World Journal of Gastroenterology

Submit a Manuscript: http://www.wjgnet.com/esps/
Help Desk: http://www.wjgnet.com/esps/helpdesk.aspx
DOI: 10.3748/wjg.v4.iSuppl2.4

World J Gastroenterol 1998 October 15; 4(Suppl2): 4-7
ISSN 1007-9327 (print) ISSN 2219-2840 (online)

Advances in clinical research of hepatocellular carcinoma in China

Zhao-You Tang

Zhao-You Tang, Liver Cancer Institute & Zhongshan Hospital, Shanghai Medical University, Shanghai 200032, China

Author contributions: The author solely contributed to the work.

Correspondence to: Dr. Zhao-You Tang, Liver Cancer Institute & Zhongshan Hospital, Shanghai Medical University, Shanghai 200032, China

Received: June 18, 1998
Revised: July 22, 1998
Accepted: August 8, 1998
Published online: October 15, 1998

Tang ZY. Advances in clinical research of hepatocellular carcinoma in China. *World J Gastroenterol* 1998; 4(Suppl2): 4-7 Available from: URL: http://www.wjgnet.com/1007-9327/full/v4/iSuppl2/4.htm DOI: http://dx.doi.org/10.3748/wjg.v4.iSuppl2.4

Based on the survey in 1990/1992, hepatocellular carcinoma (HCC) has become the second cancer killer in China, the mortality rate was 20.37/100000[1]. The etiological background of HCC in China includes: Viral hepatitis-around 90% of HCC in China had evidence of hepatitis B virus (HBV) infection, whereas hepatitis C virus infection was found in only 10%-30% of HCC patients. HGV-RNA was less important as compared to HBV/HCV. The second factor was aflatoxin B1 (AFB1), particularly in areas with high temperature-humidity index. In the rural areas, contamination of drinking water was claimed correlates with high HCC mortality, and microcystin was found to be promoter of hepatocarci nogenesis. The others include alcohol, smoking and genetic factors. Using trees hrew experiment, synergetic effect was found between HBV and AFB1, the incidence of HCC in HBV + AFB1 group was 52.9%, whereas it was only 12.5% in AFB1 group, 11.1% in HBV group, and 0% in the control[2]. For primary prevention, "control of water, control of crops, and prevention of hepatitis" has been advocated, and being proved to be effective since the 1970s[3]. It was reported, during the period of 1993/1994, HB vaccination has been given in 96 .9% of new born babies in the cities, and 50.8% in the rural areas. It is predicted that a decline of HCC incidence will probably happen in decades later.

In clinical aspect, lobectomy for large HCC in the 1950s has benefited to 5%-10% of HCC patients. Liver transplantation appeared in the 1960s. In the 1970s, as a result of alpha fetoprotein (AFP) serosurvey, the study of small HCC has benefited to the second part of 5%-10% of HCC patients. Diagnostic level of HC C has been greatly improved due to the rapid progress of medical imaging. The advances in regional cancer therapies and multimodality combination treatment have resulted in cytoreduction and sequential resection for initially unresectable HCC, which will benefit to the third part of 5%-10% of HCC patients. In the 1990s, the rapid progress of molecular biology will be certainly of implication in the diagnosis and treatment of HCC, and the study of recurrence and metastasis have become an attractive field of study. Unfortunately, the prognosis of HCC remains disappointed. The relative 5-year survival rates reported in the United States during 1974/1976-1980/1982 and 1986/1993 were 4%, 4% and 6% in white, and being 1%, 2% and 4% in black[4]. The relative 5-year survival rates in a high risk area of China-Qidong county in the period of 1972/1981 and 1982/1991 were only 2.2% and 2.3% respectively[5].

DIAGNOSIS OF HCC

No remarkable progress was made in the field of tumor marker for HCC. A report said that detection of fragment of fibronectin in plasma was helpful for diagnosis of HCC, the value in HCC patients was 28.91 g/mL ± 1.96 g/mL, being 9.60 g/mL ± 2.42 g/mL for chronic liver disease, and 4.32 g/mL ± 3.10 g/mL in normal control[6]. Spiral CT was claimed of value for diagnosis, the sensitivity was 89% in the arterial phase, 72% in portal phase and being 91% for double phase[7].

LONG-TERM SURVIVORS RELATED TREATMENT

By the end of 1992, at the Liver Cancer Institute of Shanghai Medical University (author's institution), 320 HCC patients have survived more than 5 years, 100 of them survived more than 10 years. Most of the long-term survivors came from small HCC resection, the second source being large HCC resection, and cytoreduct ion and sequential resection ranked third, palliative surgery other than resection ranked fourth. At the author's institution, treatment modalities that result ed in prolonging survival included: (1) Small HCC resection, the 5-year survival was 63.4% in 806 cases. (2) Large HCC resection, the 5-year survival was 39 .6% in 1061 cases. (3) Cytoreduction and sequential resection for initially unresectable HCC, the 5-year survival was 64.7% in 93 cases who had tumor cytor eduction by hepatic artery ligation and cannulation; in another 70 cases, sequential resection was done after cytoreduction by transcatheter arterial chemoembolization (TACE), the 5-year survival was 56.0%. (4) Reresection for recurrence , the 5-year survival of 155 patients was 50.9% calculated from the first resection. (5) Palliative surgery other than resection, the 5-year survival of 784 cases (including some patients who had sequential resection) was 21.6%. Cheng *et al*[8] reported that the 5-year survival of 240 patients treated by TACE was 18.9% (including some patients who had sequential resection. Other treatment that resulted in long-term survivor included radiotherapy combined wi th Chinese traditional medicine, *etc*. In short, surgery played the most important role, however, the role of regional cancer therapies seems increasing

SURGICAL TREATMENT

The advances of surgical treatment for HCC in China might include: Early resection, first stage resection for HCC in difficult location, re-resection, cytoreduction and sequential resection for unresectable HCC, and palliative surgery other than resection[9]. The 5-year survival of 2051 HCC resections was 36.1% reported by Wu *et al*[10], and being 50.6% at the author's ins titution (*n* = 1866).

Small HCC resection: The encouraging result of small HCC resection was mainly a result of screening in high risk population and yearly checkup using AFP and ultrasonography. At the author's institution, a prospective controlled trial of screening every 6 months indicated that the percentage of subclinical HCC, resectability rate, and 2-year survival rate were 76.3%, 70.8%, and 77.5% respectively, much higher than that in the control group (0%)[11]. However, the retrospective analysis in Qidong County demonstrated that screening group was only slightly superior to that of nonscreening group, the 5-year survival was 4.0% (being 8.3% for subclinical HCC) versus 1.6%[12]. In the recent years, the 5-year survival of small HCC resection reported in China were around 50%: being 52% (*n* = 50) reported by Feng *et al*[13], 79.8% reported b y Wu *et al*[10], and 63.4% at the author's institution (*n* = 806).

Large HCC resection: The 5-year survival rates reported in the recent literature were: 32.9% reported by Du *et al* (*n* = 407, including small HCC)[14], 36.1% reported by Wu *et al* (*n* = 2051, including small HCC)[10], and 39.6% at the author's institution(*n* = 1061). Aggressive surgical approach was also reported for the management of tumor emboli in the main trunk of portal vein[15]. In the technical aspect of HCC resection, unilateral inflow occlusion has been employed more frequently[16,17].

Re-resection for recurrence: As reported, the 5-year survival rates calculated from the first resection were 41.5% (*n* = 49, DU *et al*)[14], 53.2% (*n* = 95, Wu *et al*)[10], and 50.9% (*n* = 155, author's institute).

Cytoreduction and sequential resection for unresectable HCC: At the author's in stitution, during 1958/1994, 663 patients with HCC were verified to be unr esectable, of them, 72 patients received sequential resection when tumor shrank after treatment; the median tumor diameter reduced from 10 cm (maximum 24 cm) to 5 cm at the sequential resection; the pre-resection treatment includi ng hepatic artery ligation (HAL) plus cannulation (HAI) (38.9%), HAL + HAI + radioi mmunotherapy/regional hyperfractionated radiotherapy (58.3%), single treatment only accounted for 2.8%; the median duration between the first and the second resection was 5 months (1-16 months); operative mortality of sequential resection was 1.4%[18,19]. The 5-year survival rates of sequential resection were 64.7% at the author's institution (*n* = 93), 61.5% reported by Wu *et al* (*n* = 73)[10], and 25% in Du *et al*'s series (*n* = 20)[14]. Besides , cytoreduction by TACE and followed by resection was also reported: the 5-year survival was 56% (*n* = 59 at the author's institution)[20], 39.2% (*n* = 33, Wang *et al*)[21], 60.5% (*n* = 11, after operative hepatic artery cannulation HACE/TAE, Peng *et al*)[22], and 62.3% (*n* = 13, after HACE/TAC-E, Yuan *et al*)[23].

Palliative surgery other than resection: Palliative surgery for HCC includes hepatic artery ligation (HAL), hepatic artery cannulation (HAI), cryotherapy, microwave, intralesional ethanol injection during operation, *etc*. At the author's institution, the 5-year survival of 235 patient with HCC treated by cryotherapy w as 39.8%, and being 55.4% for small HCC (*n* = 80); further analysis revealed that it was 26.9% in single cryotherapy subgroup (*n* = 78), 39.6% for cryothe rapy+-HAL/HAI(*n* = 58),46.0% for cryotherapy of residual cancer after resection (*n* = 27), and 60.4% for resection after cryotherapy (*n* = 72)[24]. Experimental study demonstrated that high intensive focussed ultrasound (HIFU) was one of the hopeful approach for regional therapy of HCC, and Lipiodol could enhance the response of HIFU[25,26]

NONSURGICAL TREATMENT

Regional cancer therapy is a recent trend for the treatment of HCC, which includes surgical approach as mentioned above, and nonsurgical approach. Interventional radiology and percutaneous ultrasound guided intervention are two major parts of nonsurgical approach. Recently, TACE has surpassed radioherapy to be the first choice of treatment for unresectable HCC. The 5-year survival rate reported by Cheng *et al*[8]was 18.9% (*n* = 240, including patients with sequential resection); another series was 7.5% (*n* = 621), reported by Liu *et al*[27], and patients with single HCC and without tumor emboli in the portal vein had better prognosis. The commonly used internal radiotherpy was 1311 labeled lipiodol. Radioimmunotherapy is currently under clinical trial, effective tumor shrinkage and followed by sequential resection had been reported using 1311-antiferritin/1311-anti human HCC mAb[28,29]. However, human anti-murine antibody appeared in one third of the patients even administrated intra hepatic arterially[30]. At the author's institution, chimeric human-mouse antibody has been reconstructed, and radioimmunoimaging obtained in nude mice model[31,32]. In the field of biotherapy, response observed in author ' s institution when LAK/IL-2 plus TAE were used[33]. For drug therapy, Zheng *et al*[34]reported that tamoxifen is a treatment choice for HCC patients with expression of estrogen receptor[34].

PREVENTION AND TREATMENT OF RECURRENCE AND METASTASIS

At the author's institution, the previous report indicated that the 5-year recurrent rate after curative resection was 61.5%, and being 43.5% for small HCC; using analysis of HBV-DNA integration and p53 genotype, we also demonstrated that there are both unicentric origin and multicentric origin for recurrent HCC[35]. In this paper, only invasiveness related recurrence will be discussed.

Prediction of recurrence: Predictive markers include serum marker and examination of surgical specimens, which cover molecular and cellular levels. Proliferating cell nucleus antigen (PCNA) and overexpression of p53 in immunohistochemistry indicate poor prognosis[36]. At the author's institution, poor prognosis has been observed in patients who had higher expression of matrix metalloprote inase-2 (MMP-2) in HCC than that in the surrounding liver[37].

Prevention of recurrence: Peng *et al*[38] reported that preoperative TACE was only good for HCC > 8 cm but not for HCC < 8 cm. Zhou *et al*[39] claimed that postoperative immunochemotherapy was helpful to reduce recurrent rate. Han *et al*[40] reported that postoperative intraarterial chemotherapy decreased 5-year recurrent rate, being 72.0% versus 80.7% when compared to the control, and was only 67.8% in double cannulation group.At the author's institution, 68 patients with curative resection verified by postoperative lipiodol-CT received TACE and interferon therapy, the 3-year recur rent rate was lower than that reported previously, being 14.7% *vs* 32.5%; a nother group comprised 105 patients with curative resection and treated with transhepatic arterial/portal vein chemotherapy, the 3-year recurrent rate was also lower than that reported previously, being 18% *vs* 32.5%.

Experimental model of metastasis: At the author's institution, we established a metastatic model of human HCC in nude mice (LCI-D20) after orthotopic implantation of intact HCC tissue from 30 patients' surgical specimens, the metastatic rates to lung, liver and lymph node were extremely high, and 90% of cells were a neuploid, with expression of invasive related genes, the biological characteristics remained unchanged after 50 passages[41,42]; recently, a high metastatic potential HCC cell line-MHCC97 was also established, and lung metastasis appeared after innoculation into liver of nude mice.

Molecular mechanism of HCC metastasis: At the author's institution, the followings were found to be positively related to HCC invasiveness: p16 (CDKN2) mutation, *p53* mutation, p21 (ras), mdm-2, c-erbB-2, TGF EGFR, VEGF, MMP-2, ICAM-1, *etc*; whereas the followings were negatively related to invasiveness; nm 23-H1, Kai-1, TIMP-2, E-cadherin, *etc*. However, the difference between expression in small HCC and large HCC was not significant, indicating that even small HCC still facing the problem of biological characteristics[43-54].

Experimental intervention of metastasis:Experimental

interventions have been done in metastatic model of human HCC in nude mice (LCI-D20), including: antisense H-ras, anti-HBx/anti CD3 bispecific antibody, BB94-inhibitor of MMP, a ntiangiogenic TNP-470, Suramin, CAI, and antisense VEGsF, and inhibition of tumor growth as well as inhibition of lung metastasis were observed[55-60].

PROSPECTS IN THE 21ST CENTURY

The followings are important issues to be studied: the "cost effectiveness" of screening, early diagnosis of AFP nonproducing HCC, the better combination mo de of surgery and other therapies, the problem of inadequacy of regional cancer therapies for HCC, the balance of inadequate-treatment and over-treatment, the high recurrent rate after curative resection, the multicentric origin of recurrence, the invasion to blood vessel and distant spreading, the coexisted Child C cirrhosis, *etc*. It is expected that molecular biology will certainly play an important role, however, it also take time to translate into clinical application. Therefore, prospective control trial using clinically available approaches, particularly multimodality combination treatment, remains important to improve prognosis of HCC.

REFERENCES

1 **Li LD**, Zhang SW, Lu FZ, Mu R, Sun XD, Wangpu XM et al. Spectrum of cancer death in China and characteristics of its subgroups. *Zhonghua Zhongliu Zazhi* 1997; **19**: 323-328

2 **Yan RQ**, Su JJ, Huang DR, Gan YC, Yang C, Huang GH. Human hepatitis B virus and hepatocellular carcinoma. II. Experimental induction of hepatocellular carcinoma in tree shrews exposed to hepatitis B virus and aflatoxin B1. *J Cancer Res Clin Oncol* 1996; **122**: 289-295 [PMID: 8609152 DOI: 10.1007/BF01261405]

3 **Yu SZ**. Primary prevention of hepatocellular carcinoma. *J Gastroenterol Hepatol* 1995; **10**: 674-682 [PMID: 8580413 DOI: 10.1111/j.1440-1746.1995.tb01370.x]

4 **Landis SH**, Murray T, Bolden S, Wingo PA. Cancer statistics, 1998. *CA Cancer J Clin* 1998; **48**: 6-29 [PMID: 9449931 DOI: 10.3322/canjclin.48.1.6]

5 **Chen JG**, Sankaranarayanan R, Li WG, Black RJ, Shen ZC, Yao HY et al. Analysis of survival in total population in high risk area of liver cancer—Qidong during 1972-1991. *Zhongguo Yufang Yixue Zazhi* 1997; **31**: 149-152

6 **Zhao JM**, Ze WR, Zhang YE. Detection of plasma fibronectin fragment in patients with hepatocellular carcinoma. *Zhongliu* 1997; **17**: 265-267

7 **Yan FH**, Zeng MS, Zhou KR. Value of double phase serial scanning by spiral CT in the diagnosis of small liver cancer. *Zhonghua Fangshexue Zazhi* 1996; **30**: 829-832

8 **Cheng LF**, Wang ZQ, Cai PC, Zhang YH, Liu YD. Analysis of survival in 240 patients with unresectable primary liver cancer treated by hepatic arterial chemoembolization. *Zhonghua Zhongliu Zazhi* 1996; **18**: 362-365

9 **Tang Z**, Yu Y, Zhou X, Yang B, Lin Z, Lu J, Ma Z, Ye S, Liu K. Three decades' experience in surgery of hepatocellular carcinoma. *Chin Med J* (Engl) 1997; **110**: 245-249 [PMID: 9594221]

10 **Wu M**, Chen H, Yao X. [Surgical treatment of primary liver cancer]. *Zhonghua Waike Zazhi* 1996; **34**: 707-710 [PMID: 9590765]

11 **Yang B**, Zhang B, Xu Y, Wang W, Shen Y, Zhang A, Xu Z. Prospective study of early detection for primary liver cancer. *J Cancer Res Clin Oncol* 1997; **123**: 357-360 [PMID: 9222303 DOI: 10.1007/BF01438313]

12 **Chen JG**, Zhang BC, Lu JH, Chen QG, Yun ZX, Shen QJ. A survey of screening for liver cancer in Qidong. *Zhonghua Zhongliu* 1996; **5**: 11-13

13 **Feng YZ**, Zhao WH, Zhou XR, Feng ZM. Clinical analysis of surgery of 50 patients with small liver cancer. *Pract Surg* 1995; **10**: 16-18

14 **Du JH**, Wang XH, Li XC. Analysis of long term results of primary liver cancer. *Zhonghua Gandan Waike Zazhi* 1995; **1**: 178-180

15 **Mei MH**, Tang JH, Chen Q, Zhang XL, Yang JH, Xu J et al. Clinical significance of removal of tumor thrombi in the main portal vein in patients with hepatocellular carcinoma. *J Hep Bil Pancr Surg* 1995; **2**: 266-272 [DOI: 10.1007/BF02350909]

16 **Lai JM**, Liang LJ, Huang JF. Unilateral inflow occlusion for hepatic resection. *Zhonghua Gandan Waike Zazhi* 1996; **1**: 9-11

17 **Luo MD**, Tang ZY. Liver resection under selective hepatic inflow and outflow occlusions.*Asian J Surg* 1997; **20**: 146-151

18 **Tang ZY**, Yu YQ, Zhou XD, Ma ZC, Yang BH, Lin ZY, Lu JZ, Liu KD, Fan Z, Zeng ZC. Treatment of unresectable primary liver cancer: with reference to cytoreduction and sequential resection. *World J Surg* 1995; **19**: 47-52 [PMID: 7740810 DOI: 10.1007/BF00316979]

19 **Tang ZY**, Uy YQ, Zhou XD, Ma ZC, Lu JZ, Lin ZY, Liu KD, Ye SL, Yang BH, Wang HW. Cytoreduction and sequential resection for surgically verified unresectable hepatocellular carcinoma: evaluation with analysis of 72 patients. *World J Surg* 1995; **19**: 784-789 [PMID: 8553666 DOI: 10.1007/BF00299771]

20 **Fan J**, Yu Y, Wu Z. [Liver resection after transcatheter hepatic arterial chemoembolization for hepatocellular carcinoma and curative effect analysis]. *Zhonghua Waike Zazhi* 1997; **35**: 710-712 [PMID: 10677986]

21 **Wang YH**, Liu YX, Feng YC, Ji XL, Zhao HL. Second stage resection following transcatheter arterial chemoembolization Clinical and pathological studies of 33 patients with hepatocellular carcinoma. *Zhonghua Gandan Waike Zazhi* 1997; **3**: 68-73

22 **Peng SY**, Lu DC, Peng CH, Jiang XC. Second stage resection for large liver cancer. *Zhonghua Gandan Waike Zazhi* 1995; **1**: 19-21

23 **Yuan YF**, Li JQ, Zhang YQ, Chen MS, Guo RP et al. Second stage resection of primary liver cancer-analysis of 13 patients. *Aizheng* (Engl) 1997; **16**: 358-360

24 **Zhou XD**, Tang ZY. Cryotherapy for primary liver cancer. *Semin Surg Oncol* 1998; **14**: 171-174 [PMID: 9492887 DOI: 10.1002/(SICI)1098-2388(199803)14:2<171::AID-SSU9>3.0.CO;2-2]

25 **Cheng SQ**, Zhou XD, Tang ZY, Yu Y, Wang HZ, Bao SS, Qian DC. High-intensity focused ultrasound in the treatment of experimental liver tumour. *J Cancer Res Clin Oncol* 1997; **123**: 219-223 [PMID: 9177494 DOI: 10.1007/s004320050050]

26 **Cheng SQ**, Zhou XD, Tang ZY, Yu Y, Bao SS, Qian DC. Iodized oil enhances the thermal effect of high-intensity focused ultrasound on ablating experimental liver cancer. *J Cancer Res Clin Oncol* 1997; **123**: 639-644 [PMID: 9620223 DOI: 10.1007/s004320050118]

27 **Liu Y**, Jia YC, Tian JM, Wang ZT, Ye H, Lu JP et al. Factors influencing survival of primary liver cancer after transcatheter arterial chemoembolization. *Zhonghua Zhongliu Zazhi* 1996; **18**: 359-361

28 **Tang ZY**, Zeng ZC, Liu KD, Yu YQ, Lu JZ, Xie H. Intrahepatic arterial I 131 anti hepatocellular carcinoma (HCC) monoclonal antibody combined with hepatic artery ligation for treatment of unresectable HCC. *Antibody Immunoconj Radiophar* 1993; **6**: 167-175

29 **Xiang M**, Zhu SL, Lin YZ, Wu DM, Xie H. Observation on targeting therapy using 131I Hepama-1 monoclonal antibody. *Linchuang Zhongliuxue Zazhi* 1998; **25**: 289-291

30 **Zeng ZC**, Tang ZY, Liu KD, Lu JZ, Cai XJ, Xie H. Human anti-(murine Ig) antibody responses in patients with hepatocellular carcinoma receiving intrahepatic arterial 131I-labeled Hepama-1 mAb. Preliminary results and discussion. *Cancer Immunol Immunother* 1994; **39**: 332-336 [PMID: 7987865]

31 **Zhou G**, Liu KD, Tang ZY, Chen YH, Wu XF, Schroeder CH. Reconstruction and expression of chimeric anti-HBx antibody in Escherichia coli. *J Cancer Res Clin Oncol* 1997; **123**: 325-330 [PMID: 9222298 DOI: 10.1007/s004320050065]

32 **Gong Y**, Liu KD, Zhou G, Xue Q, Chen SL, Tang ZY. Tumor radioimmunoimaging of chimeric antibody in nude mice with hepatoma xenograft. *World J Gastroenterol* 1998; **4**: 7-9 [PMID: 11819217 DOI: 10.3748/wjg.v4.i1.7]

33 **Gan YH**, Ye SL, Tang ZY, Wu ZQ, Xia JL, Zheng N. Effect of intrahepatic arterial infusion of LAK cell and chemoembolization in the treatment of liver cancer. *Shanghai Yike Daxue Xuebao* 1997; **24**: 235-237

34 **Zhen TR**, Zhang QZ, Xie ZF, Lin AZ, Wang RP, Lin XD. Estrogen receptor and short term result of anti-estrogen therapy for advanced liver cancer. *Zhonghua Zhongliu Zazhi* 1997; **19**: 451-453

35 **He B**, Tang ZY, Liu KD, Zhou G. Analysis of the cellular origin of hepatocellular carcinoma by p53 genotype. *J Cancer Res Clin Oncol* 1996; **122**: 763-766 [PMID: 8954175 DOI: 10.1007/BF01209125]

36 **Li JQ**, Zhang CQ, Zhang YQ, Feng XT, Yuan YF, Chen MS et al. Immunohistochemical study of PCNA and p53 in primary liver cancer—an implication for prognosis and treatment. *J Exp Clin Cancer Res* 1996; **15**: 77-82

37 **Bu W**, Huang X, Tang Z. [The role of MMP-2 in the invasion and metastasis of hepatocellular carcinoma (HCC)]. *Zhonghua Yixue Zazhi* 1997; **77**: 661-664 [PMID: 9772533]

38 **Peng SY**, Lu DC, Jiang XC, Peng CH. Effect of preoperative hepatic arterial chemoembolization in liver cancer resection. *Zhonghua Gandan Waike Zazhi* 1996; **2**: 12-15

39 **Zhou W**, Wu M, Chen H. [The effects of combined hepatectomy and immuno-chemotherapy on postoperative recurrence rate of primary liver cancer]. *Zhonghua Waike Zazhi* 1995; **33**: 35-37 [PMID: 7774443]

40 **Han YZ**,Zhang L,Liang ZZ,Han F.Prevention of recurrence with blood vessel chemoperfusion after large liver cancer resection. *Linchuang Zhongliuxue Zazhi* 1998; **25**: 352-353

41 **Sun FX**, Tang ZY, Lui 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 [PMID: 8603818 DOI: 10.1002/(SICI)1097-0215(19960410)66:2<239::AID-IJC17>3.0.CO;2-7]

42 **He B**, Liu YK, Tang ZY, Xue Q. Gene mutation and expression in metastatic model of human hepatocellular carcinoma in nude mice established by orthotopic implantation. *Zhonghua Ganzangbing Zazhi* 1997; **5**: 245

43 **Tang Z**, Qin L, Wang X, Zhou G, Liao Y, Weng Y, Jiang X, Lin Z, Liu K, Ye S. Alterations of oncogenes, tumor suppressor genes and growth factors in hepatocellular carcinoma: with relation to tumor size and invasiveness. *Chin Med J (Engl)* 1998; **111**: 313-318 [PMID: 10374394]

44 **Tang ZY**. Studies on small hepatocellular carcinoma-clinical aspect and molecular biology. *Hepatol Rapid Lit Rev* 1996; **1**: Ⅶ-ⅩⅥ

45 **Qin L**, Tang Z, Liu K, Ye S, Zhou G. P53 mutations may be related to tumor invasiveness of human hepatocellular-carcinoma in china. *Oncol Rep* 1995; **2**: 1175-1179 [PMID: 21597878 DOI: 10.3892/or.2.6.1175]

46 **Qiu SJ**, Ye SL, Wu ZQ, Tang ZY. p53 mutation in codon 249 is related to the formation of tumor thrombus. *Zhonghua Ganzangbing Zazhi* 1997; **5**: 139-141

47 **Qin L**, Tang Z, Liu K, Ye S, He B, Zhang Y, Zhou G. Alterations of CDKN2(p16/MTS1) exon 2 in human hepatocellular carcinoma. *Oncol Rep*

1996; **3**: 405-408 [PMID: 21594383 DOI: 10.3892/or.3.2.405]
48 **Qiu S**, Ye S, Wu Z. [The expression of mdm2 gene related to the invasiveness of human hepatocellular carcinoma]. *Zhonghua Zhongliu Zazhi* 1997; **19**: 256-259 [PMID: 11038752]
49 **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
50 **Yao M**, Zhou XD, Zha XL, Shi DR, Fu J, He JY, Lu HF, Tang ZY. Expression of the integrin alpha5 subunit and its mediated cell adhesion in hepatocellular carcinoma. *J Cancer Res Clin Oncol* 1997; **123**: 435-440 [PMID: 9292706 DOI: 10.1007/BF01372547]
51 **Sun JJ**, Zhou XD, Liu YK, Tang ZY. Study on the relationship between expression and intercellular adhesion molecule-1 and invasion and metastasis of liver cancer. *Zhonggua Aizheng Zazhi* 1997; **7**: 161-164
52 **Ye YJ**, Yu YQ, Tang ZY, Wan DF, Lu JZ, He LP. Construction of nm23-H1 cDNA clone the relationship between its mRNA expression and metastasis in hepatocellular carcinoma. *Zhonghua Shiyan Waike Zazhi* 1998; **15**: 17-18
53 **Ye Y**, Yu Y, Wan D, Tang Z, Lu J, He L. [The relationship between nm23-H1 loss of heterozygosity and metastasis in hepatocellular carcinoma]. *Zhonghua Waike Zazhi* 1998; **36**: 161-163 [PMID: 11825358]
54 **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 [PMID: 9646228]
55 **Liao Y**, Tang ZY, Sun FX, Ye SL, Liu KD, Huang Z. The effect of antisense H-ras on growth and metastasis of a high metastatic tumor model of human hepatoma in nude mice LCI-D20. *Zhonghua Yixue Zazhi* 1996; **76**: 650-653
56 **Liao Y**, Tang ZY, Liu KD, Ye SL, Huang Z. Apoptosis of human BEL-7402 hepatocellular carcinoma cells released by antisense H-ras DNA--in vitro and in vivo studies. *J Cancer Res Clin Oncol* 1997; **123**: 25-33 [PMID: 8996537 DOI: 10.1007/BF01212611]
57 **Liao Y**, Tang Z, Liu K, Ye S, Li J, Huang Z, Wang D, Segal D. Preparation and application of anti-HBx/anti-CD3 bispecific monoclonal antibody (BsAb) retargeting effector cells for lysis of human hepatoma xenografts in nude mice. *Oncol Rep* 1996; **3**: 637-644 [PMID: 21594426 DOI: 10.3892/or.3.4.637]
58 **Bu W**, Tang ZY, Sun FX, Xue Q, Chen J, Gao DM. Inhibition of tumor growth, invasion and metastasis of hepatocellular carcinoma using metalloproteinase inhibitor Batimastat. *Zhonghua Yixue Zazhi* 1997; **77**: 699-700
59 **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 [PMID: 9260590 DOI: 10.1007/BF01240121]
60 **Li XM**, Tang ZY, Xue Q, Liu YK, Ye SL, Zhang XR. Suramin inhibits growth and metastasis of human hepatocellular carcinoma in nude mice. *Zhonghua Shiyan Waike Zazhi* 1998; **15**: 3-4

E- Editor: Li RF

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