Hepatocellular Carcinoma-Cause, Treatment and Metastasis

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Received 2001-07-13 Accepted 2001-07-13

INTRODUCTION

Liver cancer is the 4th most common cause of death from cancer, the highest age-standardised mortality rate is in China (34.7/105, 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%. 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.

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. In Italy, for attributable risk (AR) of HCC, heavy alcohol intake ranked first (45%), HCV second (36%) and HBV third (22%). The risk of dietary iron overload was 4.1 for HCC in black Africans, 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.

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. 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.

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. 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. Moreover, HBV-X might play a role in hepatic inflammation by up-regulating interleukin-6 production, which can eventually lead to HCC. Transactivation of the transforming growth factor alpha (TGF-alpha) gene by HBV preS1 was observed which provides a clue for understanding the viral hepatocarcinogenesis. Synergy between TGF-alpha and HBsAg in hepatic cellular proliferation and carcinogenesis was also reported.

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. A significant declining trend of HCC mortality rate ratios was observed in the vaccination group, but not in the reference group.

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. 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. 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. IFN therapy also decreased the development of HCC related HCC. HCC rates in the IFN treated and untreated groups were 7.6% and 12.4% at the 10th year respectively. Patients with HCV-related cirrhosis also benefit from IFN treatment. IFN therapy significantly reduces the risk for HCC, especially among virologic or biochemical responders of patients with chronic hepatitis C. 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. 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. 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%. 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.

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

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%. Another 65 patients with unresectable HCC down-staged by transcatheater arterial chemoembolization (TACE) followed by resection, the 5-year survival was 56.0%. 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[63]. 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 hepectomy (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-Fluourouracil, 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 131I-labeled lipiodol (2.2 Gbq) was 10% when compared with 0% in TACE group (70mg cisplatin)[66]. Another RCT indicated that styrne 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[70]. 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%)[73]. PMCT is difficult for small HCC on the surface of liver, however, PMCT can be performed safely in such patients[73]. After PMCT, a second biopsy on 19 patients showed complete destruction of tumor in 18 patients[73].

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%[75]. 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[75].

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\[90\]. 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\[91\]. At the author’s institution, long-term follow-up study indicated that a combination of surgery and intrahepatic arterial infusion of 131I-anti-HCC mAb improved survival of unresectable HCC\[92\].

**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/m² q3w) for unresectable HCC\[93\]. 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\[94\]. 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\[95\]. 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\[96\].

**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\[97-99\]. A lack of efficacy of antiandrogen treatment was found for unresectable HCC in a RCT\[100\]. Oral beta all transretinoic acid (50mg/m² t.i.d.) was also ineffective against HCC\[101\]. Interestingly, Octreotide, a somatostatin analogue, improves survival of inoperable HCC in another RCT\[102\]. Randomized controlled trial of interferon treatment for advanced HCC indicated that its administration prompts no benefit in terms of tumor progression rate and survival\[103\].

**Gene therapy—“progress but many stone yet unturned”**

Gene therapy for HCC remains an attractive field. Experimental studies using cytokine genes (tumor necrosis factor, interleukin-2, interferon), suicide and p53 genes; using retrovirus, adenovirus and Epstein-barr virus as vectors; using AFP enhancer; using intraarterial administration, etc. have been reported\[96,100\]. Data from both the literature\[100-102\] and from the author’s institution\[103\] demonstrated that human melanoma 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\[104\].

**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\[105-107\], human macrophage metalloelastase gene\[108\], p27\[109\], p53 mutation\[110\], expression of p73\[111\], telomerase activity\[112\], 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\[113\]. Although many authors supported the strategy of postoperative chemoembolization, its effectiveness might be due to suppression of intrahepatic micrometastases rather than multicentric carcinogenesis\[114\]. Postoperative intraarterial chemotherapy has also been claimed to improve survival\[115,116\]. Recently, a RCT showed that postoperative adjuvant systemic chemotherapy using epirubicin and mitomycin C has a tendency to reduce recurrence rate\[117\]. However, two RCTs failed to demonstrate the effectiveness of postoperative adjuvant therapy. The adjuvant chemotherapy with epirubicin and carmuste after radical resection of HCC was not effective\[118\]. Postoperative chemotherapy using intravenous epirubicin and intraarterial iodized oil and cisplatin was associated with more frequent extrahepatic recurrences and a worse outcome\[119\]. Interestingly, a RCT revealed that oral polyphenolic acid prevents second primary HCC after surgical resection, and reconfirmed after longer follow-up study\[120,121\]. Recently, a RCT study indicated that a single 1850 MBq dose of intraarterial 131I-lipiodol increased the 3-year overall survival from 46.3% in the control to 86.4% in the treatment group\[122\].

**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\[123-125\]. 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, TGFβ, 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. The biological characteristics of small HCC was slightly better than that of large HCC. The following blood test have been tried with potential clinical implication: thrombomodulin, ICAM-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[160]. The presence of at least three novel tumor suppressor loci on 8p in HCC was reported[165], 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 angiogenic 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 another 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%,[180]. 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 inhibit 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.

**ACKNOWLEDGEMENT**

The author express sincere gratitude to Professor W. Y. Lau, Department of Surgery, The Chinese University of Hong Kong, for his kind assistance in preparing this manuscript.

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Edited by Pan BR