World Journal of Gastroenterology

Submit a Manuscript: http://www.wjgnet.com/esps/
Help Desk: http://www.wjgnet.com/esps/helpdesk.aspx
DOI: 10.3748/wjg.v20.i44.16630

World J Gastroenterol 2014 November 28; 20(44): 16630-16638
ISSN 1007-9327 (print) ISSN 2219-2840 (online)

TOPIC HIGHLIGHT

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

Advances in non-surgical management of primary 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, University of Sydney, NSW 2145, Australia
Author contributions: Chen X contributed to the conception, design, and creation of the first draft; Liu HP and Li M assisted with manuscript writing, the reference search, and table generation; Qiao L made considerable language edits and revisions to the manuscript, and approved the final version for publication.
Correspondence to: Liang Qiao, MD, PhD, Storr Liver Unit, Westmead Millennium Institute, Department of Medicine and Western Clinical School, University of Sydney, Westmead, NSW 2145, Australia. liang.qiao@sydney.edu.au
Telephone: +61-2-86273534
Received: May 9, 2014 Revised: June 17, 2014
Accepted: July 22, 2014
Published online: November 28, 2014

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 are ineligible for 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 progress of non-surgical management for HCC.

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 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 quality of life to some extent. Some of these strategies have been extensively used in clinical practice as the preferred approaches for 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; 20(44): 16630-16638 Available from: URL: http://www.wjgnet.com/1007-9327/full/v20/i44/16630.htm DOI: http://dx.doi.org/10.3748/wjg.v20.i44.16630

INTRODUCTION

Primary liver cancer, with 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

Table 1 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 system[1]

Criteria	Positive	Negative
Tumor size[2]	> 50%	< 50%
Ascites	Clinically detectable	Clinically absent
Albumin	< 3 mg/dL	> 3 mg/dL
Bilirubin	> 3 mg/dL	< 3 mg/dL

[1]Stage 1: No positive criteria; Stage 2: 1-2 positive criteria; Stage 3: 3-4 positive criteria; [2]Measured 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	
Uni-nodular 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

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, with the incidence rate increasing 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 lost their opportunities for surgical treatment when diagnosis was confirmed. Moreover, only 15% of 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 has a significant impact on therapeutic outcomes. Many different staging systems have been developed, including the American Joint Committee on Cancer Tumor Node Metastasis staging system (Table 1), Okuda staging system (Table 2)[4], Cancer of the Liver Italian Program Scoring System (Table 3)[5,6], Barcelona Clinic Liver Cancer (BCLC) System (Table 4)[7,8], 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 less than 5 cm in diameter and/or having a tumor number less than 3. In this review article, we aim to summarize the recent advances in 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 photocoagulation, and freezing treatment.

PEI

In this procedure, 95% alcohol is slowly injected into the tumor mass *via* a puncture needle previously inserted 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 those 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].

Table 4 Barcelona Clinic Liver Cancer staging system

Stage	PST[1]	Tumor stage[2]/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 elevated bilirubin	Liver transplantations or PEI/RFA[3,4]
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 anti-tumoral agents
D (terminal)	> 2	Any of the above	Child-Pugh C	Symptomatic treatment

[1]PST evaluated using the World Health Organization's performance status scoring system (also known as the Eastern Cooperative Oncology Group System or the Zubrod system); [2]N1 or M1 under American Joint Committee on Cancer's Tumor Node Metastasis staging system; [3]Recommended in the absence of associated diseases; [4]PEI/RF is recommended in the presence of associated diseases. PEI: Percutaneous ethanol injection; PST: Performance status; REA: Radiofrequency ablation; TACE: Transarterial 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	⩾ 1 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.

The therapeutic efficacy of PEI for HCC has been adversely linked to 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 injections and large amounts of alcohol are sometimes required to achieve a better therapeutic effect, but this may cause cumulative damage and 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 then cause necrosis and 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 patients unsuitable for resection; (2) a single tumor with a maximum diameter ⩽ 5 cm or multiple but fewer than 3 tumors with a 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 RF heat through nearby major blood vessels, thereby potentially reducing the curative effect and damaging adjacent organs; 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 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 diameter are also suitable for MCT without 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 and percutaneously in 31 cases. High-risk conditions (defined as unfavorable tumor location such as those invisible by na-

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

The commonly encountered complications of MCT include skin burns, liver capsule bleeding, and severe pain. In cases where the tumor size is > 5 cm in diameter, cancer cells may become thermoresistant and active proliferation may occur, thereby 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 or damaged tissue through ablation. Thus, HIFU is a hyperthermia therapy, a class of clinical therapies that use temperature to treat diseases. This minimally invasive therapeutic procedure directs acoustic energy into the disease 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 one 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 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*[23] showed that in six HCC patients whose tumors were located in difficult locations (*i.e.*, adjacent to a main hepatic blood vessel, heart, bowel, stomach, gall bladder, or bile ducts), treatment with HIFU achieved complete response in all patients without any complications.

Targeted cryoablation therapy

Helium cryoablation is a minimally-invasive freezing technique used to treat solid tumors through extremely low temperature. Within a few seconds, the tip temperature of the therapeutic device can drop to -140 ℃, and then quickly rise to 20-45 ℃. The unique freeze-thaw cycles 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 cryoablation on target tissue could be influenced by many factors, including freezing temperature, freezing rate, thawing rate, and the frequency that the 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, in addition to reducing overall mortality and improving quality of life[25].

TRANSCATHETER ARTERIAL CHEMOEMBOLIZATION

Normal liver has a dual blood supply system: 25%-30% of said blood supply comes from the hepatic artery and 70%-75% from portal vein system. In the case of HCC, 90%-99% of the 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 exerting 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 incapable of having their tumors radically resected; (2) no thrombosis in the portal vein trunk; (3) tumor occupies less than 70% of the whole liver; (4) de-bulking 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 a 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, while 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 have potential therapeutic benefits in patients with advanced HCC. It has been verified that HCC is almost equally sensitive to radiation therapy as poorly-differentiated nasopharyngeal squamous cell carcinoma[34]. Some recently developed stereotactic radiotherapy techniques (including gamma knife, X knife, three-dimensional conformal radiotherapy (3DCRT), and intensity modulated radiation therapy) may improve irradiation capacity and minimize X-ray damage to normal liver tissue. Image guided radiotherapy techniques shows even more enhanced therapeutic effects, as this technique takes into account 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 cases had a reduction in their primary tumor lesions, 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 large HCC and very late HCC, either alone or in combination with other treatment modalities[36,37]. For the palliative therapy for larger or metastatic tumors, radiotherapy can help relieve 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 a reduced tolerance to radiation therapy. Thus, the correct safe dosage and partition of radiation have not yet been standardized. At present, in order to improve efficacy and reduce adverse reactions, radiation is usually given in a small and extended course, with the 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* the hepatic artery has been shown to shrink the tumor, relieve symptoms, and prolong 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 the 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 compromised detoxifying capacity of the liver (*e.g.*, due to reduced activity of CYP450 system) all contribute to the poor absorption, distribution, and bioavailability of conventional chemotherapeutic drugs. As a result, it can be difficult for chemotherapeutic drugs to achieve the therapeutically relevant level, the diseased liver may have an increased susceptibility to developing liver dysfunction, and patients are vulnerable to developing 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 the 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 overall survival, and serious adverse reactions such as neutropenia are 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 in addition to having adverse effects can be severe[48-50]. Combinatorial chemotherapies have also failed to improve overall survival in HCC patients[51,52].

BIOTHERAPY

Immunotherapy

In recent years, tremendous progress has been made in immunotherapy for HCC. Interferon is the cornerstone of treatment for viral hepatitis, but its application in the management of advanced HCC is still controversial. A high dose of interferon (2.5×10^7-50×10^7 IU/m^2, 3 times per week) has been found to improve overall survival of HCC patients in 30% of cases[53]. The main drawback of interferon treatment is its adverse reactions, but these can be minimized when interferon is used at a lower dose (3×10^6 IU/m^2, 3 times per week). A 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 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 is the multi-kinase angiogenesis inhibitor sorafenib, a FDA approved agent for the treatment of advanced HCC that has shown promising results[58,59]. However, large clinical trials have revealed that less than 50% of patients respond to sorafenib treatment, and in said responders this agent only increases 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, while 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 their therapeutic effects remain to be further determined[63-65].

HORMONAL THERAPIES

Sex steroid hormones can interact with 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, endometrial, and prostate cancers. In HCC, sex hormone receptors such as estrogen receptor, progesterone receptor, and androgen receptor are all expressed[66]. The liver is sensitive to sex hormone stimulation, which may 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 a lack of sufficient evidence to prove the therapeutic advantage of hormonal therapy for liver cancer.

COMBINED MODALITY THERAPIES

Since single agent treatments only have limited therapeutic benefits, it is reasonable to assume that a combination of more than one treatment option may produce better therapeutic outcomes. However, no standard combinatorial protocols are available. It is generally believed that 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, in particular tumor staging, patient age, co-morbidities, and availability of treatment modalities. The reasonable selection of available treatment options is key to improving 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 Zazhi* 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]

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-Cl nic 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]

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**: Rutherford A **E- Editor**: Wang CH

Published by **Baishideng Publishing Group Inc**
8226 Regency Drive, Pleasanton, CA 94588, USA
Telephone: +1-925-223-8242
Fax: +1-925-223-8243
E-mail: bpgoffice@wjgnet.com
Help Desk: http://www.wjgnet.com/esps/helpdesk.aspx
http://www.wjgnet.com

ISSN 1007-9327