• REVIEW •

Hepatocellular Carcinoma-Cause, Treatment and Metastasis

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Abbreviation HCC-hepatocellular carcinoma, HBV-hepatitis B virus, HCV-hepatitis C virus, HGV-hepatitis G virus, TTV-transfusion transmitted virus, AFB1-aflatoxin B1, IFN-interferon, OLT-orthotopic liver transplantation, PH-partial hepatectomy, RCT-randomized controlled trial, TACE-transcatheter arterial chemoembolization, PEI-percutaneous ethanol injection, PMCT-percutaneous microwave coagulation therapy, RF-radiofrequency, AFP-alpha fetoprotein, VEGF-vascular endothelial growth factor.

Abstract

In the recent decades, the incidence of hepatocellular carcinoma (HCC) has been found to be increasing in males in some countries. In China, HCC ranked second of cancer mortality since 1990s. Hepatitis B and C viruses (HBV and HCV) and dietary aflatoxin intake remain the major causative factors of HCC. Surgery plays a major role in the treatment of HCC, particularly for small HCC. Downstaging unresectable huge HCC to smaller HCC and followed by resection will probably be a new approach for further study. Liver transplantation is indicated for small HCC, however, some issues remain to be solved. Different modes of "regional cancer therapy for HCC" have been tried. Systemic chemotherapy has been disappointing in the past but the future can be promising. Biotherapy, such as cytokines, differentiation inducers, anti-angiogenic agents, gene therapy and tumor vaccine will probably play a role, particularly in the prevention of tumor recurrence. HCC invasiveness is currently the major target of study. Tremendous works have been done at the molecular level, which will provide clues for biomarker of HCC progression as well as targets for intervention.

Subject headings carcinoma, hepatocellular/etiology; carcinoma, hepatocellular/surgery; carcinoma, hepatocellular/drug therapy; liver neoplasms/etiology; liver neoplasms/surgery; liver neoplasms/drug therapy; human; review

INTRODUCTION

Liver cancer is the 4th most common cause of death from cancer, the highest age-standardised mortality rate is in China ($34.7/10^5$, the 2nd cancer killer since 1990s), which alone accounts for 53% of all liver cancer deaths worldwide[1]. Recently, the incidence of HCC has been found to be increasing particularly in males in countries such as Japan, Italy, France, Switzerland, United Kingdom and the United States[2-4]. Clinical advances have mainly been made in the fields of medical imaging, surgery, regional cancer therapy and biotherapy. Rapidly growing knowledge in basic science appears at the molecular level, particularly in the study of HCC invasiveness. Although a lot of news from bench to bedside on the advances made in HCC has appeared, the overall dismal outcome of patients with HCC changed very little. In the United States, the relative 5 -year survival for liver cancer only increased from 4% (1974-76) to 6% (1986 -93) in white, and from 1% to 4% in black[5]. In Shanghai, the relative 5-year survival of liver cancer in 1988-91 was 4.4%[6]. These indicate that there is still a long way to go in conquering HCC.

CAUSE AND PREVENTION

Viral hepatitis B (HBV) and/or C (HCV), aflatoxin and alcohol are major risk factors of HCC

However, the importance of these different factors varies in different geographic areas. HBV is more predominant in Chinese, Southeast Asian and African patients with HCC, whereas HCV is common in HCC patients in developed countries (Japan, France, Italy and others). The prevalence of hepatitis B surface antigen (HBsAg) and antibody to HCV (anti-HCV) in HCC patients were reported to be 63.2% and 11.2% respectively in China[7], which was similar to that reported in the past.Prospective studies showed that there is an additive effect of HCV and HBV infection on HCC development[8]. Cirrhotic patients infected with HCV type 1b carry a significantly higher risk of developing HCC than patients infected by other HCV types[9-11]. An association was found between high serum alanine aminotransferase levels and more rapid development and high incidence rate of HCC in patients with HCV-associated cirrhosis[12]. In a transgenic mice, it was found that the core protein of HCV induces HCC[13].

Hepatitis G virus (HGV) and transfusion-transmitted virus (TTV) infection might not play an important role

Based on the data from China, Japan, Africa, United Kingdom and others, HGV might not play an important role in the development of HCC[14-18]. A case-control study also failed to support the hypothesis of an association between transfusion-transmitted virus (TTV) infection and HCC[19]. However, some authors claimed that HGV and TTV could not be completely excluded as causative agents[20-22].

In China, HBV and HCV (mainly HBV), aflatoxin and contamination of drinking water (such as microcystin, a promoter of hepatocarcinogenesis) remain as major risk factors of HCC, and alcohol should be added in northern China

A study showed that exposure to aflatoxin metabolite M1 (AFM1) can account for a substantial part of the risk of HCC[23].

Other risk factors have also been reported

In Japan, alcohol consumption and cigarette smoking were also risk factors of HCC, and synergism between them was observed[24,25]. In Italy, for attributable risk (AR) of HCC, heavy alcohol intake ranked first (45%), HCV second (36%) and HBV third (22%)[26]. The risk of dietary iron overload was 4.1 for HCC in black Africans[27], which is similar to that of haemochromatosis in Caucasians. A role of family history independent from and interacting with known risk factors for HCC was also reported, the odds ratio was reported to be 2.4[28].

HCC risk is high in individuals with both aflatoxin B1 (AFB1)-DNA adducts and HBsAg, suggesting a viral-chemical interaction

Furthermore, AFB1 exposure correlates with a specific mutation at codon 249 of the p53 tumor suppressor gene in HCC, indicating a molecular pathogenesis[29]. How the four major risk factors (HBV, AFB1, p53 mutation and male gender) for HCC interact to produce malignant liver tumors were also demonstrated in transgenic mouse models[30].

X protein of HBV is one of the target of how HBV induces HCC

The incidence of HCC was as high as 86% in a HBV-X transgenic mice[31]. It was also found that the structure of the X gene is modified in the majority of tumorous livers, suggesting a potential role of mutated X proteins in HBV-related liver oncogenesis[32]. Moreover, HBV-X might play a role in hepatic inflammation by up-regulating interleukin-6 production, which can eventually lead to HCC[33]. Transactivation of transforming growth factor alpha (TGF-alpha) gene by HBV preS1 was observed which provides a clue for understanding viral hepatocarcinogenesis[34]. Synergy between TGF-alpha and HBsAg in hepatocellular proliferation and carcinogenesis was also reported[35].

All of these indicate a multifactorial and multistep development of HCC. Interaction among HBV/HCV, aflatoxin, alcohol, and genetic susceptibility might be important.

The dawn of HCC prevention has been shown

Few approaches of HCC prevention have been emerged, namely: prevention of HBV infection using vaccine, avoid exposure to carcinogens and promoters by changing drinking water, and to prevent viral hepatitis B or C progressing to cirrhosis and HCC by interferon (IFN) therapy. Result from a universal hepatitis B vaccination program indicated that the incidence of HCC in children has declined[36]. A significant declining trend of HCC mortality rate ratios was observed in the vaccination group, but not in the reference group[37]. In Qidong County of China, after people changed their source of drinking water from pond-ditch water (microcystin was found) to deep-well water, the mortality rate of HCC stabilized and even decreased slowly[38]. An analysis of patients with chronic hepatitis, liver cirrhosis, chronic hepatitis bearing HCC and liver cirrhosis bearing HCC, found that the incidence of HCC in the control group was 10.4/100 person-year, while that in the IFN treated group was 1.2/100 person-year[39]. IFN decreased HCC incidence in patients with HBV related cirrhosis. The cumulative occurrence rates of HCC in the treated group and the untreated group were 17.0% and 30.8%, respectively, at the end of 10 years[40]. IFN therapy also decreased the development of HCV related HCC. HCC rates in the IFN treated and untreated groups were 7.6% and 12.4% at the 10th year respectively[41]. Patients with HCV-related cirrhosis also benefit from IFN treatment[42]. IFN therapy significantly reduces the risk for HCC, especially among virologic or biochemical responders of patients with chronic hepatitis C[43]. For those nonresponder, retreatment with IFN-alpha appeared to have the additional effect of suppressing the development of HCC in patients who had incomplete responses to the initial treatment, even when the HCV was not cleared with retreatment[44]. Currently, lamivudine or ribavirin, antiviral agent, is added to the treatment of HBV or HCV, however, long-term follow-up study is needed to evaluated whether this additional treatment will increase the efficacy of HCC prevention.

SURGERY OF HCC

Small HCC resection plays an important role to improve HCC prognosis

Small HCC resection has resulted in marked increase in 5-year survival rate from 20%-30% to 40%-60%. At the author's institution, the 5-year survival rate of 963 patients with small HCC (≤5cm) resection was 65.1%, whereas it was only 36.1% for large HCC resection (*n*=1308); of the 368 HCC patients with 5-year survival, 198 (53.8%) patients received small HCC resection[45,46]. Early HCC with well differentiated cancer containing Glisson's triad has been recognized as an entity with a high rate of surgical cure, the 5-year survival was as high as 93%[47]. A comparison between subclinical HCC and symptomatic HCC revealed that operability was higher (26.8% versus 7.9%), and cumulative survival rate was also higher[48].

Makuuchi *et al* (1998) have performed 367 hepatectomies on 352 patients since 1990, the 5-year survival rate was 47.4%[49]. At the author's institution, HCC resection has been performed on 2119 patients between 1979-1998, the 5-year survival rate was 51.5%[50]. Recently, perioperative blood transfusion and diabetes mellitus were found to be prognostic factors after HCC resection[51,52]. An experimental study indicated that partial hepatectomy was associated with increased levels of TGF-alpha, TGF-beta, and basic fibroblast growth factor (bFGF) in the liver and accelerates local tumor growth[53].

Down-staging of unresectable huge HCC to smaller HCC followed by resection will probably be a new approach for further study

At the author's institution, the 5-year survival of 108 patients with this approach (down-staging by hepatic artery ligation, cannulation, cryosurgery, etc.) was 64.7%[45]. Another 65 patients with unresectable HCC down-staged by transcatheter arterial chemoembolization (TACE) followed by resection, the 5-year survival was 56.0%[54]. The 5-year survival rates

were similar to that of small HCC resection, which coincided with a reduction of median tumor size from 10.0cm to 5.0cm during the resection of this approach[55]. However, a well designed randomized trial is needed for a final evaluation.

Orthotopic liver transplantation (OLT) is a reasonable treatment for small HCC if partial hepatectomy (PH) is impossible

For decades, the role of OLT in the treatment of HCC has been unclear. In the early 1990s, it was accepted that small HCC was indicated for OLT. However, only retrospective data were available for the comparison between OLT and PH in the treatment of HCC. The 5-year survival rate of 422 HCC patients with OLT was 44.4%, and tumor histologic grade and tumor size (>5cm) were linked to recurrence-free patient survival[56]. A comparison between PH ($n = 294$) and OLT ($n = 270$) showed that survival was comparable, but operative mortality was lower in PH group, and concluded that HCC developing in a well compensated cirrhotic liver initially may be treated with PH, and OLT should be applied selectively to those patients with tumor recurrence and/or progressive hepatic failure[57]. A proper selection of candidates for PH gives better results than OLT, because of the increasing waiting time for OLT[58]. OLT is a reasonable treatment for patients with early stage tumors if PH is impossible. The oncological advantage of OLT compared with PH, however, is questionable[59]. As survival after PH and OLT for early stage HCC does not reveal a significant difference, resection of these tumors is still justifiable[60]. When compared with PH, OLT for resectable HCC offers substantial survival benefit among well-targeted subgroups of patients as long as an organ donor is available within 6 to 10 months time delay. However, the marginal cost-effectiveness ratios incurred by this strategy are higher than that of many other current medical interventions[61]. This might be of particular impact for developing countries where HCC is endemic.

NONSURGICAL THERAPIES FOR HCC

There is still a long way to go of nonsurgical therapies for HCC

Nonsurgical therapies for HCC generally include regional cancer therapies, radiotherapy, chemotherapy and biotherapy. Unfortunately, a systemic review of 37 RCTs to examine the effect of different treatments for non resectable patients indicated that only 3 modalities were minimally and uncertainly effective (embolization, tamoxifen and IFN)[62]. Another overview of 30 RCTs for unresectable HCC found that no treatment has clearly proven efficacy in survival. 5-Fluorouracil, adriamycin and transarterial chemotherapy were not associated with survival benefit at 1 year. The number of RCTs was insufficient to enable a conclusion to be reached for IFN and PEI (percutaneous ethanol injection). Controversy persists concerning tamoxifen efficacy[63].

Regional cancer therapy for HCC is one of the nonsurgical therapies that develops recently

Based on the advances of early detection and medical imaging, more HCCs can be diagnosed with small and localized lesions. As a result, regional cancer therapies have developed in the recent decades. Unfortunately, the number of RCTs was insufficient to make any conclusion as yet.

Transcatheter chemoembolization (TACE) is one choice of the treatment for unresectable but not far advanced HCC, particularly for patients with multifocal HCCs and with acceptable liver functions. However, some RCTs failed to demonstrate that TACE improve the survival with unresectable or advanced HCC[64,65]. A RCT found that the 4-year survival of intrahepatic-arterial ^{131}I-labeled lipiodol (2.2 GBq) was 10% when compared with 0% in TACE group (70mg cisplatin)[66]. Another RCT indicated that styrene maleic acid neocarzinostatin in Lipiodol was better than epirubicin in Lipiodol[67]. A comparison of planned periodic TACE and TACE based on tumor response found that the 3-year survival rates were 0% and 15% respectively in Okuda 2 stage, the mean time between the first and the third courses of TACE was 4 months and 14 months respectively, indicating the efficacy of TACE increased when it was used selectively and was repeated only when necessary[68]. The overall 5-year survival rate after TACE treatment is around 6%-8%. TACE resulted in prolongation of survival in patients with tumor volumes of less than 200mL, tumor-to-liver volume ratios of less than 5%, and iodized oil retention greater than or equal to 75%[69]. Complications of TACE were encountered in 4.4% of cases, of which, hepatic failure and down-staging of cirrhosis remain a problem[70].

Percutaneous ethanol injection (PEI) is a treatment choice of unresectable small HCC. The 4-year survival rate was 39% in 47 small HCC patients with cirrhosis, however, the 4-year recurrence rate was as high as 79%[71]. Local recurrence depends predominantly on the biologic characteristics of the tumor (histologic grade and intrahepatic recurrence), regardless of the efficacy of PEI[72]. For large (>5cm) HCC, PEI performed in a single session under general anesthesia was an alternative. In a series of 108 patients, the 4-year survival rates were 44% for single encapsulated HCC (5 cm - 8.5 cm), 18% for single infiltrating HCC (5cm-10cm) or multiple HCC and 0% for advanced disease, the mortality was 0.7% and major complications 4.6%[73]. A RCT study comparing 50% acetic acid and PEI indicated that local recurrence rate was lower and 2-year survival rates higher with acetic acid[74].

Percutaneous microwave coagulation therapy (PMCT) is an extension of PEI, the 5-year survival for patients with well-differentiated HCC treated with PMCT and PEI were comparable, however, among the patients with moderately or poorly differentiated HCC, 5-year survival with PMCT (78%) was better than with PEI (35%)[75]. PEI is difficult for small HCC on the surface of liver, however, PMCT can be performed safely in such patients[76]. After PMCT, a second biopsy on 19 patients showed complete destruction of tumor in 18 patients[77].

Radiofrequency (RF) hyperthermia is another mode of regional cancer therapy. Of the 73 HCC patients treated with RF and evaluated by CT, complete response rate was 10%, partial response rate 21%, and 5-year survival 17.5%[78]. A comparison was made between RF and PEI in the treatment of small HCCs. It was found that RF ablation resulted in a higher rate of complete necrosis (90% versus 80%) and requires fewer treatment sessions than PEI. However, the complication rate was higher with RF ablation than with PEI[79].

The inadequacy for complete control of cancer nodule is one of the major problems of regional cancer therapies. Therefore, surgery remains the choice of treatment for curatively resectable HCC with Child A cirrhosis until a RCT clarifies the situation. In general, TACE is a treatment choice

for multinodular and large unresectable HCC (a part of TNM Stage II, IIIA, IIIB and IVA; with Child A or Child B cirrhosis). The other regional therapies may be used on unresectable small HCC which is not multinodular.

Three-dimensional conformal radiotherapy will probably play a role for HCC treatment in the future

A pilot study indicated that three-dimensional conformal radiotherapy helped to avoid excessive exposure of the liver and adjacent organs and made it a safer treatment modality for unresectable HCC[80]. Selective internal radiation therapy using 90Y microspheres (median 3.0 GBq) was effective for selected cases of nonresectable HCC. There was a 50% reduction in tumor volume in 26.7% of patients after the first treatment, the nontumorous liver appeared more tolerant to internal radiation than external beam radiation. This treatment may help to convert nonresectable tumors to resectable ones[81]. At the author's institution, long-term follow-up study indicated that a combination of surgery and intrahepatic arterial infusion of ^{131}I-anti-HCC mAb improved survival of unresectable HCC[82].

Systemic chemotherapy for HCC has been disappointing in the past, but in the future can be promising

Neither complete response nor partial response was observed using paclitaxel (175mg/m^2 q3w) for unresectable HCC[83]. However, a phase II study with cisplatin, doxorubicin, 5-fluorouracil, and IFN-alpha in advanced unresectable HCC demonstrated that complete pathological remission was possible, partial response rate was 26%, no viable tumor cells were found in four out of nine resected specimens[84]. Based on the study of the expression of drug resistance-related genes in three human hepatoma cell lines, it was demonstrated that IFN-alpha modulated the mechanism of resistance to cisplatin in liver cancer[85]. Individual patient with complete remission of multiple HCC associated with HCV-related decompensated liver cirrhosis by oral administration of enteric-coated tegafur/uracil has been reported[86].

Biotherapy will play a role in the treatment of HCC in the future

However, the results were still controversial. Many RCTs of tamoxifen for advanced HCC were negative[87-90]. A lack of efficacy of antiandrogen treatment was found for unresectable HCC in a RCT[91]. Oral beta all transretinoic acid (50mg/m^2 t.i.d.) was also ineffective against HCC[92]. Interestingly, Octreotide, a somatostatin analogue, improves survival of inoperable HCC in another RCT[93]. Randomized controlled trial of interferon treatment for advanced HCC indicated that its administration prompts no benefit in terms of tumor progression rate and survival[94].

Gene therapy-"progress but many stone yet unturned[95]"

Gene therapy for HCC remains an attractive field. Experimental studies using cytokine genes (tumor necrosis factor, interleukin-2, interferon), suicide and *p*53 genes; using retrovirus, adenovirus and Epstein-barr virus as vectors; using AFP enhancer; using intraarterial administration, etc. have been reported[96-108]. Data from both the literature[109-112] and from the author's institution[113] demonstrated that human malenoma antigen (MAGE) gene expression is frequent in HCC, suggesting that HCC patients may be good candidates for specific immunotherapy (tumor vaccine) using MAGE encoded antigen. Dendrite cells are good candidates for this particular purpose[114].

METASTASIS OF HCC

Invasiveness of HCC has become a major target of recent research

The high recurrent rate in the liver with mainly intrahepatic metastatic spread remains a major obstacle to further improvement on the long-term survival after curative HCC resection. Therefore, research on the invasiveness of HCC has become a major target. Clinically, targets include prediction, treatment and prevention; in the laboratory, investigations include metastatic model, molecular events, angiogenesis, intervention, etc.

A routine biomarker for prediction of metastasis and recurrence is not yet available

Although many biomarkers have been tried, such as AFPmRNA, circulating VEGF and PD-ECGF[115,116], human macrophage metalloelastase gene[117], p27[118], p53 mutation[119], expression of p73[120], telomerase activity[121], etc.

Both pre- and postoperative chemotherapy or chemoembolization have not adequately proved to be effective for prevention of metastatic recurrence

Convincing evidence is lacking to support systemic preoperative chemoembolization in patients with initially resectable HCC[122]. Although many authors supported the strategy of postoperative chemoembolization, its effectiveness might be due to suppression of intrahepatic micrometastases rather than multicentric carcinogenesis[123]. Postoperative intraarterial chemotherapy has also been claimed to improve survival[124,125]. Recently, a RCT showed that postoperative adjuvant systemic chemotherapy using epirubicin and mitomycin C has a tendency to reduce recurrence rate[126]. However, two RCTs failed to demonstrate the effectiveness of postoperative adjuvant therapy. The adjuvant chemotherapy with epirubicin and carmofur after radical resection of HCC was not effective[127]. Postoperative chemotherapy using intravenous epirubicin and intraarterial iodized oil and cisplatin was associated with more frequent extrahepatic recurrences and a worse outcome[128]. Interestingly, a RCT revealed that oral polyprenoic acid prevents second primary HCC after surgical resection, and reconfirmed after longer follow-up study[129,130]. Recently, a RCT study indicated that a single 1850 MBq dose of intra-arterial ^{131}I-lipiodol increased the 3-year overall survival from 46.3% in the control to 86.4% in the treatment group[131].

The molecular basis of "HCC invasiveness" is similar to that of other solid cancers, its complexity represents as multi-genes involvement and multi-step process

Numerous papers have been published concerning the molecular basis of "HCC invasiveness" in the literature[132-150]. At the author's institution, studies concerning HCC invasiveness could be summarized into the followings: a Factors that positively related to invasiveness included: p16 and p53 mutation, H-ras, c-erbB-2, mdm2, TGFα, epidermal growth factor receptor (EGF-R), matrix metalloproteinase-2 (MMP-2), urokinase-type plasminogen activator (uPA), its receptor (uPA-R) and inhibitor (PAI-1),

intercellular adhesion molecule-1 (ICAM-1), vascular endothelial growth factor (VEGF), platelet-derived endothelial cell growth factor (PD-ECGF), basic fibroblast growth factor (bFGF), etc. On the other hand, factors that negatively related to HCC invasiveness included: nm23-H1, Kai-1, tissue inhibitor of metalloproteinase-2 (TIMP-2), integrin α5, E-cadherin, etc. b The biological characteristics of small HCC was slightly better than that of large HCC c The following blood test have been tried with potential clinical implication: thrombomodulin, ICAM-1, PAI-1, VEGF, bFGF, etc. Serum ICAM-1 content was higher in patients with metastasis than those without metastasis. Loss of heterozygosity (LOH) at D14S62 and D14S51 (on chromosome 14q) in plasma DNA were also related to metastatic recurrence. The combination of several items that mentioned above increased sensitivity[151-164].

Comparison between primary HCC tumors and their metastatic lesions using comparative genomic hybridization (CGH) indicated that chromosome 8p deletion might contribute to HCC metastasis[165]. The presence of at least three novel tumor suppressor loci on 8p in HCC was reported[166], and DLC-1 might be one of the related tumor suppressor gene[167].

Metastatic human HCC model in nude mice (LCI-D20) and HCC cell line with metastatic potential (MHCC97) have been established[168,169]

Using corneal micropocket model in nude mice, the difference of angiogenesis induced by LCI-D20 and LCI-D35 (a low metastatic model) was also demonstrated[170]. Highly metastatic HCCs induced in male F344 rats and a transplantable lymph node metastatic mouse model of HCC were also reported[171,172]. These will provide a tool for the study of the mechanism and the intervention of metastasis.

Angiogenesis is closely related to HCC invasiveness

Vascular endothelial growth factor (VEGF) gene and protein expression are involved in the progression of HCC[173-175], and that VEGF 121 and 165 isoforms play a critical role in angiogenesis of HCC[176]. However, some author reported that VEGF might be associated with the angiogenic process of the cirrhotic liver, but not with the angiogenesis of HCC[177]. VEGF level increased after TACE, indicating that VEGF may be a marker for tumor ischemia[178]. Angiogenesis in HCC depends on the net balance between human macrophage metalloelastase (a potent angiogenesis inhibitor) and VEGF gene expressions[179]. Platelet-derived endothelial cell growth factor (PD-ECGF), another angiogenic factor, is also involved in HCC progression[180]. The enhanced gene expression of angiopoietin-2 may also contribute to the hypervascular phenotype[181]. Angiogenesis in HCC can be evaluated by CD34 immunohistochemistry[182,183]. At author's institution, using CD34 staining to measure microvessel density (MVD), we found that MVD was only useful for small HCC resection, the 5-year survival after resection of hypovascular type small HCC was double to that of hypervascular type, being 74.6% versus 34.7%[184]. As small HCCs increase in size and become increasingly dedifferentiated, the number of portal tracts apparently decreases and intratumoral arterioles develop. These findings may reflect changes in the hemodynamics as the HCC develops[185].

Experimental intervention of HCC metastases is progressing

Many approaches have been tried in preventing metastases, and anti-angiogenesis is one of the major target. For example, anti-angiogenic agent TNP-470, a derivative of fumagillin, was found to inhibited tumor growth and metastasis in nude mice bearing human HCC and suppressed the progression of experimentally-induced HCC in rats[186,187]. High-dose and long-term therapy with IFN-alpha inhibited tumor growth and recurrence in nude mice bearing human HCC xenografts with high metastatic potential in a dose-dependent manner, and the preventive effect was mediated by anti-angiogenesis[188]. However, its clinical significance has to be assessed by a RCT. Other experimental interventions for metastasis were also reported, such as matrix metalloproteinase inhibitor BB-94[189], 4-[3,5- Bis (trimethylsilyl) benzamido] benzoic acid (TAC-101)[190], antisense H-ras oligodeoxynucleotides[191], synthetic β peptide[192], etc.

In short, much has been done and much remains to be done. Well designed RCTs are needed for a more clear conclusion in many treatment modalities that are in debate. Some agents that have not been effective for advanced HCC may still be tried in the prevention of metastases and recurrence with a much smaller tumor burden. In the 21st century, prevention is doubtlessly of prime importance, however, detection of small HCC and studies on HCC invasiveness remain critical issues for further improvement of prognosis of HCC.

REFERENCES

1   Pisani P, Parkin M, Bray F, Ferlay J. Estimsates of the worldwide moratlty from 25 Cancers in 1990. *Int J Cancer*, 1999;83:18-29
2   Tominaga S, Kuroishi T, Aoki K (UICC)(eds). *Cancer* mortality statistics in 33 countries 1953-1992. Nagoya: Roppo Shupan Co., 1998:69
3   Taylor-Robinson SD, Foster GR, Arora S, Hargreaves S, Thomas HC. Increase in primary liver *Cancer* in the UK, 1979-1994. *Lancet*, 1997;350:1142-1143
4   El Serag HB, Mason AC. Rising incidence of hepatocellular carcinoma in the United States. *N Engl J Med*, 1999;340:745-750
5   Landis SH, Murray T, Bolden S, Wingo PA. *Cancer* statistics, 1998. *Ca-Cancer J Clin*, 1998;48:6-29
6   Jin F, Xiang YB, Gao YT. Cancer survival in Shanghai, People's Republic of China. In Sankaranaryanan R, Black RJ, Parkin DM (eds) Cancer survival in developing countries. IARC scientific publications No. 145. Lyon: International Agency for Research on Cancer. 1998: 37-50
7   Zhang JY, Dai M, Wang X, Lu WQ, Li DS, Zhang MX, Wang KJ, Dai LP, Han SG, Zhou YF, Zhuang H. A case-control study of hepatitis B and C virus infection as risk factors for hepatocellular carcinoma in Henan, China. *Int J Epidemiol*, 1998;27:574-578
8   Tsai JF, Jeng JE, Ho MS, Chang WY, Hsieh MY, Lin ZY, Tsai JH. Effect of hepatitis C and B virus infection on risk of hepatocellular carcinoma: a prospective study. *Br J Cancer*, 1997;76:968-974
9   Bruno S, Silini E, Crosignani A, Borzio F, Leandro G, Bono F, Asti M, Rossi S, Larghi A, Cerino A, Podda Mondelli MU. Hepatitis C virus genotypes and risk of hepatocellular carcinoma in cirrhosis: a prospective study. *Hepatology*, 1997;25:754-758
10 Tanaka H, Tsukuma H, Yamano H, Okubo Y, Inoue A, Kasahara A, Hayashi N. Hepatitis C virus 1b (II) infection and development of chronic hepatitis, liver cirrhosis and hepatocellular carcinoma: a case-control study in Japan. *J*

Epidemiol, 1998;8:244-249

11 Tagger A, Donato F, Ribero ML, Chiesa R, Portera G, Gelatti U, Albertini A, Fasola M, Boffetta P, Nardi G. Case-control study on hepatitis C virus (HCV) as a risk factor for hepatocellular carcinoma: the role of HCV genotypes and the synergism with hepatitis B virus and alcohol. Brescia HCC Study. *Int J Cancer*, 1999;81:695-699

12 Tarao K, Rino Y, Ohkawa S, Shimizu A, Tamai S, Miyakawa K, Aoki H, Imada T, Shindo K, Okamoto N, Totsuka S. Association between high serum alanine aminotransferase levels and more rapid development and higher rate of incidence of hepatocellular carcinoma in patients with hepatitis C virus-associated cirrhosis. *Cancer*, 1999;86:589-595

13 Moriya K, Fujie H, Shintani Y, Yotsuyanagi H, Tsutsumi T, Ishibashi K. The core protein of hepatitis C virus induces hepatocellular carcinoma in transgenic mice. *Nature Med*, 1998;4:1065-1067

14 Lightfoot K, Skelton M, Kew MC, Yu MC, Kedda MA, Coppin A, Hodkinson J. Does hepatitis GB virus-C infection cause hepatocellular carcinoma in black Africans? *Hepatology*, 1997;26:740-742

15 Kanda T, Yokosuka O, Imazeki F, Tagawa M, Ehata T, Saisho H, Omata M. GB virus-C RNA in Japanese patients with hepatocellular carcinoma and cirrhosis. *J Hepatol*, 1997;27:464-469

16 Cao K, Mizokami M, Orito E, Ding X, Ueda R, Chen G, Yu SZ, Tokudome S. GB virus C/hepatitis G virus infection among patients with hepatocellular carcinoma in the inshore area of the Yangtze River, China. *J Gastroenterol Hepatol*, 1998;13:1241-1248

17 Hollingsworth RC, Minton EJ, Fraser Moodie C, Metivier E, Rizzi PM, Irving WL, Jenkins D, Ryder SD. Hepatitis G infection: role in cryptogenic chronic liver disease and primary liver cell Cancer in the UK. Trent Hepatitis C virus Study Group. *J Viral Hepat*, 1998;5:165-169

18 Abe K, Edamoto Y, Park YN, Nomura AM, Taltavull TC, Tani M, Thung SN. In situ detection of hepatitis B, C, and G virus nucleic acids in human hepatocellular carcinoma tissues from different geographic regions. *Hepatology*, 1998;28:568-572

19 Tagger A, Donato F, Ribero ML, Binelli G, Gelatti U, Portera G, Albertini A, Fasola M, Chiesa R, Nardi G. A case-control study on a novel DNA virus (TT virus) infection and hepatocellular carcinoma. The Brescia HCC Study. *Hepatology*, 1999;30:294-299

20 Tagger A, Donato F, Ribero ML, Chiesa R, Tomasoni V, Portera G, Gelatti U, Albertini A, Fasola M, Nardi G. A case-control study on GB virus C/hepatitis G virus infection and hepatocellular carcinoma. Brescia HCC Study. *Hepatology*, 1997;26:1653-1657

21 Yuan JM, Govindarajan S, Ross RK, Yu MC. Chronic infection with hepatitis G virus in relation to hepatocellular carcinoma among non-Asians in Los Angeles County, California. *Cancer*, 1999;86:936-943

22 Nakagawa N, Ikoma J, Ishihara T, Yasui N, Fujita N, Iwasa M, Kaito M, Watanabe S, Adachi Y. High prevalence of transfusion-transmitted virus among patients with non-B, non-C hepatocellular carcinoma. *Cancer*, 1999;86:1437-1440

23 Sun Z, Lu P, Gail MH, Pee D, Zhang Q, Ming L, Wang J, Wu Y, Liu G, Wu Y, Zhu Y. Increased risk of hepatocellular carcinoma in male hepatitis B surface antigen carriers with chronic hepatitis who have detectable urinary aflatoxin metabolite M1. *Hepatology*, 1999;30:379-383

24 Kuper H, Tzonou A, Kaklamani E, Hsieh CC, Lagiou P, Adami HO, Trichopoulos D, Stuver SO. Tobacco smoking, alcohol consumption and their interaction in the causation of hepatocellular carcinoma. *Int J Cancer*, 2000;85:498-502

25 Mori M, Hara M, Wada I, Hara T, Yamamoto K, Honda M, Naramoto J. Prospective study of hepatitis B and C viral infections, cigarette smoking, alcohol consumption, and other factors associated with hepatocellular carcinoma risk in Japan. *Am J Epidemiol*, 2000;151:131-139

26 Donato F, Tagger A, Chiesa R, Ribero ML, Tomasoni V, Fasola M, Gelatti U, Portera G, Boffetta P, Nardi G. Hepatitis B and C virus infection, alcohol drinking, and hepatocellular carcinoma: a case-control study in Italy. Brescia HCC Study. *Hepatology*, 1997;26:579-584

27 Mandishona E, MacPhail AP, Gordeuk VR, Kedda MA, Paterson AC, Rouault TA, Kew MC. Dietary iron overload as a risk factor for hepatocellular carcinoma in Black Africans. *Hepatology*, 1998;27:1563-1566

28 Donato F, Gelatti U, Chiesa R, Albertini A, Bucella E, Boffetta P, Tagger A, Ribero ML, Portera G, Fasola M, Nardi G. A case-control study on family history of liver Cancer as a risk factor for hepatocellular carcinoma in North Italy. Brescia HCC Study. *Cancer* Causes Control, 1999;10:417-421

29 Lunn RM, Zhang YJ, Wang LY, Chen CJ, Lee PH, Lee CS, Tsai WY, Santella RM. p53 mutations, chronic hepatitis B virus infection, and aflatoxin exposure in hepatocellular carcinoma in Taiwan. *Cancer Res*, 1997;57:3471-3477

30 Ghebranious N, Sell S. Hepatitis B injury, male gender, aflatoxin, and p53 expression each contribute to hepatocarcinogenesis in transgenic mice. *Hepatology*, 1998;27:383-391

31 Yu DY, Moon HB, Son JK, Jeong S, Yu SL, Yoon H, Han YM, Lee CS, Park JS, Lee CH, Hyun BH, Murakami S, Lee KK. Incidence of hepatocellular carcinoma in transgenic mice expressing the hepatitis B virus X-protein. *J Hepatol*, 1999;31:123-132

32 Poussin K, Dienes H, Sirma H, Urban S, Beaugrand M, Franco D, Schirmacher P, Brechot C, Paterlini BP. Expression of mutated hepatitis B virus X genes in human hepatocellular carcinomas. *Int J Cancer*, 1999;80:497-505

33 Lee Y, Park US, Choi I, Yoon SK, Park YM, Lee YI. Human interleukin 6 gene is activated by hepatitis B virus-X protein in human hepatoma cells. *Clin Cancer Res*, 1998;4:1711-1717

34 Ono M, Morisawa K, Nie J, Ota K, Taniguchi T, Saibara T, Onishi S. Transactivation of transforming growth factor alpha gene by hepatitis B virus preS1. *Cancer Res*, 1998;58:1813-1816

35 Jakubczak JL, Chisari FV, Merlino G. Synergy between transforming growth factor alpha and hepatitis B virus surface antigen in hepatocellular proliferation and carcinogenesis. *Cancer Res*, 1997;57:3606-3611

36 Chang MH, Chen CJ, Lai MS, Hsu HM, Wu TC, Kong MS. Universal hepatitis?B vaccination in Taiwan and the incidence of hepatocellular carcinoma in children. *N Engl J Med*, 1997;336:1855-1859

37 Lee CL, Ko YC. Hepatitis B vaccination and hepatocellular carcinoma in Taiwan. *Pediatrics*, 1997;99:351-353

38 Yu SZ. Primary prevention of hepatocellular carcinoma. *J Gastroenterol Hepatol*, 1995;10:674-682

39 Kuwana K, Ichida T, Kamimura T, Ohkoshi S, Ogata N, Harada T, Endoh K, Asakura H. Risk factors and the effect of interferon therapy in the development of hepatocellular carcinoma: a multivariate analysis in 343 patients. *J Gastroenterol Hepatol*, 1997;12:149-155

40 Ikeda K, Saitoh S, Suzuki Y, Kobayashi M, Tsubota A, Fukuda M, Koida I, Arase Y, Chayama K, Murashima N, Kumada H. Interferon decreases hepatocellular?carcinogenesis in patients with cirrhosis caused by the hepatitis B virus: a pilot study. *Cancer*, 1998;82:827-835

41 Ikeda K, Saitoh S, Arase Y, Chayama K, Suzuki Y, Kobayashi M, Tsubota A, Nakamura I, Murashima N, Kumada H, Kawanishi M. Effect of interferon therapy on hepatocellular carcinogenesis in patients with chronic hepatitis type C: A long-term observation study of 1,643 patients using statistical bias correction with proportional hazard analysis. *Hepatology*, 1999;29:1124-1130

42 Everson CT, Jensen DM, Draig JR, VanLeeusen DJ, Bain VG, Ehrinpreis MN. Efficacy of interferon treatment for patients with chronic hepatitis C: comparison of response in cirrhosis, fibrosis, or nonfibrosis. *Hepatology*, 1999;30:271-276

43 Yoshida H, Shiratori Y, Moriyama M, Arakawa Y, Ide T, Sata M, Inoue O, Yano M, Tanaka M, Fujiyama S, Nishiguchi S, Kuroki T, Imazeki F, Yokosuka O, Kinoyama S, Yamada G, Omata M. Interferon therapy reduces the risk for hepatocellular carcinoma: national surveillance program of cirrhotic and noncirrhotic patients with chronic hepatitis C in Japan. IHIT Study Group. Inhibition of Hepatocarcinogenesis by Interferon Therapy. *Ann Intern Med*, 1999;131:174-181

44 Toyoda H, Kumada T, Nakano S, Takeda I, Sugiyama K, Kiriyama S, Sone Y, Hisanaga Y. The effect of retreatment with interferon-alpha on the incidence of hepatocellular carcinoma in patients with chronic hepatitis C. *Cancer*, 2000;88:58-65

45 Tang ZY. Hepatocellular carcinoma. *J Gastroenterol Hepatol*, 2000;15(Suppl):C1-8

46 Zhou XD, Tang ZY, Yang BH, Lin ZY, Ma ZC, Ye SL, Wu ZQ, Fan J, Qin LX, Zheng BH. Experience of 1000 patients who underwent hepatectomy for small hepatocellular carcinoma. *Cancer*, 2001;91:1479-1486

47 Takayama T, Makuuchi M, Hirohashi S, Sakamoto M,

Yamamoto J, Shimada K, Kosuge T, Okada S, Takayasu K, Yamasaki S. Early hepatocellular carcinoma as an entity with a high rate of surgical cure. *Hepatology*, 1998;28:1241-1246

48   Yuen MF, Cheng CC, Lauder IJ, Lam SK, Ooi CG, Lai CL. Early detection of hepatocellular carcinoma increases the chance of treatment: Hong Kong experience. *Hepatology*, 2000;31:330 -335

49   Makuuchi M, Takayama T, Kubota K, Kimura W, Midorikawa Y, Miyagawa S, Kawasaki S. Hepatic resection for hepatocellular carcinoma-Japanese experience. *Hepatogastroenterology*, 1998;45(Suppl 3):1267-1274

50   Tang ZY, Yu YQ, Zhou XD, Ma ZC, Wu ZQ. Progress and prospects in hepatocellular carcinoma surgery. *Ann Chir*, 1998; 52:558-563

51   Asahara T, Katayama K, Itamoto T, Yano M, Hino H, Okamoto Y, Nakahara H, Dohi K, Moriwaki K, Yuge O. Perioperative blood transfusion as a prognostic indicator in patients with hepatocellular carcinoma. *World J Surg*, 1999;23:676-680

52   Ikeda Y, Shimada M, Hasegawa H, Gion T, Kajiyama K, Shirabe K, Yanaga K, Takenaka K, Sugimachi K. Prognosis of hepatocellular carcinoma with diabetes mellitus after hepatic resection. *Hepatology*, 1998;27:1567-1571

53   Picardo A, Karpoff HM, Ng B, Lee J, Brennan MF, Fong Y. Partial hepatectomy accelerates local tumor growth: potential roles of local cytokine activation. *Surgery*, 1998;124:57-64

54   Fan J, Tang ZY, Yu YQ, Wu ZQ, Ma ZC, Zhou XD, Zhou J, Qiu SJ, Lu JZ. Improved survival with resection after transcatheter arterial chemoembolization (TACE) for unresectable hepatocellular carcinoma. *Dig Surg*, 1998;15:674-678

55   Tang ZY, Yu YQ, Zhou XD, Ma ZC, Lu JZ, Lin ZY, Liu KD, Ye SL, Yang BH, Wang HW, Sun HC. Cytoreduction and sequential resection for surgically verified unresectable hepatocellular carcinoma-evaluation with analysis of 72 patients. *World J Surg*, 1995;19:784-789

56   Klintmalm GB. Liver transplantation for hepatocellular carcinoma: a registry report of the impact of tumor characteristics on outcome. *Ann Surg*, 1998;228:479-490

57   Yamamoto J, Iwatsuki S, Kosuge T, Dvorchik I, Shimada K, Marsh JW, Yamasaki S, Starzl TE. Should hepatomas be treated with hepatic resection or transplantation? *Cancer*, 1999; 86:1151-1158

58   Llovet JM, Fuster J, Bruix J. Intention-to-treat analysis of surgical treatment for early hepatocellular carcinoma: resection versus transplantation. *Hepatology*, 1999;30:1434-1440

59   Otto G, Heuschen U, Hofmann WJ, Krumm G, Hinz U, Herfarth C. Survival and recurrence after liver transplantation versus liver resection for hepatocellular carcinoma: a retrospective analysis. *Ann Surg*, 1998;227:424-432

60   Pichlmayr R, Weimann A, Oldhafer KJ, Schlitt HJ, Tusch G, Raab R. Appraisal of transplantation for malignant tumours of the liver   with special reference to early stage hepatocellular carcinoma. *Eur J Surg Oncol*, 1998;24:60-67

61   Sarasin FP, Giostra E, Mentha G, Hadengue A. Partial hepatectomy or orthotopic liver transplantation for the treatment of resectable hepatocellular carcinoma A cost-effectiveness perspective. *Hepatology*, 1998;28:436-442

62   Simonetti RG, Liberati A, Angiolini C, Pagliaro L. Treatment of hepatocellular carcinoma: a systematic review of randomized controlled trials. *Ann Oncol*, 1997;8:117-136

63   Mathurin P, Rixe O, Carbonell N, Bernard B, Cluzel P, Bellin MF, Khayat D, Opolon P, Poynard T. Review article: Overview of medical treatments in unresectable hepatocellular carcinoma-an impossible meta-analysis? *Aliment Pharmacol Ther*, 1998;12: 111-126

64   Bruix J, Llovet JM, Castells A, Montana X, Bru C, Ayuso MC, Vilana R, Rodes J. Transarterial embolization versus symptomatic treatment in patients with advanced hepatocellular carcinoma: results of a randomized, controlled trial in a single institution. *Hepatology*, 1998;27:1578-1583

65   Pelletier G, Ducreux M, Gay F, Luboinski M, Hagege H, Dao T, Van Steenbergen W, Buffet C, Rougier P, Adler M, Pignon JP, Roche A. Treatment of unresectable hepatocellular carcinoma with lipiodol chemoembolization: a multicenter randomized trial. Groupe CHC. *J Hepatol*, 1998;29:129-134

66   Raoul JL, Guyader D, Bretagne JF, Heautot JF, Duvauferrier R, Bourguet P, Bekhechi D, Deugnier YM, Gosselin M. Prospective randomized trial of chemoembolization versus intra-arterial injection of ^{131}I-labeled-iodized oil in the treatment of hepatocellular carcinoma. *Hepatology*, 1997;26:1156-1161

67   Abe S, Okubo Y, Ejiri Y, Kume K, Otsuki M. Focal therapeutic efficacy of transcatheter arterial infusion of styrene maleic acid neocarzinostatin for hepatocellular carcinoma. *J Gastroenterol*, 2000;35:28-33

68   Ernst O, Sergent G, Mizrahi D, Delemazure O, Paris JC, Lhermin * C. Treatment of hepatocellular carcinoma by transcatheter arterial chemoembolization: comparison of planned periodic chemoembolization and chemoembolization based on tumor response. *Am J Roentgenol*, 1999;172:59-64

69   Vogl TJ, Trapp M, Schroeder H, Mack M, Schuster A, Schmitt J, Neuhaus P, Felix R. Transarterial chemoembolization for hepatocellular carcinoma: volumetric and morphologic CT criteria for assessment of prognosis and therapeutic success-results from a liver transplantation center. *Radiology*, 2000;214: 349-357

70   Sakamoto I, Aso N, Nagaoki K, Matsuoka Y, Uetani M, Ashizawa K, Iwanaga S, Mori M, Morikawa M, Fukuda T, Hayashi K, Matsunaga N. Complications associated with transcatheter arterial embolization for hepatic tumors. *Radiographics*, 1998;18:605-619

71   Lin SM, Lin DY, Lin CJ. Percutaneous ethanol injection therapy in 47 cirrhotic patients with hepatocellular carcinoma 5cm or less: a long-term result. *Int J Clin Pract*, 1999;53:257-262

72   Hasegawa S, Yamasaki N, Hiwaki T, Sako K, Komorizono Y, Baba Y, Imamura Y, Kubozono O, Yoshida A, Arima T. Factors that predict intrahepatic recurrence of hepatocellular carcinoma in 81 patients initially treated by percutaneous ethanol injection. *Cancer*, 1999;86:1682-1690

73   Livraghi T, Benedini V, Lazzaroni S, Meloni F, Torzilli G, Vettori C. Long-term results of single session percutaneous ethanol injection in patients with large hepatocellular carcinoma. *Cancer*, 1998;83:48-57

74   Ohnishi K. Comparison of percutaneous acetic acid injection and percutaneous ethanol injection for small hepatocellular carcinoma. *Hepatogastroenterology*, 1998;45(Suppl 3):1254-1258

75   Seki T, Wakabayashi M, Nakagawa T, Imamura M, Tamai T, Nishimura A, Yamashiki N, Okamura A, Inoue K. Percutaneous microwave coagulation therapy for patients with small hepatocellular carcinoma: comparison with percutaneous ethanol injection therapy. *Cancer*, 1999;85:1694-1702

76   Ohmoto K, Tsuduki M, Shibata N, Takesue M, Kunieda T, Yamamoto S. Percutaneous microwave coagulation therapy for hepatocellular carcinoma located on the surface of the liver. *Am J Roentgenol*, 1999;173:1231-1233

77   Dong BW, Liang P, Yu XL, Zeng XQ, Wang PJ, Su L, Wang XD, Xin H, Li S. Sonographically guided microwave coagulation treatment of liver *Cancer*: an experimental and clinical study. *Am J Roentgenol*, 1998;171:449-454

78   Nagata Y, Hiraoka M, Nishimura Y, Masunaga S, Mitumori M, Okuno Y, Fujishiro M, Kanamori S, Horii N, Akuta K, Sasai K, Abe M, Fukuda Y. Clinical results of radiofrequency hyperthermia for malignant liver tumors. *Int J Radiat Oncol Biol Phys*, 1997;38:359-365

79   Livraghi T, Goldberg SN, Lazzaroni S, Meloni F, Solbiati L, Gazelle GS. Small hepatocellular carcinoma: treatment with radio-frequency ablation versus ethanol injection. *Radiology*, 1999;210:655-661

80   Cheng SH, Lin YM, Chuang VP, Yang PS, Cheng JC, Huang AT, Sung JL. A pilot study of three-dimensional conformal radiotherapy in unresectable hepatocellular carcinoma. *J Gastroenterol Hepatol*, 1999;14:1025-1033

81   Lau WY, Ho S, Leung TW, Chan M, Ho R, Johnson PJ, Li AK. Selective internal radiation therapy for nonresectable hepatocellular carcinoma with intraarterial infusion of 90yttrium microspheres. *Int J Radiat Oncol Biol Phys*, 1998;40:583-592

82   Zeng ZC, Tang ZY, Liu KD, Lu JZ, Xie H, Yao Z. Improved long-term survival for unresectable hepatocellular carcinoma (HCC) with a combination of surgery and intrahepatic arterial infusion of ^{131}I-anti-HCC mAb. Phase I/II clinical trials. *J Cancer Res Clin Oncol*, 1998;124:275-280

83   Chao Y, Chan WK, Birkhofer MJ, Hu OY, Wang SS, Huang YS, Liu M, Whang Peng J, Chi KH, Lui WY, Lee SD. Phase II and pharmacokinetic study of paclitaxel therapy for unresectable hepatocellular carcinoma patients. *Br J Cancer*, 1998;78:34-39

84   Leung TW, Patt YZ, Lau WY, Ho SK, Yu SC, Chan AT, Mok TS, Yeo W, Liew CT, Leung NW, Tang AM, Johnson PJ. Complete pathological remission is possible with systemic combination chemotherapy for inoperable hepatocellular carcinoma. *Clin Cancer Res*, 1999;5:1676-1681

85   Takeuchi A, Kaneko S, Matsushita E, Urabe T, Shimoda A, Kobayashi K. Interferonalpha modulates resistance to cisplatin in

three human hepatoma cell lines. *J Gastroenterol*, 1999;34:351-358

86   Ishikawa T, Ichida T, Ishimoto Y, Yokoyama J, Nomoto M, Ebe Y, Usuda H, Naito M, Asakura H. Complete remission of multiple hepatocellular carcinomas associated with hepatitis C virus-related, decompensated liver cirrhosis by oral administration of enteric coated tegafur/uracil. *Am J Gastroenterol*, 1999;94:1682-1685

87   Liu CL, Fan ST, Ng IO, Lo CM, Poon RT, Wong J. Treatment of advanced hepatocellular carcinoma with tamoxifen and the correlation with expression of hormone receptors: a prospective randomized study. *Am J Gastroenterol*, 2000;95:218-222

88   Castells A, Bruix J, Bru C, Ayuso C, Roca M, Boix L, Vilana R, Rodes J. Treatment of hepatocellular carcinoma with tamoxifen: a double-blind placebo-controlled trial in 120 patients. *Gastroenterology*, 1995;109:917-922

89   Riestra S, Rodriguez M, Delgado M, Suarez A, Gonzalez N, de la Mata M, Diaz G, Messner M, Fugarolas G, Rodrigo L. Tamoxifen does not improve survival of patients with advanced hepatocellular carcinoma. *J Clin Gastroenterol*, 1998;26:200-203

90   Liu CL, Fan ST, Ng IO, Lo CM, Poon RT, Wong J. Treatment of advanced hepatocellular carcinoma with tamoxifen and the correlation with expression of hormone receptors: a prospective randomized study. *Am J Gastroenterol*, 2000;95:218-222

91   Grimaldi C, Bleiberg H, Gay F, Messner M, Rougier P, Kok TC, Cirera L, Cervantes A, De Greve J, Paillot B, Buset M, Nitti D, Sahmoud T, Duez N, Wils J. Evaluation of antiandrogen therapy in unresectable hepatocellular carcinoma: results of a European Organization for Research and Treatment of Cancer multicentric double-blind trial. *J Clin Oncol*, 1998;16:411-417

92   Meyskens FL Jr, Jacobson J, Nguyen B, Weiss GR, Gandara DR, MacDonald JS. Phase II trial of oral beta-all trans-retinoic acid in hepatocellular carcinoma (SWOG- 9157). *Invest New Drugs*, 1998;16:171-173

93   Kouroumalis E, Skordilis P, Thermos K, Vasilaki A, Moschandrea J, Manousos ON. Treatment of hepatocellular carcinoma with octreotide: a randomised controlled study. *Gut*, 1998;42:442-447

94   Llovet JM, Sala M, Castells L, Suarez Y, Vilana R, Bianchi L, Ayuso C, Vargas V, Rodes J, Bruix J. Randomized controlled trial of interferon treatment for advanced hepatocellular carcinoma. *Hepatology*, 2000;31:54-58

95   Schuster MJ, Wu GY. Gene therapy for hepatocellular carcinoma-progress but many stones yet unturned. *Gastroenterology*, 1997;112:656-659

96   Ueki T, Nakata K, Mawatari F, Tsuruta S, Ido A, Ishikawa H, Nakao K, Kato Y, Ishii N, Eguchi K. Retrovirus-mediated gene therapy for human hepatocellular carcinoma transplanted in athymic mice. *Int J Mol Med*, 1998;1:671-675

97   Mawatari F, Tsuruta S, Ido A, Ueki T, Nakao K, Kato Y, Tamaoki T, Ishii N, Nakata K. Retrovirus-mediated gene therapy for hepatocellular carcinoma: selective and enhanced suicide gene expression regulated by human alpha-fetoprotein enhancer directly linked to its promoter. *Cancer Gene Ther*, 1998; 5:301-306

98   Uto H, Ido A, Hori T, Hirono S, Hayashi K, Tamaoki T, Tsubouchi H. Hepatomaspecific gene therapy through retrovirus-mediated and targeted gene transfer using an adenovirus carrying the ecotropic receptor gene. *Biochem Biophys Res Commun*, 1999;265:550-555

99   Harada Y, Iwai M, Tanaka S, Okanoue T, Kashima K, Maruyama Tabata H, Hirai H, Satoh E, Imanishi J, Mazda O. Highly efficient suicide gene expression in hepatocellular carcinoma cells by epstein-barr virus-based plasmid vectors combined with polyamidoamine dendrimer. *Cancer Gene Ther*, 2000; 7:27-36

100 Kuriyama S, Masui K, Kikukawa M, Sakamoto T, Nakatani T, Nagao S, Yamazaki M, Yoshiji H, Tsujinoue H, Fukui H, Yoshimatsu T, Ikenaka K. Complete cure of established murine hepatocellular carcinoma is achievable by repeated injections of retroviruses carrying the herpes simplex virus thymidine kinase gene. *Gene Ther*, 1999;6:525-533

101 Kawashita Y, Ohtsuru A, Kaneda Y, Nagayama Y, Kawazoe Y, Eguchi S, Kuroda H, Fujioka H, Ito M, Kanematsu T, Yamashita S. Regression of hepatocellular carcinoma *in vitro* and *in vivo* by radiosensitizing suicide gene therapy under the inducible and spatial control of radiation. *Hum Gene Ther*, 1999;10:1509-1519

102 He P, Tang ZY, Liu BB, Ye SL, Liu YK. The targeted expression of the human interleukin-2/interferon alpha2b fused gene in alpha-fetoprotein-expressing hepatocellular carcinoma

cells. *J Cancer Res Clin Oncol*, 1999;125:77-82

103 Anderson SC, Johnson DE, Harris MP, Engler H, Hancock W, Huang WM, Wills KN, Gregory RJ, Sutjipto Wen SF, Lofgren S, Shepard HM, Maneval DC. p53 gene therapy in a rat model of hepatocellular carcinoma: intra-arterial delivery of a recombinant adenovirus. *Clin Cancer Res*, 1998;4:1649-1659

104 Ohguchi S, Nakatsukasa H, Higashi T, Ashida K, Nouso K, Ishizaki M, Hino N, Kobayashi Y, Uematsu S, Tsuji T. Expression of alpha-fetoprotein and albumin genes in human hepatocellular carcinomas: limitations in the application of the genes for targeting human hepatocellular carcinoma in gene therapy. *Hepatology*, 1998;27:599-607

105 Cao G, Kuriyama S, Du P, Sakamoto T, Kong X, Masui K, Qi Z. Complete regression of established murine hepatocellular carcinoma by *in vivo* tumor necrosis factor alpha gene transfer. Gastroenterology, 1997;112:501-510

106 Kanai F, Lan KH, Shiratori Y, Tanaka T, Ohashi M, Okudaira T, Yoshida Y, Wakimoto H, Hamada H, Nakabayashi H, Tamaoki T, Omata M. *In vivo* gene therapy for alpha-Fetoprotein-producing hepatocellular carcinoma by adenovirus mediated transfer of cytosine deaminase gene. *Cancer Res*, 1997;57:461-465

107 Bui LA, Butterfield LH, Kim JY, Ribas A, Seu P, Lau R, Glaspy JA, McBride WH, Economou JS. *In vivo* therapy of hepatocellular carcinoma with a tumor-specific adenoviral vector expressing interleukin-2. *Hum Gene Ther*, 1997;8:2173-2182

108 Miyatake SI, Tani S, Feigenbaum F, Sundaresan P, Toda H, Narumi O, Kikuchi H, Hashimoto N, Hangai M, Martuza RL, Rabkin SD. Hepatoma-specific antitumor activity of an albumin enhancer/promoter regulated herpes simplex virus *in vivo*. *Gene Ther*, 1999;6:564-572

109 Suzuki K, Tsujitani S, Konishi I, Yamaguchi Y, Hirooka Y, Kaibara N. Expression of MAGE genes and survival in patients with hepatocellular carcinoma. *Int J Oncol*, 1999;15:1227-1232

110 Chen CH, Huang GT, Lee HS, Yang PM, Yan MD, Chen DS, Sheu JC. High frequency of expression of MAGE genes in human hepatocellular carcinoma. *Liver*, 1999;19:110-114

111 Kariyama K, Higashi T, Kobayashi Y, Nouso K, Nakatsukasa H, Yamano T, Ishizaki M, Kaneyoshi T, Toshikuni N, Ohnishi T, Fujiwara K, Nakayama E, Terracciano L, Spagnoli GC, Tsuji T. Expression of MAGE-1 and 3 genes and gene products in human hepatocellular carcinoma. *Br J Cancer*, 1999;81:1080-1087

112 Tahara K, Mori M, Sadanaga N, Sakamoto Y, Kitano S, Makuuchi M. Expression of the MAGE gene family in human hepatocellular carcinoma. *Cancer*, 1999;85:1234-1240

113 Liu BB, Ye SL, He P, Liu YK, Tang ZY. MAGE-1 and related MAGE gene expression may be associated with hepatocellular carcinoma. *J Cancer Res Clin Oncol*, 1999;125:685-689

114 DeMatos P, Abdel Wahab Z, Vervaert C, Seigler HF. Vaccination with dendritic cells inhibits the growth of hepatic metastases in B6 mice. *Cell Immunol*, 1998;185:65-74

115 Jin no K, Tanimizu M, Hyodo I, Nishikawa Y, Hosokawa Y, Endo H, Doi T, Mandai K, Ishitsuka H. Circulating platelet-derived endothelial cell growth factor increases in hepatocellular carcinoma patients. *Cancer*, 1998;82:1260-1267

116 Jinno K, Tanimizu M, Hyodo I, Nishikawa Y, Hosokawa Y, Doi T, Endo H, Yamashita T, Okada Y. Circulating vascular endothelial growth factor (VEGF) is a possible tumor marker for metastasis in human hepatocellular carcinoma. *J Gastroenterol*, 1998;33:376-382

117 Rivas MJ, Arii S, Furutani M, Harada T, Mizumoto M, Nishiyama H, Fujita J, Imamura M. Expression of human macrophage metalloelastase gene in hepatocellular carcinoma: correlation with angiostatin generation and its clinical \ significance. *Hepatology*, 1998;28:986-993

118 Ito Y, Matsuura N, Sakon M, Miyoshi E, Noda K, Takeda T, Umeshita K, Nagano H, Nakamori S, Dono K, Tsujimoto M, Nakahara M, Nakao K, Taniguchi N, Monden M. Expression and prognostic roles of the G1-Smodulators in hepatocellular carcinoma: p27 independently predicts the recurrence. *Hepatology*, 1999;30:90-99

119 Honda K, Sbis E, Tullo A, Papeo PA, Saccone C, Poole S, Pignatelli M, Mitry RR, Ding S, Isla A, Davies A, Habib NA. p53 mutation is a poor prognostic indicator for survival in patients with hepatocellular carcinoma undergoing surgical tumour ablation. *Br J Cancer*, 1998;77:776-782

120 Tannapfel A, Wasner M, Krause K, Geissler F, Katalinic A, Hauss J, Engeland K, Wittekind C. Expression of p73 and its

relation to histopathology and prognosis in hepatocellular carcinoma. *J Natl Cancer Inst*, 1999;91:1154-1158

121 Suda T, Isokawa O, Aoyagi Y, Nomoto M, Tsukada K, Shimizu T, Suzuki Y, Naito A, Igarashi H, Yanagi M, Takahashi T, Asakura H. Quantitation of telomerase activity in hepatocellular carcinoma:a possible aid for a prediction of recurrent diseases in the remnant liver. *Hepatology*, 1998;27:402-406

122 Paye F, Jagot P, Vilgrain V, Farges O, Borie D, Belghiti J. Preoperative chemoembolization of hepatocellular carcinoma: a comparative study. *Arch Surg*, 1998;133:767-772

123 Tanaka K, Shimada H, Togo S, Takahashi T, Endo I, Sekido H, Yoshida T. Use of transcatheter arterial infusion of anti Cancer agents with lipiodol to prevent recurrence of hepatocellular carcinoma after hepatic resection. *Hepatogastroenterology*, 1999; 46:1083-1088

124 Asahara T, Itamoto T, Katayama K, Ono E, Dohi K, Nakanishi T, Kitamoto M, Azuma K, Ito K. Adjuvant hepatic arterial infusion chemotherapy after radical hepatectomy for hepatocellular carcinoma-results of long-term follow-up. *Hepatogastroenterology*, 1999;46:1042-1048

125 Ueno S, Tanabe G, Yoshida A, Yoshidome S, Takao S, Aikou T. Postoperative prediction of and strategy for metastatic recurrent hepatocellular carcinoma according to histologic activity of hepatitis. *Cancer*, 1999;86:248-254

126 Huang YH, Wu JC, Lui WY, Chan GY, Tsay SH, Chiang JH, King KL, Huo TI, Chang FY, Lee SD. Prospective case-controlled trial of adjuvant chemotherapy after resection of hepatocellular carcinoma. *World J Surg*, 2000;24:551-555

127 Ono T, Nagasue N, Kohno H, Hayashi T, Uchida M, Yukaya H, Yamanoi A. Adjuvant chemotherapy with epirubicin and carmofur after radical resection of hepatocellular carcinoma: a prospective randomized study. *Semin Oncol*, 1997;24(Suppl 6):18-25

128 Lai EC, Lo CM, Fan ST, Liu CL, Wong J. Postoperative adjuvant chemotherapy after curative resection of hepatocellular carcinoma: a randomized controlled trial. *Arch Surg*, 1998; 133:183-188

129 Muto Y, Moriwaki H, Ninomiya M, Adachi S, Saito A, Takasaki KT, Tanaka T, Tsurumi K, Okuno M, Tomita E, Nakamura T, Kojima T. Prevention of second primary tumors by an acyclic retinoid, polyprenoic acid, in patients with hepato cellular carcinoma. Hepatoma Prevention Study Group. *N Engl J Med*, 1996;334:1561-1567

130 Muto Y, Moriwaki H, Saito A. Prevention of second primary tumors by an acyclic retinoid in patients with hepatocellular carcinoma (letter). *N Engl J Med*, 1999;340:1046-1047

131 Lau WY, Leung TW, Ho SK, Chan M, Machin D, Lau J, Chan AT, Yeo W, Mok TS, Yu SC, Leung NW, Johnson PJ. Adjuvant intra-arterial iodine-131-labelled lipiodol for resectable hepatocellular carcinoma: a prospective randomised trial. *Lancet*, 1999;353:797-801

132 Ueki T, Fujimoto J, Suzuki T, Yamamoto H, Okamoto E. Expression of hepatocyte growth factor and its receptor c-met proto-oncogene in hepatocellular carcinoma. *Hepatology*, 1997; 25:862-866

133 Kawate S, Fukusato T, Ohwada S, Watanuki A, Morishita Y. Amplification of c-myc in hepatocellular carcinoma: correlation with clinicopathologic features, proliferative activity and p53 overexpression. *Oncology*, 1999;57:157-163

134 Morita Y, Hayashi Y, Wang Y, Kanamaru T, Suzuki S, Kawasaki K, Ohta K, Yamamoto M, Saitoh Y, Itoh H, Doe WF. Expression of urokinase-type plasminogen activator receptor in hepatocellular carcinoma. *Hepatology*, 1997;25:856-861

135 Yamamoto H, Itoh F, Adachi Y, Sakamoto H, Adachi M, Hinoda Y, Imai K. Relation of enhanced secretion of active matrix metalloproteinases with tumor spread in human hepatocellular carcinoma. *Gastroenterology*, 1997;112:1290-1296

136 Ogata R, Torimura T, Kin M, Ueno T, Tateishi Y, Kuromatsu R, Shimauchi Y, Sakamoto M, Tamaki S, Sata M, Tanikawa K. Increased expression of membrane type 1 matrix metalloproteinase and matrix metalloproteinase-2 with tumor dedifferentiation in hepatocellular carcinomas. *Hum Pathol*, 1999;30:443-450

137 De Petro G, Tavian D, Copeta A, Portolani N, Giulini SM, Barlati S. Expression of urokinase-type plasminogen activator (u-PA), uPA receptor, and tissue-type PA messenger RNAs in human hepatocellular carcinoma. *Cancer Res*, 1998;58:2234-2239

138 Masumoto A, Arao S, Otsuki M. Role of beta1 integrins in adhesion and invasion of hepatocellular carcinoma cells. *Hepatology*, 1999;29:68-74

139 Torimura T, Ueno T, Kin M, Ogata R, Inuzuka S, Sugawara H, Kurotatsu R, Shimada M, Yano H, Kojiro Tanikawa K, Sata M. Integrin alpha-6-beta1 plays a significant role in the attachment of hepatoma cells to laminin. *J Hepatol*, 1999;31:734-740

140 Junbo H, Li Q, Zaide W, Yunde H. Increased level of serum hepatocyte growth factor/scatter factor in liver Cancer is associated with tumor metastasis. *In vivo*, 1999;13:177-180

141 Kanamaru T, Yamamoto M, Morita Y, Itoh T, Kuroda Y, Hisatomi H. Clinical implications of telomerase activity in resected hepatocellular carcinoma. *Int J Mol Med*, 1999;4:267-271

142 Shimada M, Hasegawa H, Gion T, Utsunomiya T, Shirabe K, Takenaka K, Otsuka T, Maehara Y, Sugimachi K. The role of activity in hepatocellular carcinoma. *Am J Gastroenterol*, 2000; 95:748-752

143 Le Bail B, Faouzi S, Boussarie L, Guirouilh J, Blanc JF, Carles J, Bioulac Sage P, Balabaud C, Rosenbaum J. Osteonectin/SPARC is overexpressed in human hepatocellular carcinoma. *J Pathol*, 1999;189:46-52

144 Huang GT, Lee HS, Chen CH, Sheu JC, Chiou LL, Chen DS. Correlation of E-cadherin expression and recurrence of hepatocellular carcinoma. *Hepatogastroenterology*, 1999;46:1923-1927

145 Guo XZ, Friess H, Di Mola FF, Heinicke JM, Abou Shady M, Graber HU, Baer HU, Zimmermann A, Korc M. KAI1, a new metastasis suppressor gene, is reduced in metastatic hepatocellular carcinoma. *Hepatology*, 1998;28:1481-1488

146 Ohtake T, Fujimoto Y, Ikuta K, Saito H, Ohhira M, Ono M, Kohgo Y. Proline-rich antimicrobial peptide, PR-39 gene transduction altered invasive activity and actin structure in human hepatocellular carcinoma cells. *Br J Cancer*, 1999;81:393-403

147 Lin LI, Lee PH, Wu CM, Lin JK. Significance of nm23 mRNA expression in human hepatocellular carcinoma. *AntiCancer Res*, 1998;18:541-546

148 Hui AM, Li X, Makuuchi M, Takayama T, Kubota K. Over-expression and lack of retinoblastoma protein are associated with tumor progression and metastasis in hepatocellular carcinoma. *Int J Cancer*, 1999;84:604-608

149 Shen L, Fang J, Qiu D, Zhang T, Yang J, Chen S, Xiao S. Correlation between DNA methylation and pathological changes in human hepatocellular carcinoma. *Hepatogastroenterology*, 1998; 45:1753-1759

150 Ozaki I, Yamamoto K, Mizuta T, Kajihara S, Fukushima N, Setoguchi Y, Morito F, Sakai T. Differential expression of laminin receptors in human hepatocellular carcinoma. *Gut*, 1998;43: 837-842

151 Wang XM, Tang ZY, Xue Q, Hong XY, Bao WH, Zou HQ. Transforming growth?factor a induces proliferation and expression of epidermal growth factor receptor in hepatocellular carcinoma cells. *J Exp Clin Cancer Res*, 1995;14:179-184

152 Qin LX, Tang ZY, Liu KD, Ye SL, Zhou G. p53 mutations may be related to tumor invasiveness of human hepatocellular carcinoma in China. *Oncol Reo*, 1995;2:1175-1179

153 Jiang XP, Tang ZY, Liu KD, Zhou XD, Lin ZY, Ling MY, Wu XF. mRNA levels of nm23 in murine ascites hepatoma (H22) clones with different lymphatic metastatic potential. *J Cancer Res Clin Oncol*, 1996;122:55-58

154 Qin LX, Tang ZY, Liu KD, Ye SL, He B, Zhang Y, Zhou G. Alterations of CDKN2 (P16/MTS1) exon 2 in human hepatocellular carcinoma. *Oncol Rep*, 1996;3:405-408

155 Yao M, Zhou XD, Zha XL, Shi DR, Fu J, He JY, Lu HF, Tang ZY. Expression of the integrin a5 subunit and its mediated cell adhesion in hepatocellular carcinoma. *J Cancer Res Clin Oncol*, 1997;123:435-440

156 Qiu SJ, Ye SL, Wu ZQ, Tang ZY, Liu YK. The expression of the mdm2 gene may be related to the aberration of the p53 gene in human hepatocellular carcinoma. *J Cancer Res Clin Oncol*, 1998; 124:253-258

157 Sun HC, Tang ZY, Zhou G, Li XM. Kai-1 gene expression in hepatocellular carcinoma and its relationship with intrahepatic metastases. *J Exp Clin Cancer Res*, 1998;17:307-311

158 Zheng XY, Ling ZY, Tang ZY, Liu YK, Feng XL, Zhuang W. The abundance of NM23-H1 mRNA is related with insitu microenvironment and intrahepatic metastasis in hepatocellular carcinoma. *J Exp Clin Cancer Res*, 1998;17:337-341

159 Sun JJ, Zhou XD, Liu YK, Tang ZY, Feng JX, Zhou G, Xue Q, Chen J. Invasion and metastasis of liver Cancer: expression of

intercellular adhesion molecule 1. *J Cancer Res Clin Oncol*, 1999;125:28-34

160 Shao DM, Wang QH, Chen C, Shen ZH, Yao M, Zhou XD, Tang ZY, Gu JX. N-Actylglucosaminyltransferase V activity in metastatic models of human hepatocellular carcinoma in nude mice. *J Exp Clin Cancer Res*, 1999;18:331-335

161 Zheng Q, Tang ZY, Xue Q, Shi DR, Song HY, Tang HB. Invasion and metastasis of hepatocellular carcinoma in relation to urokinase-type plasminogen activator, its receptor and inhibitor. *J Cancer Res Clin Oncol,* 2000;126:641-646

162 Tang ZY, Qin LX, Wang XM, Zhou G, Liao Y, Weng Y, Jiang XP, Lin ZY, Liu KD, Ye SL. Alterations of oncogenes, tumor suppressor genes and growth factors in hepatocellular carcinoma: with relation to tumor size and invasiveness. *Chin Med J*, 1998; 111:313-318

163 Tang ZY, Zhou XD, Lin ZY, Yaang BH, Ma ZC, Ye SL, Wu ZQ, Fan J, Liu YK, Liu KD, Qin LX, Tian J, Sun HC, He B, Xia JL, Qiu SJ, Zhou J. Surgical treatment of hepatocellular carcinoma and related basic research with special reference to recurrence and metastasis. *Chin Med J*, 1999;112:887-891

164 Tang ZY. Surgery of hepatocellular carcinoma with special reference to studies on metastasis and recurrence. *Gastroenterol Today*, 2000;4:191-195

165 Qin LX, Tang ZY, Sham JST, Ma ZC, Ye SL, Zhou XD, Wu ZQ, Trent JM, Guan XY. The association of chromosome 8p deletion and tumor metastasis in human hepatocellular carcinoma. *Cancer Res*, 1999;59:5662-5665

166 Pineau P, Nagai H, Prigent S, Wei Y, Gyapay G, Weissenbach J, Tiollais P, Buendia MA, Dejean A. Identification of three distinct regions of allelic deletions on the short arm of chromosome 8 in hepatocellular carcinoma. *Oncogene*, 1999;18:3127-3134

167 Yuan BZ, Miller MJ, Keck CL, Zimonjic DB, Thorgeirsson SS, Popescu NC. Cloning, characterization, and chromosomal localization of a gene frequently deleted in human liver Cancer (DLC-homologous to rat RhoGAP. *Cancer Res*, 1998;58:2196-2199

168 Sun FX, Tang ZY, Liu KD, Ye SL, Xue Q, Gao DM, Ma ZC. Establishment of a metastatic model of human hepatocellular carcinoma in nude mice via orthotopic implantation of histologically intact tissues. *Int J Cancer*, 1996;66:239-243

169 Tian J, Tang ZY, Ye SL, Liu YK, Lin ZY, Chen J, Xue Q. New human hepatocellular carcinoma (HCC) cell line with highly metastatic potential (MHCC97) and its expression of the factors associated with metastasis. *Br J Cancer*, 1999;81:814-821

170 Sun HC, Li XM, Xue Q, Chen J, Gao DM, Tang ZY. Study of angiogenesis induced by metastatic and non-metastatic liver Cancer by corneal micropocket model in nude mice. *World J Gastroenterol*, 1999;5:116-118

171 Masui T, Nakanishi H, Inada K, Imai T, Mizoguchi Y, Yada H, Futakuchi?M, Shirai T, Tatematsu M. Highly metastatic hepatocellular carcinomas induced in male F344 rats treated with N-nitrosomorpholine in combination with other hepatocarcinogens show a high incidence of p53 gene mutations along with altered mRNA expression of tumor-related genes. *Cancer Lett*, 1997;112:33-45

172 Li HF, Ling MY, Xie Y, Xie H. Establishment of a lymph node metastatic model of mouse hepatocellular carcinoma Hca-F cells in C3H/Hej mice. *Oncol Res*, 1998;10:569-573

173 Li XM, Tang ZY, Zhou G, Lui YK, Ye SL. Significance of vascular endothelial growth factor mRNA expression in invasion and metastasis of hepatocellular carcinoma. *J Exp Clin Cancer Res*, 1998;17:13-17

174 Li XM, Tang ZY, Qin LX, Zhou J, Sun HC. Serum vascular endothelial growth factor is a predictor of invasion and metastasis in hepatocellular carcinoma. *J Exp Clin Cancer Res*, 1999; 18:511-517

175 Miura H, Miyazaki T, Kuroda M, Oka T, Machinami R, Kodama T, Shibuya M, Makuuchi M, Yazaki Y, Ohnishi S. Increased expression of vascular endothelial growth factor in human hepatocellular carcinoma. *J Hepatol*, 1997;27:854-861

176 Torimura T, Sata M, Ueno T, Kin M, Tsuji R, Suzaku K, Hashimoto O, Sugawara H, Tanikawa K. Increased expression of vascular endothelial growth factor is associated with tumor progression in hepatocellular carcinoma. *Hum Pathol*, 1998;29: 986-991

177 El Assal ON, Yamanoi A, Soda Y, Yamaguchi M, Igarashi M, Yamamoto A, Nabika T, Nagasue N. Clinical significance of microvessel density and vascular endothelial growth factor expression in hepatocellular carcinoma and surrounding liver: possible involvement of vascular endothelial growth factor in the angiogenesis of cirrhotic liver. *Hepatology*, 1998;27:1554-1562

178 Suzuki H, Mori M, Kawaguchi C, Adachi M, Miura S, Ishii H. Serum vascular endothelial growth factor in the course of transcatheter arterial embolization of hepatocellular carcinoma. *Int J Oncol*, 1999;14:1087-1090

179 Gorrin Rivas MJ, Arii S, Mori A, Takeda Y, Mizumoto M, Furutani M, Imamura M. Implications of human macrophage metalloelastase and vascular endothelial growth factor gene expression in angiogenesis of hepatocellular carcinoma. *Ann Surg*, 2000;231:67-73

180 Zhou J, Tang ZY, Fan J, Wu ZQ, Li XM, Liu YK, Liu F, Sun HC, Ye SL. Expression of platelet-derived endothelial cell growth factor and vascular endothelial growth factor in hepatocellular carcinoma and portal vein tumor thrombus. *J Cancer Res Clin Oncol*, 2000;126:57-61

181 Tanaka S, Mori M, Sakamoto Y, Makuuchi M, Sugimachi K, Wands JR. Biologic significance of angiopoietin-2 expression in human hepatocellular carcinoma. *J Clin Invest*, 1999;103:341-345

182 Tanigawa N, Lu C, Mitsui T, Miura S. Quantitation of sinusoid-like vessels in hepatocellular carcinoma: its clinical and prognostic significance. *Hepatology*, 1997;26:1216-1223

183 Kimura H, Nakajima T, Kagawa K, Deguchi T, Kakusui M, Katagishi T, Okanoue T, Kashima K, Ashihara T. Angiogenesis in hepatocellular carcinoma as evaluated by CD34 immunohistochemistry. *Liver*, 1998;18:14-19

184 Sun HC, Tang ZY, Li XM, Zhou YN, Sun BR, Ma ZC. Microvessel density of hepatocellular carcinoma: its relationship with prognosis. *J Cancer Res Clin Oncol*, 1999;125:419-426

185 Nakashima Y, Nakashima O, Hsia CC, Kojiro M, Tabor E. Vascularization of small hepatocellular carcinomas: correlation with differentiation. *Liver*, 1999;19:12-18

186 Xia JL, Yang BH, Tang ZY, Sun FX, Xue Q, Gao DM. Inhibitory effect of the angiogenesis inhibitor TNP-470 on tumor growth and metastasis in nude mice bearing human hepatocellular carcinoma. *J Cancer Res Clin Oncol*, 1997;123:383-387

187 Kin M, Torimura T, Ueno T, Nakamura T, Ogata R, Sakamoto M, Tamaki S, Sata M. Angiogenesis inhibitor TNP-470 suppresses the progression of experimentally-induced hepatocellular carcinoma in rats. *Int J Oncol*, 2000;16:375-382

188 Wang L, Tang ZY, Qin LX, Wu XF, Sun HC, Xue Q, Ye SL. High-dose and long-term therapy with interferon-alfa inhibits tumor growth and recurrence in nude mice bearing human hepatocellular carcinoma xenografts with high metastatic potential. *Hepatology*, 2000;32:43-48

189 Bu W, Tang ZY, Sun FX, Ye SL, Liu KD, Xue Q, Chen J, Gao DM. Effects of matrix metalloproteinase inhibitor BB-94 on liver Cancer growth and metastasis in a patient-like orthotopic model LCI-D20. *Hepato-Gastroenterol*, 1998;45:1056-1061

190 Murakami K, Matsuura T, Sano M, Hashimoto A, Yonekura K, Sakukawa R, Yamada Y, Saiki I. 4-[3,5 Bis (trimethylsilyl) benzamido] benzoic acid (TAC-101) inhibits the intrahepatic spread of hepatocellular carcinoma and prolongs the life span of tumor-bearing animals. *Clin Exp Metastasis*, 1998;16:633-643

191 Liao Y, Tang ZY, Ye SL, Liu KD, Sun FX, Huang Z. Modulation of apoptosis, tumorigenesity and metastatic potential with antisense H-ras oligodeoxynucleotides in a high metastatic tumor model of hepatoma: LCI-D20. *Hepatogastroenterology*, 2000;47:365-370

192 Sun JJ, Zhou XD, Liu YK, Tang ZY, Sun RX, Zhao Y, Uemura T. Inhibitory effects of synthetic β peptide on invasion and metastasis of liver Cancer. *J Cancer Res Clin Oncol*, 2000; 126:595-600

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