PST1 | Tumor stage2/cancer symptoms | Hepatic function | Recommended treatment |
| 0 (very early) | 0 | Single nodule < 2 cm | Child-Pugh A; normal portal pressure; normal bilirubin | Resection |
| A (early) | 0 | Single nodule < 5 cm  Up to 3 nodules, < 3 cm each | Child-Pugh A; elevated portal pressure and/or elevatedbilirubin | Liver transplantations or PEI/RFA3,4 |
| B (intermediate) | 0 | Large, multinodular; no cancer symptoms | Child-Pugh A-B | TACE |
| C (advanced) | 1-2 | Portal invasion, extrahepatic disease, or cancer symptoms | Child-Pugh A-B | New antitumoral agents |
| D (terminal) | > 2 | Any of the above | Child-Pugh C | Symptonmatic treatment |

1PST evaluated using the World Health Organization's performance status scoring system (also known as the Eastern CooperativeOncology Group System or the Zubrod system); 2N1 or M1 under American Joint Committee on Cancer's tumor-node-metastasis staging system; 3Recommended in the absence of associated diseases; 4PEI/RF is recommended in the presence of associated diseases. PEI: Percutaneous ethanol injection; PST: Performance status; REA: Radiofrequency ablation; TACE: Transarteral chemoembolization.

**Table 5 Chinese University Prognostic Index risk groups in hepatocellular carcinoma**

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
| **Parameter** | **Weight (CUPI Score)** | | | | | | |
| Bilirubin (mg/mL) | | < 1.9 | 0 | 1.9-2.8 | 3 | > 2.9 | 4 |
| Ascites | | Present | 3 |  |  |  |  |
| Alkaline phosphatase | | ≥ l ka IU/L | 3 |  |  |  |  |
| TNM stage | | I and II | -3 | IIIa and IIIb | -1 | IVa and IVb | 0 |
| AFP (ng/mL) | | ≥ FP | 2 |  |  |  |  |
| Disease symptoms on presentation | | None | -4 |  |  |  |  |

Adapted from Leung *et al*[9]. CUPI: Chinese University Prognostic Index; TNM: Tumor-node-metastasis; AFP: alpha fetoprotein.