

## Hepatocellular Carcinoma: the Curative Attempts

*Yongsong Guan\**

**Abstract: Objective** The curative result or long-term survival of hepatocellular carcinoma (HCC) has been pursued ever since its discovery even most of the cases are evaluated as absolute-non-cure before their management. A number of treatment approaches have been applied and option for a certain case is absolutely necessary. The objective of this article is to evaluate today's treatment methods and find some information for the option. **Methods** The characteristics of most of these approaches are studied and compared for their role in the curative management. The key points, advantages and disadvantages of these approaches are discussed. **Results** Current treatments fall into categories of surgical, percutaneous, chemical and physical as well as biomedical ones. Different modes of regional cancer therapy for HCC have been tried, but the relative efficacy remains unclear. Anti-angiogenic agents, gene therapy and tumor vaccine will probably play a role, particularly in the prevention of tumor recurrence. Some issues remain to be solved. **Conclusion** For the recent future, the ideal strategy for curative results might be the establishment of a comprehensive way of combined approaches.

**Key words:** hepatocellular carcinoma; treatment; curative; approaches

### INTRODUCTION

Hepatocellular carcinoma (HCC) is one of the most common malignancies in China and Southeast Asia<sup>[1]</sup>. It occurs with great frequency in Asia and Africa and is becoming more common in the United States as a complication of chronic Hepatitis C. Its mortality is secondary to lung cancer in urban and gastric carcinoma in countryside in China<sup>[2]</sup>. However, the curative result or long-term survival has been pursued ever since its discovery even most of the cases are evaluated as absolute-non-cure before their management<sup>[3-6]</sup>. Until now, many therapeutic approaches have been applied clinically such as surgery, interventional or micro-traumatic techniques, physical or chemical methods as well as biomedical pathways. Numerous variables could influence the prognosis or recurrence of HCC, including tumor size and number, parameters of hepatic function and combined therapies<sup>[5]</sup>. For single tumors smaller than 5 cm or up to three nodules smaller than 3 cm, surgical resection, liver transplantation and percutaneous treatment may offer good anti-tumoral results, as well as improved patient survival<sup>[6]</sup>. An overall consideration must be made before we take the choice of a therapeutic tool to cure the patient.

### CONTEMPORARY TOOLS

A number of approaches have been applied to treat HCC, with the list ever being increasing: surgical removal, cryosurgery, liver transplantation, transcatheter arterial embolization (TAE) or transcatheter arterial chemoembolization (TACE), percutaneous ethanol injection(PEI), radiofrequency ablation (RFA), radiation

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\* Corresponding to Yongsong Guan (1958.8-), male, associate professor of Department of Interventional Radiology, West China Hospital, Sichuan University; Main research field: interventional radiology especially the management of vascular diseases and malignant tumors; Address: Department of Interventional Radiology, West China Hospital, Chengdu, Sichuan Province, Postcode: 610041.

therapy, systemic chemotherapy<sup>[7]</sup>, laser-induced interstitial thermotherapy<sup>[8]</sup>, percutaneous microwave coagulation (PMC)<sup>[9]</sup>, high-intensity focused ultrasound (HIFU)<sup>[10]</sup>, implantation of irradiative particles<sup>[11]</sup>, natural herbs and extracts<sup>[12]</sup>, immunotherapy<sup>[4, 13]</sup>, gene therapy<sup>[14]</sup> and supportive care.

### SURGERY

Partial resection or entire liver transplantation gives the expectation of permanent cure and long-term survival. Although resection has been enjoying the popularity of curative for a long time, the resection rate still remains less than 20% and the recurrence rate after a “radical” or curative resection persists to more than 77% within 2 years. But transplantation for a long-term survival has been challenged by the embarrassment of delayed remote metastases. Cryotherapy has gained importance as a locally ablative treatment option for patients with non-resectable liver tumors manifested during the laparotomy<sup>[15, 16]</sup>.

#### 1. Partial hepatectomy

Surgeries have been used for the treatment of primary tumors, intrahepatic recurrences, peritoneal recurrences and needle tract implantation caused by the percutaneous needle biopsy. Repeated aggressive surgeries could provide good local control<sup>[17]</sup>. Sometimes the resection is limited<sup>[18]</sup>. On multivariate analysis, hypoalbuminemia, thrombocytopenia, elevated serum creatinine, major hepatic resection, and transfusion are the significant predictors of hospital mortality, whereas concomitant extrahepatic procedure, thrombocytopenia, and transfusion are the predictors of morbidity. And reduced perioperative transfusion is the main contributory factor for improved outcome<sup>[19]</sup>. In selected patients without cirrhosis, HCC can be treated successfully by surgical resection, independent of the tumor diameter; the 5-year survival rate can reach to 68%<sup>[20]</sup>. An animal experiment demonstrated that liver lobectomy should be recommended for massive HCC because tumor-related mortality rate was more than a dozen times higher in the non-surgery group, compared with the surgery group<sup>[21]</sup>.

#### 2. Liver transplantation

The association of HCC and chronic hepatitis C virus (HCV) infection has been identified as a potential contraindication for orthotopic liver transplantation (LT) because of lower survival rate compared with other indications. An author investigated a large cohort of U.S. patients, and concluded that HCC does not have an impact on the survival of LT patients infected with HCV<sup>[22]</sup>. For Child class B and C patients with a small HCC, LT offers the best results. Living donor LT should be considered using the same criteria as that used for cadaveric transplantation<sup>[23]</sup>.

#### 3. Cryosurgery

The trauma of the procedure and local treatment failure need to be minimized and survival results need to be optimized. Cryotherapy has been used via the laparotomized and laparoscopic approaches while more and more cases are treated in the percutaneous way<sup>[24-27]</sup>. The only radical modality of treatment is still anatomical resection of the liver. Investigations are under way designed to study efficiency of thermo-(cryo) destruction of solitary and single liver metastases if surgical resection is beyond the bounds of possibility<sup>[25]</sup>. Cryosurgery can be employed in patients with unresectable hepatic metastases when the tumor size and the number of metastases are limited. However, local recurrence can result from incomplete ablation. Cytoablation of hepatic metastases can be safely achieved with combined hepatic resection and cryosurgery in selected patients<sup>[26-29]</sup>. Nitrous oxide<sup>[30]</sup>, liquid nitrogen<sup>[31]</sup> and argon gas have been used as cryogens. Intraoperative sonography provides a guidance modality to accurately place cryosurgery probes in liver masses. Tumor recurrence can be detected well with computed

tomography or magnetic resonance imaging following hepatic cryosurgery [32].

### INTERVENTIONAL OR MICRO-TRAUMATIC PERCUTANEOUS TECHNIQUES

Apart from TACE, several local ablative techniques have been developed, aiming to produce selective tumor destruction and thus increase the rate of patients amenable to curative-intent treatments [28]. Among these techniques, cryoablation and radiofrequency ablation only have proven to have a curative potential, while transarterial chemoembolization and alcohol injection should be considered as palliative options only [29]. Percutaneous hepatic cryoablation in combination with PEI has been used in patients with unresectable HCC [27]. Pre-transplant therapy such as TACE, PEI and RFA may be needed to sustain patients who are waiting for donor livers [30-35].

#### 1. TAE or TACE

Embolization or chemoembolization are therapeutic alternatives for patients who do not benefit from curative therapies [6,35]. For patients without distant metastasis, regardless of the resectability of the primary tumor, TACE may be considered the initial and only preoperative treatment, and it may be repeated [34]. TACE combined with percutaneous injection of chemical agents and acetic acids is efficacious to increase the survival rate of patients with HCC [36]. There is limited evidence and consensus regarding optimal choice and dosage of chemical agents utilized for hepatic artery chemoembolization [37]. Some author concluded that TAE has a higher antitumor effect than TAI, but does not significantly improve the survival of patients with HCC [38]. Parameters include (a) methods selected for catheter placement; (b) embolic materials used, details of embolized arteries, and frequency of recanalization; (c) ability to prevent gastrointestinal symptoms by avoiding inflow of anticancer drugs into extrahepatic adjacent organs and to maintain distribution of contrast agents in liver, as well as management of difficulties encountered; (d) complications related to catheter system implantation or to long-term TACE and management of such complications; and (e) final success in performing scheduled TACE while maintaining distribution over liver via a single route without gastrointestinal symptoms caused by inflow of anticancer drugs [6,39]. Vascular administration of adenoviral vector soaked in absorbable gelatin sponge particles has been employed in animals [40].

#### 2. PEI

Ablation of liver tumors is currently the main alternative to formal liver resection [41]. PEI is a procedure of easy execution, good tolerability and low cost, which can be applied during repeated sessions [6]. PEI may provide long-term disease control if the extent of liver tumors is limited (3 or less in number and less than 3 cm in diameter) [7]. Quantified ethanol at intervals of 3-5 d could improve the curative effect of hepatocarcinoma. The treatment efficacy is more remarkable for tumors < or =3 cm in diameter [42]. Conventional PEI can be combined with percutaneous intraarterial ethanol injection but severe complications could occur such as liver abscess and fatal acute pancreatitis [43]. As one of the multimodal interventional therapies, PEI still represents a safe and economically sound treatment for HCC [44-46]. Percutaneous acetic acid injection (PAI) is also effective as a loco-regional therapy for HCC, and percutaneous hot water injection therapy (PHoT) has been devised for the heat coagulation necrosis effect of boiled hot saline [33, 47, 48]. Combined PAI and RFA were able to increase the diameter of coagulation necrosis without significantly increasing complications [49]. PAI and PEI are equally effective in the treatment of HCC [50]. For small HCC, either PAI or TACE therapy could be recommended as the primary treatment modality [33,51] and induction of complete tumor necrosis may reduce intrahepatic metastasis

and prolong survival <sup>[52]</sup>. Recent studies have shown that RFA can achieve more effective local tumor control than PEI <sup>[53]</sup>. In an animal model, acetic acid produced significantly larger zones of tumor coagulation compared with ethanol when injected into VX2 carcinoma in equal volumes <sup>[54]</sup>. Monitoring acetic acid mixed with iodinated contrast agent on fluoroscopy can detect extratumoral diffusion and may optimize its distribution <sup>[55]</sup>. PEI is a useful alternative where RFA is unavailable <sup>[56]</sup>. Persistent retention of acetic acid is associated with a favorable response and may predict complete tumor necrosis <sup>[57]</sup>. Sequential therapy with TACE and PAI is superior to repeated PAI alone for patients with large HCC <sup>[58]</sup> and combined with percutaneous injection of chemical agents is also beneficial <sup>[36]</sup>.

### 3. Percutaneous cryoablation

It is one of the ablative techniques that offer a promising therapeutic modality <sup>[59]</sup>. This therapy combined with TACE is a choice of treatment for liver carcinoma <sup>[29]</sup>. Percutaneous cryoablation offers a safe and possibly curative treatment option for patients with HCC that cannot be surgically removed, and its integration with PEI, may serve as an alternative to partial liver resection in selective patients <sup>[27]</sup>.

### 4. Interstitial laser photocoagulation (ILP)

Similar to radiofrequency, this is another image-guided thermal ablation method <sup>[9,60,61]</sup>, and combined with temporary hepatic artery occlusion during a single session has been used as an effective local treatment <sup>[62]</sup>. It appears that there is little difference in outcome between RFA and ILP, but prospective, randomized studies are needed <sup>[63,64]</sup>.

### 5. RFA

It is one of the image-guided thermal ablation methods <sup>[9]</sup>. Two major limitations for radiofrequency are, first, the risk to provoke heat biliary lesion in case of tumors located proximally to hilar plate, and second, the risk of insufficient ablation due to a cooling effect <sup>[28]</sup>. RFA is the preferred local ablation therapy for most small HCC <sup>[56]</sup>. Addition of PAI to RFA substantially increases tumor destruction compared with RFA or injection therapy alone <sup>[51]</sup>. RFA seems a potentially promising technique for the treatment of small hepatocellular carcinoma and more randomised clinical trials are needed <sup>[65,66]</sup>. However, its use is restricted by the difficulty encountered when using imaging studies to monitor the areas of ablation during and after the procedure <sup>[64]</sup>.

### 6. PMC

Because PMC is indicated as an alternative to resection for hepatocellular carcinoma patients with advanced liver cirrhosis, intrahepatic recurrences are frequent <sup>[9]</sup>. The heat causes coagulation, followed by cellular death as soon as the temperature in the target area exceeds 60 degrees C <sup>[56]</sup>. The rate of side effects do not differ significantly from other interventions, but significantly more treatment sessions are needed with percutaneous microwave coagulation to achieve complete tumor ablation <sup>[65]</sup>.

### 7. HIFU

HIFU is a noninvasive treatment modality that induces complete coagulative necrosis of a deep tumor through the intact skin <sup>[10]</sup>. Some author concluded that HIFU could enhance a systemic antitumor cellular immunity in addition to local tumor destruction in patients with solid malignancies <sup>[67]</sup> and that patients undergoing complete HIFU ablation may demonstrate conversion from presence to absence of circulating tumor-specific marker mRNA so HIFU would not enhance the potential risk of metastasis in patients with malignant diseases <sup>[68]</sup>. HIFU appears to be effective, safe, and feasible in the treatment of patients with HCC <sup>[10]</sup>, but the curative effect remains to be observed and the combined use of HIFU with other modalities such as TACE worth trying.

### 8. Implantation of irradiative particles

CT-guided brachytherapy displays broader indications compared to RFA or ILA<sup>[11]</sup>. Several sources have been applied such as Iridium-192((192) Ir)<sup>[11]</sup> and Yttrium-90 ((90)Y)<sup>[69-71]</sup>. Radioactive microsphere (90)Y therapy is increasingly used for primary and metastatic solid tumors in the liver. Microsphere agents (glass or resin) consist of yttrium-90 (a pure beta emitter) microspheres, which are injected into the hepatic arteries with resulting high total doses of radiation, preferentially in the periphery of tumors. Normal liver parenchyma showed little radiation effect away from the tumors. Heterogeneous high-dose regions in the tumor were produced by both glass and resin microspheres. CT-guided brachytherapy alone or in combination with laser-induced thermotherapy (LITT) has been used in patients with liver malignancies. Three-dimensional CT data for dosimetry is safe and effective<sup>[72]</sup>.

### 9. Electrolysis

Electrolysis has been used for the treatment of non-resectable HCC<sup>[73]</sup>, and compared with other established and experimental ablation procedures<sup>[59]</sup>. Electrolysis is slower than other forms of ablative therapy. However, it is reliable and predictable in producing hepatic necrosis in a dose-dependent manner<sup>[74]</sup>. Electrolysis is a non-thermal technique and shows to be safe and effective in close proximity to major intrahepatic veins due to a subtle electrochemical action rather than a rapid "burn" when a single awkwardly placed metastasis deems a patient unresectable<sup>[75]</sup>. And it could reduce the risk of systemic inflammatory response, acute respiratory distress syndrome and other immune response mediated end-organ damage not as other ablative methods are limited by the development of a systemic inflammatory response mediated by cytokines such as interleukin-8 (IL-8) and tumor necrosis factor alpha (TNF-alpha)<sup>[76]</sup>. Under general anesthesia, electrolysis is presently limited to tumors smaller than 5 cm, due to the protracted nature of its administration<sup>[77]</sup>.

## PHYSICAL AND CHEMICAL METHODS

Some of them have shifted to the interventional ones such as thermotherapy and cryotherapy. And this cancer seems to be stubborn as it is resistant to any chemical agents developed until now.

### 1. Radiotherapy

Radiotherapy has been used mostly as a salvage therapy in combination with other locoregional modalities. Despite the incorporation of 3-dimensional conformal technology, radiation-induced liver injury remains an important problem, especially for patients with hepatitis B-related cirrhosis<sup>[7]</sup>. 3-Dimensional conformal hypofractionated single high-dose radiotherapy combined with TACE has been evaluated in the treatment of portal vein tumor thrombus in unresectable HCC patients<sup>[78]</sup>. Currently, various radiation technologies have been adopted for the radiotherapy of HCC, and advanced systems are primarily based on the concept of radiosurgery by the rapid developments in technical strategy for radiation oncology<sup>[79]</sup>. Intra-arterial radiation therapy with <sup>131</sup>I-lipiodol is a useful therapeutic approach, and new materials such as labelling of lipiodol with <sup>188</sup>Re-SSS (<sup>188</sup>Re (S2CPh) (S3CPh)<sub>2</sub> complex) are being tested in animals<sup>[80]</sup>. Although the limited radiation tolerance of the adjacent normal liver has prohibited wider use of radiation therapy in this disease, modern radiation therapy modalities and concepts such as intensity-modulated, image-guided, and stereotactic body radiation therapy are considered as future treatment alternatives<sup>[81]</sup>. Phase II trial has been undertaken to determine the efficacy and toxicity of proton beam radiotherapy for patients with locally unresectable hepatocellular carcinoma<sup>[82]</sup>.

### 2. Chemotherapy

Systemic therapy is difficult for HCC because of the underlying cirrhosis and accompanying hypersplenism and peripheral cytopenia. HCC is typically resistant to most cytotoxic agents<sup>[7]</sup>. For patients with distant metastases, however, their complete eradication with systemic chemotherapy prior to TACE is essential<sup>[34]</sup>. No survival advantages have been demonstrated with intra-arterial or systemic chemotherapy, hormonal compounds, or radiation<sup>[83]</sup>. Future research on drug therapy for HCC will focus on identification of tumor-specific targets<sup>[7]</sup>. New agents, such as inhibitors of the tyrosine kinase receptors of growth factors and antiangiogenic agents, are currently being tested in phase II/III trials<sup>[83]</sup>. Better chemopreventive and chemotherapeutic treatments are being investigated<sup>[84-88]</sup>.

## BIOMEDICAL APPROACHES

### 1. Biochemical modulation

Biochemical modulation with high-dose tamoxifen may sensitize HCC cells to doxorubicin-induced apoptosis and improve the clinical response to doxorubicin in patients with advanced HCC<sup>[7]</sup> but did not prove to be useful in improving the quality of life<sup>[6]</sup>. Tamoxifen also has anti-estrogenic activity. Thalidomide, which inhibits angiogenesis induced by vascular endothelial growth factor and basic fibroblast growth factor, can produce a response in some HCC patients<sup>[7]</sup>. However, thalidomide mostly may offer HCC patients disease stabilization, monotherapy at the high doses studied cannot be recommended for the treatment of HCC in view of its significant neurologic toxicity<sup>[88]</sup>. Apoptosis in human hepatoma cells can be induced by Octreotide, a somatostatin analogue, which may be related to the mechanism of antineoplastic action of Octreotide in hepatoma<sup>[89]</sup>. Impaired glucose metabolism affects the growth rate of the tumor and postprandial hyperinsulinaemia is associated with accelerated its growth<sup>[90]</sup>. With long acting octreotide, complete regression of advanced HCC has been reported<sup>[91]</sup>. Modulation of the open time of the mitochondrial permeability transition pore which causes release of cytochrome c may result in cell death<sup>[92]</sup>.

### 2. Hormonal therapy

Hormonal therapy implies the treatment that adds, blocks or removes hormones; it is also called hormone therapy, hormone treatment, or endocrine therapy. Both estrogen and androgen receptors can be found on the membrane of HCC cells, theoretically justifying hormonal therapy for this type of neoplasia<sup>[6]</sup>. Hormone therapy with antioestrogens and androgens<sup>[66]</sup> has also been applied clinically. An anti-estrogenic activity has also been observed in the flavanone naringenin<sup>[85]</sup>. Antiandrogenic treatment with leuprorelin or flutamide has been investigated in male patients with advanced HCC, but no benefit in survival was found<sup>[93]</sup>. One study shows that megestrol acetate inhibited the growth of HepG2 cells grown in vitro and in vivo<sup>[94]</sup>. Trials of tamoxifen for HCC have conflicting results<sup>[95, 96]</sup>.

### 3. Natural anti-tumor ingredients

Up to now, searching for non-toxic and natural origin substances that induced the differentiation of cancer cells is a key for anticancer therapy<sup>[97]</sup>. Some herbs have effects on tumor growth-inhibitory activity and cancer chemopreventive activity as potential cancer chemopreventive agents in humans<sup>[84]</sup>. Dietary powdered green tea had both antiproliferative activity toward hepatoma cells and hypolipidemic activity in the hepatoma bearing rats. The hepatoma-induced endogenous hyperlipidemia is characterized by rises in the serum cholesterol (hypercholesterolemia) and triglyceride (hypertriglyceridemia) levels<sup>[98]</sup>. Numerous natural ingredients contribute to the immunoenhancing and antitumor properties such as the leaves of *Macaranga triloba*<sup>[86]</sup>, antioxidants in

foods such as phenolic compounds and carotenoids<sup>[99,100]</sup>, curcuminoids<sup>[101,102]</sup>, resveratrol (a phytoalexin in grapes and red wine)<sup>[103, 104]</sup>, reishi<sup>[105]</sup>, triterpenoids (ganoderic acid -R, -T, -U, -V, -W, -X, -Y, and -Z)<sup>[106,107]</sup>, Korean red ginseng extract<sup>[108]</sup>, polysaccharide-rich substance<sup>[109]</sup>, saikosaponins<sup>[110]</sup>, baicalin and baicalein<sup>[111]</sup>, organic germanium<sup>[112]</sup>, quercetin<sup>[113]</sup>, beta-carotene<sup>[114]</sup>, citrus bioflavonoid complex<sup>[115]</sup>, bilberry extract<sup>[116]</sup>, rutin<sup>[117]</sup>, zinc<sup>[118]</sup>, selenium<sup>[119]</sup>, as well as compounds released in fermented milks<sup>[120]</sup>. Also effective are Chinese folk medicines such as Xiao Chai Hu Tang<sup>[121]</sup> and natural musk<sup>[122]</sup>, one of the important ingredients of Pien Tze Huang - well known for its therapeutic activity in treating liver diseases.

#### 4. Immunotherapy

Data suggest that maintenance of immune stimulation can significantly reduce the risk of cancer. Adoptive immunotherapy with lymphokine activated killer cells (LAK cells) is useful and effective for patients with multiple HCC<sup>[4]</sup>. One study suggests that the combined treatment with interferon-beta and perindopril resulted in a marked increase of apoptosis in the tumor, and might be an effective new strategy for chemoprevention against HCC<sup>[123]</sup>. Living BCG has been tried more than a decade ago<sup>[124]</sup>, but with unsatisfactory progress. Harnessing the immune system to treat chronic diseases or cancer is a major goal of immunotherapy. Among others, impediments to this aim include host failure to identify tumor antigens, tolerance to self and negative immunoregulatory mechanisms<sup>[125]</sup>. Autologous cancer vaccines<sup>[126]</sup> and autologous lymphocytes<sup>[127]</sup> have been developed for immunotherapy. After decades of disappointment, active immunotherapy with vaccines, as well as passive immunotherapy using unmodified and armed monoclonal antibodies, is emerging as useful immunotherapeutic strategies<sup>[125]</sup>. The degree of hepatocellular dysfunction is known to be the main factor related to patient survival<sup>[6]</sup>.

#### 5. Genetics

Gene therapy is one of the newest approaches to cancer treatment and is in the very early stages of clinical trials. There is the limitation of efficacy if the present product is administered by the intravenous route. Catheter-mediated hepatic arterial embolization increases transduction efficiency of adenoviral vector in hepatocytes<sup>[40]</sup>. There are different types of gene therapy<sup>[128-132]</sup>. One type involves putting back genes into cancer cells to induce apoptosis. Adenovirus-mediated p53 gene therapy and introduction of wild-type p53 into tumor cells represents a potentially valuable tool for the therapy of many types of human cancers<sup>[129]</sup>. Another type of gene therapy attempts to introduce a gene that can switch on a drug inside cancer cells. And new vectors of genes are being constructed and therapeutic effects improved for HCC<sup>[132, 133]</sup>.

### SUMMARY

Surgical resection, liver transplantation and cryosurgery are considered the best curative options for HCC. Regional interventional therapies have led to a major breakthrough in the management of unresectable HCC<sup>[45]</sup>, which occurs primarily in individuals with cirrhosis, a condition that increases the risk of performing potentially curative surgical therapy. However, the safety of surgical resections can be greatly improved because of advances in radiologic assessment, patient selection, and perioperative care<sup>[23]</sup>. Systemic chemotherapy is of uncertain benefit but widely applicable<sup>[66]</sup>. The relative efficacy of TAE/TACE, PEI, and other locoregional treatment modalities, such as radiofrequency ablation or cryosurgery, remains unclear<sup>[7]</sup>. Ablation technologies may be separated into three categories: chemical (PEI), cold-based (cryotherapy), and heat-based (RFA and microwave ablation or laser hyperthermia)<sup>[41]</sup>. RFA seems to be the most promising form of thermal ablative therapy, but its

techniques need to be refined in order to achieve the same oncological radicality of malignant liver tumors as achieved by surgical resection<sup>[64]</sup>. Most combined multimodal interventional therapies reveal their enormous advantages as compared with any single therapeutic regimen alone, and play more important roles in treating unresectable HCC<sup>[45]</sup>. The present ultimate goal of treatment of HCC is to prolong the quality of life by eradicating the malignancy while preserving hepatic function<sup>[23]</sup>. No strong evidence could be found that any chemotherapy, hormonal therapy, or immunotherapy regimen trialed to date benefits survival in HCC<sup>[96, 134]</sup>. For the recent future, the ideal strategy for curative results might be the establishment of a comprehensive way of combined approaches. Future directions in ablation will include the use of adjunctive agents such as chemotherapeutics, further advances in energy delivery, improved imaging and lesion targeting<sup>[135]</sup>, and continued refinements of current technology and technique<sup>[41, 136]</sup>. Serum albumin and alanine aminotransferase levels are significant independent predictors of recurrence. Achieving complete necrosis of HCC at first treatment to prevent local recurrence is important for improving the prognosis of patients with HCC. In addition, ameliorating hepatitis, by antiviral treatment for example, to maintain hepatic function is also important for improving both the prognosis and the prevention of the recurrence<sup>[5]</sup>. An early diagnosis of these tumors is of great importance in order to offer the possibility of curative treatment. For an early diagnosis, abdominal ultrasound and serum alpha-fetoprotein determinations at 6-month intervals are suggested for all patients with cirrhosis of the liver, since this disease is considered to be the main risk factor for the development of the neoplasia<sup>[6]</sup>.

### REFERENCES

1. Huynh H, Do PT, Nguyen TH, et al. Extracellular signal-regulated kinase induces cyclin D1 and Cdk-2 expression and phosphorylation of retinoblastoma in hepatocellular carcinoma. *Int J Oncol*. 2004, 25(6): 1839-1847.
2. Tang ZY. Hepatocellular carcinoma-cause, treatment and metastasis. *World J Gastroenterol*. 2001, 7: 445-454.
3. Nakamura M, Nagano H, Sakon M, et al. A case of long-term survivor with multiple pulmonary metastases of HCC after hepatic resection. *Gan To Kagaku Ryoho*. 2004, 31(11): 1939-1942.
4. Takeda T, Watanabe M, Umeshita K, et al. Long-term prognosis of hepatocellular carcinoma patients treated with adoptive immunotherapy. *Gan To Kagaku Ryoho*. 2004, 31(11): 1646-1648.
5. Arimura E, Nakamuta M, Kotoh K, et al. Evaluation of prognosis and recurrence of hepatocellular carcinoma treated from 1988 to 2002 at Department of Medicine III, Kyushu University Hospital. *Fukuoka Igaku Zasshi*. 2004, 95(8): 195-200.
6. Franca AV, Elias Junior J, Lima BL, et al. Diagnosis, staging and treatment of hepatocellular carcinoma. *Braz J Med Biol Res*. 2004, 37(11): 1689-1705.
7. Hsu C, Cheng JC, Cheng AL. Recent advances in non-surgical treatment for advanced hepatocellular carcinoma. *J Formos Med Assoc*. 2004, 103(7): 483-495.
8. Nikfarjam M, Christophi C. Interstitial laser thermotherapy for liver tumours. *Br J Surg*. 2003, 90(9): 1033-1047.
9. Aramaki M, Kawano K, Ohno T, et al. Microwave coagulation therapy for unresectable hepatocellular carcinoma. *Hepatogastroenterology*. 2004, 51(60): 1784-1787.
10. Wu F, Wang ZB, Chen WZ, et al. Extracorporeal High Intensity Focused Ultrasound Ablation in the Treatment of Patients with Large Hepatocellular Carcinoma. *Ann Surg Oncol*. 2004 [Epub ahead of print].
11. Ricke J, Wust P, Stohmann A, et al. CT-Guided brachytherapy. A novel percutaneous technique for interstitial ablation of liver metastases. *Strahlenther Onkol*. 2004, 180(5): 274-280.
12. Silverman SG, Sun MR, Tuncali K, et al. Three-dimensional assessment of MRI-guided percutaneous cryotherapy of liver metastases. *AJR Am J Roentgenol*. 2004, 183(3): 707-712.
13. Sugiki T, Yamamoto M, Aruga A, et al. Immunohistological evaluation of single small hepatocellular carcinoma with negative staining of monoclonal antibody Hepatocyte Paraffin 1. *J Surg Oncol*. 2004, 88(2): 104-107.
14. Faivre J, Clerc J, Gerolami R, et al. Long-term radioiodine retention and regression of liver cancer after sodium iodide symporter gene transfer in wistar rats. *Cancer Res*. 2004, 64(21): 8045-8051.
15. Silverman SG, Sun MR, Tuncali K, et al. Three-dimensional assessment of MRI-guided percutaneous cryotherapy of liver

- metastases. *AJR Am J Roentgenol.* 2004, 183(3): 707-712.
16. Seifert JK, Junginger T. Cryotherapy for liver tumors: current status, perspectives, clinical results, and review of literature. *Technol Cancer Res Treat.* 2004, 3(2): 151-163.
  17. Takahashi H, Konishi M, Nakagohri T, et al. Aggressive multimodal treatment for peritoneal dissemination and needle tract implantation of hepatocellular carcinoma: a case report. *Jpn J Clin Oncol.* 2004, 34(9): 551-555.
  18. Ikegami T, Ezaki T, Ishida T, et al. Limited hepatic resection for hepatocellular carcinoma in the caudate lobe. *World J Surg.* 2004, 28(7): 697-701.
  19. Poon RT, Fan ST, Lo CM, et al. Improving perioperative outcome expands the role of hepatectomy in management of benign and malignant hepatobiliary diseases: analysis of 1222 consecutive patients from a prospective database. *Ann Surg.* 2004, 240(4): 698-708.
  20. Verhoef C, de Man RA, Zondervan PE, et al. Good Outcomes after Resection of Large Hepatocellular Carcinoma in the Non-Cirrhotic Liver. *Dig Surg.* 2003, 21(5): 380-386.
  21. Liptak JM, Dernell WS, Monnet E, et al. Massive hepatocellular carcinoma in dogs: 48 cases (1992-2002). *J Am Vet Med Assoc.* 2004, 225(8): 1225-1230.
  22. Rodriguez-Luna H, Balan V, Sharma P, et al. Hepatitis C virus infection with hepatocellular carcinoma: not a controversial indication for liver transplantation. *Transplantation.* 2004, 78(4): 580-583.
  23. Song TJ, Ip EW, Fong Y. Hepatocellular carcinoma: current surgical management. *Gastroenterology.* 2004, 127(5 Suppl 1): S248-60.
  24. Shimonov M, Shechter P, Victoria F, et al. Laparoscopic cryoablation of liver tumors. *Harefuah.* 2002, 141(5): 414-417, 500.
  25. Laz'ko VM, Shakhova TI, Pavlovs'kyi MP. The diagnosis and surgical treatment of primary malignant liver tumors and metastases. *Lik Sprava.* 1998, 7: 63-67.
  26. Johnson LB, Krebs TL, Van Echo D, et al. Cytoablative therapy with combined resection and cryosurgery for limited bilobar hepatic colorectal metastases. *Am J Surg.* 1997, 174(6): 610-613.
  27. Xu KC, Niu LZ, He WB, et al. Percutaneous cryoablation in combination with ethanol injection for unresectable hepatocellular carcinoma. *World J Gastroenterol.* 2003, 9(12): 2686-2689.
  28. Donckier V, Van Laethem JL, Ickx B, et al. Local ablative treatments for liver metastases: the current situation. *Acta Chir Belg* 2003, 103(5): 452-457.
  29. Qian GJ, Chen H, Wu MC. Percutaneous cryoablation after chemoembolization of liver carcinoma: report of 34 cases. *Hepatobiliary Pancreat Dis Int.* 2003, 2(4): 520-524.
  30. Homasson JP, Thiery JP, Angebault M, et al. The operation and efficacy of cryosurgical, nitrous oxide-driven cryoprobe. I. Cryoprobe physical characteristics: their effects on cell cryodestruction. *Cryobiology.* 1994, 31(3): 290-304.
  31. Zhou XD. Cryosurgery for primary hepatic cancer of 87 patients. *Zhonghua Wai Ke Za Zhi.* 1992, 30(6): 334-336, 381.
  32. Brewer WH, Austin RS, Capps GW, et al. Intraoperative monitoring and postoperative imaging of hepatic cryosurgery; Intraoperative monitoring and postoperative imaging of hepatic cryosurgery. *Semin Surg Oncol; Semin Surg Oncol.* 1998, 14; 14(2; 2): 129-155; 129-155.
  33. Huo T, Huang YH, Wu JC, et al. Comparison of transarterial chemoembolization and percutaneous acetic acid injection as the primary loco-regional therapy for unresectable hepatocellular carcinoma: a prospective survey. *Aliment Pharmacol Ther.* 2004, 19(12): 1301-1308.
  34. Ohtsuka Y, Matsunaga T, Yoshida H, et al. Optimal strategy of preoperative transcatheter arterial chemoembolization for hepatoblastoma. *Surg Today.* 2004, 34(2): 127-133.
  35. Wong LL, Tanaka K, Lau L, et al. Pre-transplant treatment of hepatocellular carcinoma: assessment of tumor necrosis in explanted livers. *Clin Transplant.* 2004, 18(3): 227-234.
  36. Chen HB, Huang Y, Dai DL, et al. Therapeutic effect of transcatheter arterial chemoembolization and percutaneous injection of acetic acids on primary liver cancer. *Hepatobiliary Pancreat Dis Int.* 2004, 3(1): 55-57.
  37. Reidy DL, Schwartz JD. Therapy for unresectable hepatocellular carcinoma: review of the randomized clinical trials-I: hepatic arterial embolization and embolization-based therapies in unresectable hepatocellular carcinoma. *Anticancer Drugs.* 2004, 15(5): 427-437.
  38. Ikeda M, Maeda S, Shibata J, et al. Transcatheter arterial chemotherapy with and without embolization in patients with hepatocellular carcinoma. *Oncology.* 2004, 66(1): 24-31.
  39. Yamagami T, Kato T, Iida S, et al. Value of transcatheter arterial embolization with coils and n-butyl cyanoacrylate for long-term hepatic arterial infusion chemotherapy. *Radiology.* 2004, 230(3): 792-802.

40. Park BH, Lee JH, Jeong JS, et al. Vascular administration of adenoviral vector soaked in absorbable gelatin sponge particles (GSP) prolongs the transgene expression in hepatocytes. *Cancer Gene Ther.* 2005, 12(2): 116-121.
41. Wright AS, Mahvi DM, Haemmerich DG, et al. Minimally invasive approaches in management of hepatic tumors. *Surg Technol Int.* 2003, 11: 144-153.
42. Lin LW, Lin XY, He YM, et al. Experimental and clinical assessment of percutaneous hepatic quantified ethanol injection in treatment of hepatic carcinoma. *World J Gastroenterol.* 2004, 10(21): 3112-3117.
43. Seror O, N'kontchou G, Haddar D, et al. Large infiltrative hepatocellular carcinomas: Treatment with percutaneous intraarterial ethanol injection alone or in combination with conventional percutaneous ethanol injection. *Radiology.* 2005, 234(1): 299-309.
44. Mazzanti R, Arena U, Pantaleo P, et al. Survival and prognostic factors in patients with hepatocellular carcinoma treated by percutaneous ethanol injection: a 10-year experience. *Can J Gastroenterol.* 2004, 18(10): 611-618.
45. Qian J, Feng GS, Vogl T. Combined interventional therapies of hepatocellular carcinoma. *World J Gastroenterol.* 2003, 9(9): 1885-1891.
46. Puleo S, Lombardo R, Li Destri G, et al. Multimodal therapy of hepatocarcinoma: personal experience on 90 cases. *HepatoGastroenterology.* 2000, 47(35): 1379-1381.
47. Araki Y, Hukano M, Urabe M, et al. Hepatocellular carcinoma treated by percutaneous hot saline injection. *Oncol Rep.* 2004, 12(3): 569-571.
48. Zhu WL, Zhang J, Zhang JR, et al. Comparative study of three local ablation methods for transplanted hepatocellular carcinoma in mice. *Di Yi Jun Yi Da Xue Xue Bao.* 2003, 23(12): 1297-1300.
49. Lee JM, Lee YH, Kim YK, et al. Combined treatment of radiofrequency ablation and acetic acid injection: an in vivo feasibility study in rabbit liver. *Eur Radiol.* 2004, 14(7):1303-1310.
50. Huo TI, Huang YH, Wu JC, et al. Comparison of percutaneous acetic acid injection and percutaneous ethanol injection for hepatocellular carcinoma in cirrhotic patients: a prospective study. *Scand J Gastroenterol.* 2003, 38(7): 770-778.
51. Ahmed M, Weinstein J, Liu Z, et al. Image-guided percutaneous chemical and radiofrequency tumor ablation in an animal model. *J Vasc Interv Radiol.* 2003, 14(8): 1045-1052.
52. Huo TI, Huang YH, Wu JC, et al. Induction of complete tumor necrosis may reduce intrahepatic metastasis and prolong survival in patients with hepatocellular carcinoma undergoing locoregional therapy: a prospective study. *Ann Oncol.* 2004, 15(5): 775-780.
53. Lencioni R, Cioni D, Crocetti L, et al. Percutaneous ablation of hepatocellular carcinoma: state-of-the-art. *Liver Transpl.* 2004, 10(2 Suppl 1): S91-97.
54. Shah SS, Jacobs DL, Krasinkas AM, et al. Percutaneous ablation of VX2 carcinoma-induced liver tumors with use of ethanol versus acetic acid: pilot study in a rabbit model. *J Vasc Interv Radiol.* 2004, 15(1 Pt 1): 63-67.
55. Arrive L, Rosmorduc O, Dahan H, et al. Percutaneous acetic acid injection for hepatocellular carcinoma: using CT fluoroscopy to evaluate distribution of acetic acid mixed with an iodinated contrast agent. *AJR Am J Roentgenol.* 2003, 180(1): 159-162.
56. Lin SM, Lin DY. Percutaneous local ablation therapy in small hepatocellular carcinoma. *Chang Gung Med J.* 2003, 26(5): 308-314.
57. Huo TI, Huang YH, Wu JC, et al. Persistent retention of acetic acid is associated with complete tumour necrosis in patients with hepatocellular carcinoma undergoing percutaneous acetic acid injection. *Scand J Gastroenterol.* 2004, 39(2): 168-173.
58. Huo TI, Huang YH, Wu JC, et al. Sequential transarterial chemoembolization and percutaneous acetic acid injection therapy versus repeated percutaneous acetic acid injection for unresectable hepatocellular carcinoma: a prospective study. *Ann Oncol.* 2003, 14(11): 1648-1653.
59. Garcea G, Lloyd TD, Aylott C, et al. The emergent role of focal liver ablation techniques in the treatment of primary and secondary liver tumours. *Eur J Cancer.* 2003, 39(15): 2150-2164.
60. Vogl TJ, Eichler K, Zangos S, et al. Hepatocellular carcinoma: Role of imaging diagnostics in detection, intervention and follow-up. *Rofo.* 2002, 174(11): 1358-1368.
61. Zuber-Jerger I, Geissler M, Spangenberg HC, et al. Local ablation of malignant lesions of the liver - potential applications and limitations of the different methods. *Z Gastroenterol.* 2004, 42(1): 31-38.
62. Verhoef C, Kuiper JW, Heisterkamp J, et al. Interstitial laser coagulation with temporary hepatic artery occlusion for patients with cirrhosis and irresectable hepatoma. *Br J Surg.* 2003, 90(8): 950-955.
63. Tranberg KG. Percutaneous ablation of liver tumours. *Best Pract Res Clin Gastroenterol.* 2004, 18(1): 125-145.
64. Ng KK, Lam CM, Poon RT, et al. Thermal ablative therapy for malignant liver tumors: a critical appraisal. *J Gastroenterol Hepatol.* 2003, 18(6): 616-629.

65. Galandi D, Antes G. Radiofrequency thermal ablation versus other interventions for hepatocellular carcinoma. *Cochrane Database Syst Rev.* 2004, 2: CD003046.
66. Burroughs A, Hochhauser D, Meyer T. Systemic treatment and liver transplantation for hepatocellular carcinoma: two ends of the therapeutic spectrum. *Lancet Oncol.* 2004, 5(7): 409-418.
67. Wu F, Wang ZB, Lu P, et al. Activated anti-tumor immunity in cancer patients after high intensity focused ultrasound ablation. *Ultrasound Med Biol.* 2004, 30(9): 1217-1222.
68. Wu F, Wang ZB, Jin CB, et al. Circulating tumor cells in patients with solid malignancy treated by high-intensity focused ultrasound. *Ultrasound Med Biol.* 2004, 30(4): 511-517.
69. Geschwind JF, Salem R, Carr BI, et al. Yttrium-90 microspheres for the treatment of hepatocellular carcinoma. *Gastroenterology.* 2004, 127(5 Suppl 1): S194-205.
70. Liu MD, Uaje MB, Al-Ghazi MS, et al. Use of Yttrium-90 TheraSphere for the treatment of unresectable hepatocellular carcinoma. *Am Surg.* 2004, 70(11): 947-953.
71. Kennedy AS, Nutting C, Coldwell D, et al. Pathologic response and microdosimetry of (90)Y microspheres in man: review of four explanted whole livers. *Int J Radiat Oncol Biol Phys.* 2004, 60(5): 1552-1563.
72. Ricke J, Wust P, Stohlmann A, et al. CT-guided interstitial brachytherapy of liver malignancies alone or in combination with thermal ablation: phase I-II results of a novel technique. *Int J Radiat Oncol Biol Phys.* 2004, 58(5): 1496-1505.
73. Fosh BG, Finch JG, Anthony AA, et al. Use of electrolysis for the treatment of non-resectable hepatocellular carcinoma. *ANZ J Surg.* 2003, 73(12): 1068-1070.
74. Berry DP, Garcea G, Vanderzon P, et al. Augmenting the ablative effect of liver electrolysis: using two electrodes and the pringle maneuver. *J Invest Surg.* 2004, 17(2): 105-112.
75. Wemyss-Holden SA, Dennison AR, Berry DP, et al. Local ablation for unresectable liver tumors: is thermal best? *J Hepatobiliary Pancreat Surg.* 2004, 11(2): 97-106.
76. Berry D, Garcea G, Chong C, et al. Systematic reaction to electrolytic treatment of pig livers in vivo. *ANZ J Surg.* 2004, 74(7): 586-590.
77. Finch JG, Fosh BG, Anthony AA, et al. The use of a "liquid" electrode in hepatic electrolysis. *J Surg Res.* 2004, 120(2): 272-277.
78. Wu DH, Chen IH. Efficacy of 3-dimensional conformal hypofractionated single high-dose radiotherapy combined with transcatheter arterial chemoembolization for portal vein tumor thrombus in patients with hepatocellular carcinoma. *Ai Zheng.* 2004, 23(7): 825-828.
79. Seong J. Recent developments in radiotherapy of hepatocellular carcinoma. *Korean J Hepatol.* 2004, 10(4): 241-247.
80. Garin E, Denizot B, Noiret N, et al. <sup>188</sup>Re-SSS lipiodol: radiolabelling and biodistribution following injection into the hepatic artery of rats bearing hepatoma. *Nucl Med Commun.* 2004, 25(10): 1007-1013.
81. Fuss M, Salter BJ, Herman TS, et al. External beam radiation therapy for hepatocellular carcinoma: potential of intensity-modulated and image-guided radiation therapy. *Gastroenterology.* 2004, 127(5 Suppl 1): S206-217.
82. Bush DA, Hillebrand DJ, Slater JM, et al. High-dose proton beam radiotherapy of hepatocellular carcinoma: preliminary results of a phase II trial. *Gastroenterology.* 2004, 127(5 Suppl 1): S189-193.
83. Llovet JM. Treatment of hepatocellular carcinoma. *Curr Treat Options Gastroenterol.* 2004, 7(6): 431-441.
84. Park WH, Joo ST, Park KK, et al. Effects of the Geiji-Bokryung-Hwan on carrageenan-induced inflammation in mice and cyclooxygenase-2 in hepatoma cells of HepG2 and Hep3B. *Immunopharmacol Immunotoxicol.* 2004, 26(1): 103-112.
85. Totta P, Acconcia F, Leone S, et al. Mechanisms of naringenin-induced apoptotic cascade in cancer cells: involvement of estrogen receptor alpha and beta signalling. *IUBMB Life.* 2004, 56(8): 491-499.
86. Jang DS, Cuendet M, Pawlus AD, et al. Potential cancer chemopreventive constituents of the leaves of *Macaranga triloba*. *Phytochemistry.* 2004, 65(3): 345-350.
87. Kok SH, Cheng SJ, Hong CY, et al. Norcantharidin-induced apoptosis in oral cancer cells is associated with an increase of proapoptotic to antiapoptotic protein ratio. *Cancer Lett.* 2005, 217(1): 43-52.
88. Patt YZ, Hassan MM, Lozano RD, et al. Thalidomide in the treatment of patients with hepatocellular carcinoma. *Cancer.* 2005, 103(4): 749-755.
89. Chen X, Liu Z, Ai Z. Antineoplastic mechanism of Octreotide action in human hepatoma. *Chin Med J (Engl).* 2001, 114(11): 1167-1170.
90. Saito K, Inoue S, Saito T, et al. Augmentation effect of postprandial hyperinsulinaemia on growth of human hepatocellular carcinoma. *Gut.* 2002, 51(1): 100-104.

91. Siveke JT, Herberhold C, Folwaczny C. Complete regression of advanced HCC with long acting octreotide. *Gut*. 2003, 52(10): 1531.
92. Petronilli V, Penzo D, Scorrano L, et al. The mitochondrial permeability transition, release of cytochrome c and cell death. Correlation with the duration of pore openings in situ. *J Biol Chem*. 2001, 276(15): 12030-12034.
93. Groupe d'Etude et de Traitement du. Randomized trial of leuprorelin and flutamide in male patients with hepatocellular carcinoma treated with tamoxifen. *Hepatology*, 2004, 40(6): 1361-1369.
94. Zhang K, Chow PK. The effect of megestrol acetate on growth of HepG2 cells in vitro and in vivo. *Clin Cancer Res*. 2004, 10(15): 5226-5232.
95. Nowak A, Findlay M, Culjak G, et al. Tamoxifen for hepatocellular carcinoma. *Cochrane Database Syst Rev*. 2004, 3: CD001024.
96. Nowak AK, Chow PK, Findlay M. Systemic therapy for advanced hepatocellular carcinoma: a review. *Eur J Cancer*. 2004, 40(10): 1474-1484.
97. Zeng XL, Tu ZG. Induction of differentiation by ginsenoside Rh2 in hepatocarcinoma cell SMMC-7721. *Ai Zheng*. 2004, 23(8): 879-884.
98. Zhang G, Miura Y, Yagasaki K. Effects of dietary powdered green tea and theanine on tumor growth and endogenous hyperlipidemia in hepatoma-bearing rats. *Biosci Biotechnol Biochem*. 2002, 66(4): 711-716.
99. Kojima S, Okuno M, Matsushima-Nishiwaki R, et al. Acyclic retinoid in the chemoprevention of hepatocellular carcinoma (review). *Int J Oncol*. 2004, 24(4): 797-805.
100. Nishino H, Tokuda H, Satomi Y, et al. Cancer prevention by antioxidants. *Biofactors*. 2004, 22(1-4): 57-61.
101. Cai Y, Luo Q, Sun M, et al. Antioxidant activity and phenolic compounds of 112 traditional Chinese medicinal plants associated with anticancer. *Life Sci*. 2004, 74(17): 2157-2184.
102. Joe B, Vijaykumar M, Lokesh BR. Biological properties of curcumin-cellular and molecular mechanisms of action. *Crit Rev Food Sci Nutr*. 2004, 44(2): 97-111.
103. Cao Y, Fu ZD, Wang F, et al. Anti-angiogenic activity of resveratrol, a natural compound from medicinal plants. *J Asian Nat Prod Res*. 2005, 7(3): 205-213.
104. Oak MH, El Bedoui J, Schini-Kerth VB. Antiangiogenic properties of natural polyphenols from red wine and green tea. *J Nutr Biochem*. 2005, 16(1): 1-8.
105. Cao QZ, Lin ZB. Antitumor and anti-angiogenic activity of *Ganoderma lucidum* polysaccharides peptide. *Acta Pharmacol Sin*. 2004, 25(6): 833-838.
106. Sakurai N, Kozuka M, Tokuda H, et al. Cancer preventive agents. Part 1: Chemopreventive potential of cimigenol, cimigenol-3,15-dione, and related compounds. *Bioorg Med Chem*. 2005, 13(4): 1403-1408.
107. Cui Y, Kim DS, Park KC. Antioxidant effect of *Inonotus obliquus*. *J Ethnopharmacol*. 2005, 96(1-2): 79-85.
108. Yun TK. Experimental and epidemiological evidence on non-organ specific cancer preventive effect of Korean ginseng and identification of active compounds. *Mutat Res*. 2003, 523-524: 63-74.
109. Furusawa E, Hirazumi A, Story S, et al. Antitumor potential of a polysaccharide-rich substance from the fruit juice of *Morinda citrifolia* (Noni) on sarcoma 180 ascites tumour in mice. *Phytother Res*. 2003, 17(10): 1158-1164.
110. Shyu KG, Tsai SC, Wang BW, et al. Saikosaponin C induces endothelial cells growth, migration and capillary tube formation. *Life Sci*. 2004, 76(7): 813-826.
111. Chou CC, Pan SL, Teng CM, et al. Pharmacological evaluation of several major ingredients of Chinese herbal medicines in human hepatoma Hep3B cells. *Eur J Pharm Sci*. 2003, 19(5): 403-412.
112. Aso H, Shibuya E, Suzuki F, et al. Antitumor effect in mice of an organic germanium compound (Ge-132) when different administration methods are used. *Gan To Kagaku Ryoho*. 1985, 12(12): 2345-2351.
113. Gouedard C, Barouki R, Morel Y. Dietary polyphenols increase paraoxonase 1 gene expression by an aryl hydrocarbon receptor-dependent mechanism. *Mol Cell Biol*. 2004, 24(12): 5209-5222.
114. Wettasinghe M, Bolling B, Plhak L, et al. Phase II enzyme-inducing and antioxidant activities of beetroot (*Beta vulgaris* L.) extracts from phenotypes of different pigmentation. *J Agric Food Chem*. 2002, 50(23): 6704-6709.
115. Kris-Etherton PM, Hecker KD, Bonanome A, et al. Bioactive compounds in foods: their role in the prevention of cardiovascular disease and cancer. *Am J Med*. 2002, 113 (Suppl 9B): 71S-88S.
116. Bagchi D, Sen CK, Bagchi M, et al. Anti-angiogenic, antioxidant, and anti-carcinogenic properties of a novel anthocyanin-rich berry extract formula. *Biochemistry (Mosc)*. 2004, 69(1): 75-80, 1 p preceding 75.
117. O'Brien NM, Woods JA, Aherne SA, et al. Cytotoxicity, genotoxicity and oxidative reactions in cell-culture models:

- modulatory effects of phytochemicals. *Biochem Soc Trans.* 2000, 28(2): 22-26.
118. Liu Q, Wang H, Hu D, et al. Effects of trace elements on the telomere lengths of hepatocytes L-02 and hepatoma cells SMMC-7721. *Biol Trace Elem Res.* 2004, 100(3): 215-227.
  119. Thirunavukkarasu C, Sakthisekaran D. Effect of dietary selenite on N-nitrosodiethylamine-induced and phenobarbital promoted multistage hepatocarcinogenesis in rat: reflection in some minerals. *Biomed Pharmacother.* 2003, 57(9): 416-421.
  120. Marteau PR, de Vrese M, Cellier CJ, et al. Protection from gastrointestinal diseases with the use of probiotics. *Am J Clin Nutr.* 2001, 73(2 Suppl): 430S-436S.
  121. Yoshiji H, Kuriyama S, Yoshii J, et al. Extracellular matrix remodeling may predominate over hepatocyte injury in hepatocellular carcinoma development. *Oncol Rep.* 2003, 10(4): 957-962.
  122. Chan WY, Chau FT, Lee KK, et al. Substitution for natural musk in Pien Tze Huang does not affect its hepatoprotective activities. *Hum Exp Toxicol.* 2004, 23(1): 35-47.
  123. Yoshiji H, Noguchi R, Kuriyama S, et al. Combination of interferon and angiotensin-converting enzyme inhibitor, perindopril, suppresses liver carcinogenesis and angiogenesis in mice. *Oncol Rep.* 2005, 13(3): 491-495.
  124. Torisu M, Iwasaki K, Sakata M. Immunotherapy of cancer patients with BCG: summary of ten years experience in Japan. *Dev Biol Stand.* 1986, 58(Pt A): 451-456.
  125. Waldmann TA. Immunotherapy: past, present and future. *Nat Med.* 2003, 9(3): 269-277.
  126. Ohno T. Autologous cancer vaccine: a novel formulation. *Microbiol Immunol.* 2003, 47(4): 255-263.
  127. Wissniowski TT, Hansler J, Neureiter D, et al. Activation of tumor-specific T lymphocytes by radio-frequency ablation of the VX2 hepatoma in rabbits. *Cancer Res.* 2003, 63(19): 6496-6500.
  128. Cam L, Boucquey A, Coulomb-L'hermine A, et al. Gene transfer of constitutively active caspase-3 induces apoptosis in a human hepatoma cell line. *J Gene Med.* 2005, 7(1): 30-38.
  129. Horowitz J. Adenovirus-mediated p53 gene therapy: overview of preclinical studies and potential clinical applications. *Curr Opin Mol Ther.* 1999, 1(4): 500-509.
  130. Wang XH, Li GQ. Gene therapy of hepatocellular carcinoma. *Zhonghua Gan Zang Bing Za Zhi.* 2004, 12(11): 691-692.
  131. Zhang X, Ouyang XN, Li XD, et al. Effects of tumor suppressing gene TIP30/CC3 on the growth of tumor cells. *Zhonghua Gan Zang Bing Za Zhi.* 2005, 13(1): 38-41.
  132. Wang XH, Yang JM, Cui ZF, et al. In vitro gene therapy of hepatocellular carcinoma using replication-defective and tumor-specific replication-competent adenovirus carrying interleukin-12 gene. *Zhonghua Zhong Liu Za Zhi.* 2004, 26(10): 581-584.
  133. Li N, Yuan YK, Wu J. Construction and identification of recombinant adenovirus vector harboring CTLA4Ig-IRES 2-Ikappa-Balpha gene in ECV-304 cells. *Xi Bao Yu Fen Zi Mian Yi Xue Za Zhi.* 2005, 21(1): 90-93.
  134. Lersch C, Schmelz R, Erdmann J, et al. Treatment of HCC with pravastatin, octreotide, or gemcitabine--a critical evaluation. *Hepatology.* 2004, 41(5): 1099-1103.
  135. Guan YS, Zheng XH, Zhou XP, et al. Multidetector CT in evaluating blood supply of hepatocellular carcinoma after transcatheter arterial chemoembolization. *World J Gastroenterol.* 2004, 10(14): 2127-2129.
  136. Guan YS, Zhou XP. Hepatocellular carcinoma: its blood supply and interventional management. *Zhonghua Gan Zang Bing Za Zhi.* 2003, 11(12): 765-766.

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