Metastasis and Recurrence After Surgical Resection of Hepatocellular Carcinoma: Recent Progress in Clinical and Related Basic Aspects

Lun-Xiu Qin[1] and Zhao-You Tang*,[1]

[1]*Liver Cancer Institute and Zhongshan Hospital, Fudan University, Shanghai, China*

Abstract: Metastasis and recurrence, which is caused either by intrahepatic metastasis (IM) or by metachronously multicentric carcinogenesis, has become one major obstacle for further improving the survival and prognosis of HCC patients. Many factors, such as the patient's general conditions (age, sex, co-existing hepatitis, liver function, AFP level), macroscopic tumor morphology (tumor size, number, capsule status, intra- or extra-hepatic spreading, vessel invasion), and tumor pathohistological features, as well as treatment-related factors (surgical techniques, blood transfusion), have been determined as risk factors, and proven of predicting significance for HCC recurrence. In recent years, with the understanding of tumor biology and the development of molecular biology techniques, many molecular factors (biomarkers) have been developed. Various neoadjuvant or adjuvant therapeutic approaches including pre-operative transcatheter arterial chemoembolization (TACE), post-operative TACE, systemic or locoregional chemotherapy, immunotherapy, interferon, and acyclic retinoic acid have been hoped to decrease or eliminate recurrence of HCC. However, there is no evidence demonstrate benefit from the various neoadjuvant and adjuvant therapies investigated. Most of them deserve further evaluation by randomized control trial (RCT), and among them, biotherapy could be an ideal strategy. Many kinds of treatment strategies, including surgical treatment (repeat resection and salvage transplantation), TACE, regional cancer therapies such as radiofrequency ablation (RFA), chemotherapy have been tried and proven to be potentially helpful for the control of HCC recurrence and metastasis. However, there are few RCT to evaluate the effect of these modalities on the recurrence and metastasis of HCC.

Hepatocellular carcinoma (HCC) is common worldwide, and its incidence are increasing. Much progress has been made in the past few decades, a definitive subset is cured by surgery only, and encouraging long-term survival of patients has been obtained in some clinical centers. The 5-year overall survival (OS) after curative resection of HCC could be about 50% [1-4], and the 5-year disease-free survival (DFS) was 16 % to 27.4 % [1]. However, HCC is far from a curable disease because of the high possibility of intrahepatic and/or extrahepatic recurrence and metastasis postoperatively, the 5-year recurrence rate after curative resection was 38 % to 61.5 % [1-3]. Metastasis and recurrence has become one major obstacle for further improving the survival and prognosis of HCC patients. During the past years, much effort has been made in the prediction, early detection, prevention and management of metastasis and recurrence of HCC. In this review, we will summarize the progress in the studies on metastasis and recurrence of HCC after surgical resection in recent five years.

ORIGINS OF RECURRENCE

Recurrence after surgical resection might be caused either by intrahepatic metastasis (IM) or by metachronously multicentric carcinogenesis (a newly developed lesion in the cirrhotic background), also named as uni-centric and multi-centric origins [5]. IM is a major cause of recurrence of advanced HCCs with varying degrees of vascular invasion, and those recurrent HCC in noncirrhotic liver. Over 60% of patients with multiple HCCs were resulted from IM [6].

Metachronous multicentric occurrence (MO) is a frequent cause of HCC recurrence in early stage patients with no obvious vascular invasion, particularly in those with severe liver cirrhosis or HCV-related HCC. Ikeda *et al*. conducted a long-term cohort study of 892 patients with cirrhosis caused by either HBV or HCV with 10 years of follow-up, and found that MO was the principal mechanism of recurrence after curative ablation [7]. However, this needs further evaluation. The prognosis of patients with HCC recurrence from MO (whether synchronous or metachronous) is significantly better than that of patients with recurrence due to IM [8].

Many strategies, including gross appearance, size, location and histological features of the tumors, time of recurrence, imaging patterns, and genetic markers, have been applied to discriminate these two origins of recurrences. Genetic assessment of DNA alterations may be more strict and specific than histopathological diagnosis in the differential diagnosis of IM and MO [9]. Many genetic diagnostic methods, including clonalities analysis of the integration pattern of HBV DNA in HBV carrier patients, DNA fingerprinting with loss of heterozygosity (LOH) assay and comparative genomic hybridization (CGH), and analysis of the p53 mutation patterns have been used for determining IM or MO in recurrent HCC [5, 10]. Of these molecular methods, LOH analysis can be used in most patients even before surgical resection, since this assay can be readily applied routinely to either liver biopsies or fine needle aspirates [6].

*Address correspondence to this author at the Liver Cancer Institute & Zhongshan Hospital, Fudan University, 136 Yi Xue Yuan Road, Shanghai 200032, P.R. China; Tel: +86-21-64037181; Fax: +86-21-64037181; E-mail: zytang@srcap.stc.sh.cn

1573-3947/05 $50.00+.00

Table 1. Summary of Risk Factors for Metastasis and Recurrence After Surgical Resection of Hepatocellular Carcinoma

Items	Risk factors or predictors
Co-existing liver disease	Inflammation activity [15] *ALT, GGT* *viral load, serum HBeAg* Genotype C HBV [16] Liver functional reserve [17]
Pathological features of tumor	pTNM stage[18-21] Size, number, capsule, differentiation Venous invasion; Intrahepatic metastasis (IM) Inflammatory cell infiltration (favorable factor)
Tumor-associated antigens and detection of circulating cancer cells	Serum AFP level (protein, mRNA) [22-25]*;* AFP-L3) Serum MAGE [26], hTERT [27] mRNA ;
Invasion and metastasis-related markers	Osteopontin (OPN) (tissue and serum) [28, 29] Intratumor microvessel density (MVD) level [30-32] VEGF level (tissue and serum) [33, 34] p53 gene mutation [36] Reduced expression of p27 [37], E-cadherin [38] Overexpressions of Lminin-5[39], MMP-2, MMP-9, MT1-MMP [40]
Genomic aberrations and expression profiling	Genomic aberrations 16q [41]; 8p [42, 43] *Changed* restriction landmark genomic scanning (RLGS) *spots* [45] Gene expression profiling *90 genes associated with intrahepatic metastasis* [46] *153 genes predicting signature for metastases and outcome* [29]. *12 genes predictive system* [47] Proteomics analysis *CK19* [48, 49]

RISK FACTORS AND PREDICTORS

Many factors, such as the patient's general conditions (age, sex, co-existing hepatitis, liver function, AFP level), macroscopic tumor morphology (tumor size, number, capsule status, intra- or extrahepatic spreading, vessel invasion), and tumor pathohistological features, as well as treatment-related factors (surgical techniques, blood transfusion), have been determined as risk factors, and proven of predicting significance for HCC recurrence. In recent years, with the understanding of tumor biology and the development of molecular biology techniques, many molecular factors (biomarkers) have been developed [11-13] (Table **1**).

Co-Existing Hepatitis Status and Liver Cirrhosis

HCC recurrence is strictly linked to the status of the underlying liver disease. Patients with co-existing hepatitis and liver cirrhosis have a significantly higher possibility of early tumor recurrence [14]. The inflammatory activity, viral load, and serum HBeAg positivity have also been confirmed as independent risk factors for HCC recurrence [15]. HCC with genotype C HBV has a greater possibility of recurrence than those with genotype B [16]. Functional reserve of the remnant cirrhotic liver is another independent factor for early intrahepatic recurrence. Some liver functional markers, such as alanine transaminase (ALT), gamma-glutamyl transpeptidase (GGT), serum albumin level, the preoperative indocyanine green (ICG) retention value at 15 minutes after injection, particularly the Child-Pugh classification, have been applied [17]. HCV-positive patients with AST levels above twice normal (2N) have the highest risk for intrahepatic recurrence [1].

Pathological Features of Tumor

Many pathologic features of the tumor itself, such as tumor size, number, capsule state, cell differentiation, venous invasion, presence of satellite nodules (IM), and advanced pTNM stage, are the best-established risk factors for recurrence and metastasis of HCC [18-20]. The extratumor spread, including portal vein invasion (Vp) and IM, is more accurate than any single invasiveness parameter such as Vp or IM as a predictive factor for recurrence of HCC [21]. The patients with macro- or microscopic vascular invasion, intrahepatic metastasis, poor differentiation, pleomorphism, sarcomatous change, vascular lake, and angiographic condensed pooling are more frequently found to have early massive recurrence. Marked inflammatory cell infiltration in the tumor is a favorable factor for a much lower recurrence rate, because the tumor invasion into the portal vein in the vicinity of the tumor is much lower.

Tumor-Associated Antigens and Detection of Circulating Cancer Cells

Serum AFP is useful not only for diagnosis, but also as a predictive marker for tumor invasiveness and recurrence of HCC. Patients with high AFP levels at diagnosis tended to have greater tumor size, bilobar involvement, massive or diffuse types, and portal vein thrombosis [22]. AFP is also a significant prognostic factor for recurrent HCC [23]. Lens culinaris agglutinin A-reactive fraction of AFP (AFP-L3) is a more useful indicator of distant metastasis for HCC. Periodic examination of AFP-L3 may be useful for the early detection of recurrent HCC, and it has 9-12 months of lead-time in early recognition compared with the imaging

techniques, with a sensitivity of 56% and a specificity of over 95%.

AFP mRNA in peripheral blood of HCC patients has been proposed as a predictive marker of HCC cells disseminated into the circulation and for metastatic recurrence, and AFP mRNA in perioperative period might be a predictive marker for the early intrahepatic recurrence and distant metastasis after HCC resection. The patients with positive AFP mRNA in peripheral blood have a higher possibility of extrahepatic metastasis, and those with consistent positive of AFP mRNA show the highest recurrence rate and trend to distant or multiple recurrences [24]. However, some recent reports indicated circulating AFP mRNA was transiently detected in cirrhosis with no predictive value for HCC recurrence after curative surgery [25]. A large scale of prospective study is needed to evaluate the clinical significance of AFP mRNA level.

In addition, detections of the transcripts of melanoma associated antigen gene (MAGE) [26] and human telomerase reverse transcriptase (hTERT) [27] have also been used to detect the circulating tumor cells. And they are also feasible and reliable assays for the early prediction of the relapse and prognosis of the HCC patients.

HCC Invasion and Metastasis-Related Molecular Markers

Osteopontin (OPN) overexpression has been suggested to play a role in HCC, specially in cancer-stromal interactions, and could serve as a useful marker for predicting early recurrence in early-stage HCC [28]. Recently, based on the metastasis-related expression signatures study, we revealed an important role of OPN in HCC metastasis. Overexpression of OPN is correlated with primary HCC with metastatic potential and with invasiveness of HCC cell lines *in vitro*, and an OPN-neutralizing antibody can efficiently block invasion and metastasis of highly metastatic HCC cells both *in vitro* and *in vivo*. These identify OPN as a molecular marker to define HCC patients with metastatic potential [29].

Angiogenesis, the process leading to the formation of new blood vessels from a preexisting vascular network, is necessary for tumor growth, invasion, and metastasis. Intratumor microvessel density (MVD) level is a useful prognostic marker for predicting early HCC recurrence and patients' DFS [30], specially in patients with small HCC [31, 32]. Circulating vascular endothelial growth factor (VEGF) seems to be a reliable surrogate marker of angiogenic activity and tumor progression in cancer patients. It is a significant independent predictor of tumor invasiveness, tumor recurrence, DFS, and OS in patients with resectable HCC [33, 34]. However, there is still a debate on whether serum VEGF level is a true reflection of tumor angiogenic activity in cancer patients, which originates from the finding that most VEGF in the serum is released from platelets during clotting. This unsettled issue has become a major obstacle in its clinical application [35].

Mutation of p53 gene [36], reduced expression of p27 [37] and E-cadherin [38], overexpressions of Lminin-5 (Ln-5) [39] and matrix metalloproteinases (MMPs) (MMP-2, as well as MMP-9, MT1-MMP) [40], have also been found to correlate with the tumor relapse, and are independent predictive markers for their recurrence and prognosis.

Profiling HCC and Identifying New Predictive Marker

The presence of LOH on 16q and the number of chromosomes with LOH are the most significant independent negatively predictive factors for metastasis-free survival of HCC patients after curative resection [41]. Using CGH technique, we found chromosome 8p deletions might contribute to HCC metastasis. A more accurate location was identified on 8p23.3, 8p11.2. These findings provide new targets for exploring new predictive markers for the recurrence of HCC[42-44]. The number of changed restriction landmark genomic scanning (RLGS) spots is also a useful marker for recurrence of HCC [45]. One important trend is to investigate the prognostic value of circulating DNA in plasma or serum, and its genetic alterations in cancer patients.

The cDNA microarray technology, which offers an opportunity to probe disease-related gene expressions at a global genome scale, has allowed the successful molecular classification of several human malignant tumors in regarding their stage, metastatic recurrence potentials, prognostic outcome or response to therapy. Through the investigation of the genome-wide expression profile *via* cDNA microarray consisting of 23, 000 genes, Cheung *et al*. found a total of 90 clones to be correlated with intrahepatic metastasis of HCC [46]. Recently, using a supervised machine learning algorithm approach to classify patients based on their gene expression signatures for potential to develop metastasis and for survival, we have generated a molecular signature that correctly classified patients with or without accompanying intra-hepatic metastases and have identified genes that are mostly relevant to the prediction outcome including patient survival. The expression profiles also show that primary metastasis-free HCC is distinct from primary HCC with metastasis, and metastatic tumors are indistinguishable from their primary tumors [29]. Similarly, Iizuka *et al*. also constructed a predictive system consisting of 12 genes, which could correctly predict early intrahepatic recurrence or non-recurrence in 93% of samples with a positive predictive value of 88% and a negative predictive value of 95% [47].

Proteomics offers another new strategy to identify new predictive marker for HCC metastatic recurrence. Recently, differential proteomic analysis was conducted on two HCC cell strains (MHCC97-H and MHCC97-L) with different metastatic potentials that are established from the same parent cell line MHCC97 in our institute. From the protein expression profiles, CK19 was identified as a potential predictive marker for HCC metastasis. Serum CK19 level might reflect the pathological progression in some HCC and may be a useful marker for predicting tumor metastasis and a therapeutic target for the treatment of HCC patients with metastases [48, 49].

One new trend is the combination of annotation/protein sequence analysis, transcript profiling, immunohisto-chemistry, and immunoassay, which provides a more powerful approach for delineating candidate biomarkers of cancer with potential clinical significance [50].

Clinical Staging

A clinical staging system for HCC patients, which provides guidance for patient assessment and making therapeutic decisions, is also useful for predicting the tumor recurrence [51]. The current classifications most commonly used for HCC are the UICC's tumor node metastasis (TNM), the Okuda and the Child-Pugh staging systems, and the Cancer of the Liver Italian Program (CLIP) score. In the new edition of TNM staging system (2002), the significance of vascular invasion is emphasized as the most important aspect of cancer biological characteristics, while the size of tumor is not so important as in the previous edition. According to the criteria of this new system, regardless of the tumor size, all of the solitary tumors without vascular invasion are included in T1 stage, while those with vascular invasion are in T2 or T3. The CLIP score has become the most commonly used integrated staging score, including the parameters involved in both the liver disease stage (Child-Pugh stage) and tumor stage (macroscopic tumor morphology, AFP levels, and the presence or absence of portal thrombosis), is able to accurately identify patients with different prognoses, particularly in the early phases of HCC. Although the CLIP score has been well validated by many authors in terms of its prognostic value in HCC patients, this score has some problems and limitations when applied to currently diagnosed HCC patients. A new staging system based on the Liver Cancer Study Group of Japan (LCSGJ), the Japan Integrated Staging (JIS) score is currently proposed in Japan. This staging system combines Child-Pugh grade and TNM staging by the LCSGJ criteria. The stratification ability of the JIS scoring system in selecting the best prognostic patient group is much better than that of the CLIP scoring system [52]. Recently, a new prognostic classification, the 'SLiDe' scoring system (S, stage; Li, liver damage; De, des-gamma-carboxy prothrombin), was established using 'stage' and 'liver damage' of the recently revised 4th edition of the Japanese staging system edited by the LCSGJ. Preliminary results showed that this SLiDe scoring system was statistically a better model for predicting outcome than the CLIP and the JIS scoring systems, as judged by the Akaike Information Criteria [53].

PROPHYLACTIC STRATEGIES OF HCC RECURRENCE

A number of approaches have been tried to prevent HCC recurrence after surgical resection, including pre-operative transcatheter arterial chemoembolization (TACE), post-operative TACE, systemic or locoregional chemotherapy, immunotherapy, interferon, and acyclic retinoic acid, etc. However, only a few of them were proven by evidence-based results from randomized control trial (RCT) (Table **2**).

In 2000, Chan *et al*. reviewed all of the 8 truly randomized and quasi-randomized clinical trials (totaling 548 patients) that compared HCC patients who were given and not given neoadjuvant/adjuvant therapy as a supplement to curative liver resection. Both pre- (neoadjuvant) and post-operative (adjuvant), systemic and locoregional chemo- (+/- embolization), and immunotherapy interventions were tested. Seven of the 8 trials reported no survival benefit from adjuvant therapy. Only one trial reported a statistically significant difference for survival and DFS for the treatment arm, but the results of both its arms were very poor when compared to other studies. So, there is no evidence for efficacy of any of the adjuvant protocols reviewed on the survival and prognosis of HCC patients [54]. Little [55] and Schwartz [56] also thought there was no evidence demonstrated benefit from the various neoadjuvant and adjuvant therapies investigated as yet. Recently, Mathurin *et al*. made a meta-analysis to evaluate four adjuvant therapeutic modalities including pre-operative transarterial chemotherapy (TAC), post-operative TAC, systemic chemotherapy and a combination of systemic and transarterial chemotherapy. They found only post-operative TAC improved survival and decreased the cumulative probability of no recurrence [57].

RCT have also been conducted to clarify the clinical benefits of the four kinds of adjuvant therapeutic options

Table 2. Prophylaxis Strategies for Metastasis and Recurrence of Hepatocellular Carcinoma

Prophylaxis strategies	Efficiency
Neoadjuvant chemotherapy or TACE (preTACE)	No benefit, should be avoided (2 RCTs)[58] Transarterial immunoembolization (TIE): useful [59]. 5-FU +IFN-beta: useful for HBV and HCV infections [60].
Adjuvant TACE (postTACE)	Only beneficial to patients with possible residues No benefit or even harmful to patients after a "real" curative resection [58].
Postoperative adjuvant systemic/locoregional chemotherapy	Systemic chemotherapy (3 RCTs) [65]: *not effective; worsen DFS and OS; enhance recurrence* Post-operative transcatheter arterial chemotherapy (TAC) [66] *useful for recurrence from IM* *no evidence from RCT*
Postoperative Adjuvant Biotherapy	
Adjuvant Interferon treatment	Useful proved by RCTs in both HCV- [70-72] and HBV-related patients *[58].*
Adjuvant adoptive immunotherapy	Lymphocytes activated with interleukin-2 and CD3 antibody [2]: *Effective: decreases the recurrence by 18%; improve DFS, but not OS.* Autologous formalin-fixed tumor vaccine (AFTV) (Phase II RCT) [76]*:* *reduces recurrence by 81%; improves DFS and OS*
Acyclic retinoid acid	Useful in HCV-related HCC [77-80] In combination with IFNs [81]

including adoptive immunotherapy, and interferon, acyclic retinoid, 131I-lipiodol in the prevention of HCC after curative resection. Actually, all the options reduced in part the recurrence but had drawbacks in their effectiveness, and large trials are needed to assess other important endpoints, such as clinical feasibility, risk-benefit and cost-effectiveness.

Preoperative Neoadjuvant Chemotherapy or TACE

The value of preoperative TACE (preTACE) on the recurrence still remains great controversy. In a recent review, Sun and Tang summarized the results of the two true RCTs about the effect of preTACE on the HCC recurrence after surgical resection, and found that preTACE is not helpful in terms of decreasing recurrence after resection of resectable HCC [58]. For huge resectable HCC, although preTACE induced tumor shrinkage as expected, it increased the operative difficulty with more blood loss, more extra-hepatic metastasis, higher possibility of invading adjacent organs by tumors; furthermore, it could not statistically improve the DFS, and even worsen the OS. For small HCC, preTACE induced necrosis in tumor, but it didn't improve the DFS, because preTACE was not capable to inhibit the intrahepatic micrometastatic lesions and tumor thrombus in microvessel [58]. Therefore, preTACE should be avoided for the resectable HCC, particularly in patients with advanced liver cirrhosis.

Combination of preoperative chemotherapy and immunotherapy is a hopeful new modality for prevention of recurrence. Yoshida found preoperative transarterial immunoembolization (TIE), a newly developed arterial embolization technique using OK-432 and fibrinogen, seemed to be more effective than conventional TACE against extracapsular invasion and intrahepatic metastasis, could improve the DFS after surgical resection [59]. Preoperative administration of 5-FU and IFN-beta may prevent recurrence of co-existing hepatitis B and C virus infections [60].

Postoperative Adjuvant TACE

There is still controversial with the effectiveness of post-operative TACE (postTACE) on the prevention of HCC recurrence after operation. Only a few of RCT studies have been conducted, and the results are much conflicting. There is only one RCT reporting a positive result for postTACE. In this study, Lau *et al*. found that a single 1850 MBq dose of intra-arterial 131I-lipiodol given instead of conventional lipiodol after curative resection of HCC significantly decreased the rate of HCC recurrence without major side effects and increased the 3-year OS rate from 46.3% to 86.4% [61]. This promising result was supported by another recent retrospective study, the 3-year DFS could be increased from 41.5% to 68.4%, and 3-year OS increased from 49.9% to 91.7% ($P < 0.02$) [62].

However, much different results came from the other two earlier RCT studies. Izumi *et al*. found that although postTACE could improve both DFS rate and DFS time, it had no significant effect on the 1- and 3-year OS rates, and even shorten the median survival time. postTACE may postpone but not eliminate the recurrence [63]. Lai *et al.* found that postTACE even increased the recurrence and extrahepatic metastasis rates. postTACE is harmful to patients after curative resection of HCC [64]. So, postTACE is only beneficial to part of the patients with possible HCC residues after resection (invasive type), but not effective or even harmful to the patients after a "real" curative resection [58]. A randomized study including more patients is necessary to confirm its contribution to therapeutic management.

Postoperative Adjuvant Systemic/Locoregional Chemotherapy

The role of postoperative chemotherapy in the reduction of tumor recurrence rate is still controversial. Systemic chemotherapy is generally not effective in most cases with HCC. Ono *et al*. summarized three RCTs of postoperative chemotherapy, and found postoperative chemotherapy was associated with significantly worse DFS and OS rates, enhanced the cancer recurrence in the remnant liver and deteriorated the long-term outcome in patients with cirrhosis [65].

It is believed that post-operative TAC could suppress residual liver recurrence from intrahepatic micrometastases rather than multicentric carcinogenesis. In one prospective case-controlled study, postoperative adjuvant chemotherapy, using a combination of low dose intravenous epirubicin (20 mg/m2) and mitomycin (5 mg) monthly for seven courses starting 5 to 6 weeks after surgery, has a tendency to reduce tumor recurrence rate and may improve long-term survival for high risk patients [66]. Many retrospective studies also showed the positive effect of adjuvant locoregional chemotherapy in preventing recurrence after curative resection of HCC [3]. However, no evidence from prospective RCT study indicates adjuvant chemotherapy may be useful [67].

Recently, in authors' institution, based on the experimental investigation on the human HCC model with high metastatic potential (LCI-D20), capecitabine was proved to be effective in inhibiting tumor growth and decreasing the incidence of metastatic recurrence after resection of HCC, which is potential new therapeutic way to control the recurrence and metastasis of HCC [68].

Postoperative Adjuvant Biotherapy

Biotherapy has been proven to be one hopeful strategy with a good tolerance, and it plays more and more important role in the prevention of recurrence and metastasis of HCC after operation.

Post-Operative Interferon Treatment

Postoperative interferon (IFN)-alpha therapy can decrease recurrence after resection of HCV-related HCC [69]. This result was further confirmed by pilot RCTs [70-72]. The possible mechanism of the effect of IFN on the recurrence of HCV-related HCC is that IFN could clear the HCV viremia, which is closely related to the recurrence of HCC due to MO [69, 70, 73, 74]. However, in Kubo *et al.* studies, the decrease of recurrence rate was associated with neither clearance of HCV nor normalization of serum ALT level, it might depend on direct antitumor effects or inhibition of carcinogenesis by HCV [15, 69].

In the authors' institution, one RCT was also conducted to test the effect of IFNa on recurrence in HBV-related HCC patients after curative resection. The interim results showed that long-term IFNa treatment improved DFS of patients through direct antitumor effect, which was not associated with serum conversion of HBeAg [58]. This might be attributed to antiangiogenesis effect other than the anti-proliferation property of IFN-alpha [75]. Therefore, the mechanism of IFN's effect on recurrence remains to be further investigated.

Post-Operative Adoptive Immunotherapy

Several clinical trials have been set up to test the effect of adoptive immunotherapy on recurrence in patients with HCC in early 1990s, and most of them got positive results. The most important report came from the study published in Lancet [2]. In this study, autologous lymphocytes activated vitro with recombinant interleukin-2 and antibody to CD3 were infused five times to 76 patients during the first 6 months after HCC resection. After a median follow-up of 4.4 years, they found adoptive immunotherapy could lower the recurrence rate (decreasing the frequency of recurrence by 18%) and improve significantly the recurrence-free survival ($p=0.01$) and disease-specific survival ($p=0.04$), but not OS. The possible reason might be that adoptive immunotherapy can eliminate the micrometastatic lesion in the remnant liver, but can't prevent multicentric recurrence [2]. Very recently, Kuang *et al*. conducted a Phase II RCT on 41 patients to determine the effect of autologous formalin-fixed tumor vaccine (AFTV) in protecting against postsurgical recurrence of HCC. After a median follow-up of 15 months, the risk of recurrence in vaccinated patients was reduced by 81%. Vaccination significantly prolonged the time to first recurrence and improved both the DFS and OS rates. AFTV played a significant role in preventing recurrence in patients with small tumors [76]. This promising results need to be further validated in a large-scale randomized trial.

Acyclic Retinoid Acid

Retinoid acid is an inducer of differentiation. HCC in cirrhotic patients contains lower levels of endogenous retinoids and simultaneously is insensitive to RA because of malfunction of its nuclear receptor, retinoid X receptor alpha (RXRalpha) [77, 78]. But, it is AR and not natural RA, which prevents phosphorylation of RXRalpha and restores the function of RXRalpha, making HCC cells sensitive to the endogenous ligand, 9-cis-RA. AR also enhances the sensitivity of HCC cells to interferon-alpha and -beta, and thereby indirectly promotes apoptosis induced by interferon [77]. Many trials in patients with HCV-related HCC treated by post-operative acyclic retinoic acid (ARA) have showed that long-term ARA treatment could successfully prevent the recurrence of HCC, improve the OS and DFS of HCC patients [77-80]. It might be associated with a disappearance in serum levels of AFP-L3, a marker of occult cancer clones in the liver, suggesting eradication of latent malignant clones from patients' liver (a novel concept of 'clonal deletion' with AR) [77]. Further development of more effective retinoids as well as their use in combination with other classes of anticancer agents including immunopreventive drugs like interferons may provide strategies for cancer prevention [81].

MANAGEMENT FOR RECURRENT HCC

Many kinds of treatment strategies, including surgical re-resection, TACE, regional cancer therapies such as radiofrequency ablation (RFA), chemotherapy have been tried and proven to be potentially helpful for the control of HCC recurrence and metastasis. And any treatment at recurrence has been regarded as a significant prognostic factor for patients with recurrent HCC. Therefore, in order to improve prognosis after recurrence, we should actively treat the recurrent hepatic lesions whenever possible. However, there iare few RCT to evaluate the effect of these modalities on the recurrence and metastasis of HCC. (Table **3**).

Surgical Treatment

Recently many studies have demonstrated that repeat hepatectomy is effective for treating intrahepatic recurrent HCC in selected patients, and prolong the survival [82-84]. The 5-year overall survival rate after re-resection for recurrent HCC could be 18.2% [82], 36.6% [13], 56% [83], to even 85% (recurrence after small HCC resection) [84], which are similar to the curative resection for the primary HCC. In a multivariate analysis, absence of portal invasion at the 2nd resection, tumor numbers at primary hepatectomy, and a disease-free interval after primary hepatectomy, extrahepatic recurrence, recurrent tumor number and size were independent prognostic factors after the 2nd resection. Early detection and re-resection of recurrent tumors are important and correlated with better post-recurrent survival rates [82]. Repeat hepatectomy is the preferred treatment for patients with recurrent HCC less than 3 tumor nodules and sufficient liver function, particularly for those patients with resectable recurrent HCC from MO other than that from IM [85, 86]. Further, repeat hepatectomy provides a favorable quality of life in patients with recurrent HCC. The incidence of deteriorated performance status in patients received repeat hepatic resection was lower than in those received other kinds of treatments such as hepatic arterial infusion chemotherapy because of better psychological function in patients undergoing repeat hepatic resection [87].

Aggressive management with combined resection of isolated extrahepatic recurrence and re-resection or locoregional therapy for intrahepatic recurrence may also offer long-term survival in selected patients who develop both intrahepatic and extrahepatic recurrences after hepatectomy for HCC [88]. In 2001, Zhou *et al*. reported that 3 patients who received repeated resection for solitary lung metastasis after hepatectomy for small HCC had survived 24.7, 15.8, and 7.9 years, respectively [13]. Even the patients with tumor thrombi in the inferior vena cava (IVC) from adrenal metastasis are indicated for undergoing adrenalectomy combined with intracaval thrombectomy, which could also produce a DFS over 3 years [89]**.** However, patients with multiple intra- or extra-hepatic metastases are not suitable for repeated resection [13].

Liver transplantation, which represents the simultaneous treatment of tumor and primary liver disease, has been recently suggested as a rational strategy for patients suffering from recurrent HCC after the primary resection of HCC ("salvage" transplantation), and tumor control by

Table 3. Management of Metastasis and Recurrence of Hepatocellular Carcinoma

Strategies	Efficient	Patients' selection
Surgical Treatment		
Repeat resection	Most effective, preferred treatment long-term survival a favorable quality of life	Patients with recurrent HCC <= 3 nodules and sufficient liver function Particularly, patients with recurrence from MO. Solitary extrahepatic metastasis (solitary lung, adrenal)
"Salvage" transplantation	Effective in selected patients	Recurrent tumor number: <=3 Recurrent tumor size: <=5 cm Liver function: Child-Pugh A or B or even C
Regional Cancer Therapies		
Regional ablation	Effective in selected patients	Patients with number <= 3 and size <=3cm of recurrent nodules Liver function: Child-Pugh A or B Not suitable for or willing to receiving surgery
TACE	Effective in selected patients	Patients with multiple intra-hepatic recurrence
Radiation Therapy	Effective in selected patients	Lymph node metastasis from HCC Adrenal, bone and spinal metastasis Tumor thrombi in portal vein, bile duct and IVC.
Chemotherapy	Generally, not effective TAC + systemic IFN-alpha: new trend	Multiple intra- or/and extra extrahepatic metastasis with good liver function

transplantation is possible in selected patients [90-93]. And the majority (79%) of those patients with recurrent HCC may be eligible for salvage transplantation [93]. However, certain criteria regarding the number (up to three) and size (up to 5 cm) of recurrent tumor nodules have to be observed in order to ensure a low risk of both the intra- and extra-hepatic spread after operation [92, 93]. And as the primary liver transplantation for HCC, salvage transplantation is also good choice for those patients with small recurrent HCC and decompensated liver function.

Regional Cancer Therapies

RFA is regarded as the treatment of first choice in the management of intrahepatic recurrence that is not suitable for surgery. For multifocal recurrence, TACE is needed. RFA can be useful as a complementary technique for lesions not completely treated by TACE. RFA could also be one therapeutic modality for bone metastasis from HCC [94].

Radiation Therapy

Radiation therapy could be beneficial when other therapies present some difficulties regarding the application or are performed incompletely. Radiation therapy could be considered in addition to other regional therapies for the treatment of recurrent or re-recurrent HCC, and that radiation therapy can be repeated in selected patients.

Radiation therapy could also provide clinical benefit for the patients with lymph node metastasis from HCC, who are not suitable for TACE, regional therapies and surgical resection. Recently, 29 HCC patients with abdominal lymph node metastasis received radiation therapy in author's hospital. The objective regression (complete response and partial response) rate was 100%. The 1-year and 2-year OS rates were 43.5% and 10.5%, respectively [95]. Radiation therapy could also be used to control the adrenal, bone and spinal metastasis, and tumor thrombi in portal vein, bile duct and IVC.

The major concern is that radiation therapy could suppress the patients' immunity induce distance metastasis and multiple IM after radiation therapy.

Chemotherapy

Generally, chemotherapy is not very effective for recurrence and metastasis of HCC. However, recently, Maeda found that low-dose cisplatin infusion combined with oral tegafur and uracil administration for the treatment of lung metastases from HCC may be an effective regimen with a high response rate and acceptable toxicities, although a larger study will be necessary to confirm the efficacy. The overall response rate was 50%. The quality of life of these patients is well preserved [96].

Combined therapy consisting of intraarterial chemotherapy (such as cisplatin) and systemic IFN-alpha is a trend in this area, which may be useful as a palliative treatment for HCC patients with extrahepatic metastasis [97].

SUMMARY AND PERSPECTIVE

In summary, metastasis and recurrence has become one major concern in patients with HCC after surgical resection. Knowledge of the risk factors for postoperative recurrence provides a basis for logical approaches to prevention. Identifying new indicators of tumor recurrence, evaluation of molecular markers or models for HCC classification, are main recommendations for future work. Biotherapy is one hopeful strategy with a good tolerance, and it plays more and more important role in the prevention of recurrence and metastasis of HCC after operation. The combination of intraarterial chemotherapy and systemic IFN-alpha (both

neoadjuvant and adjuvant) or adoptive immunotherapy is one new trend. Currently, the most realistic approach is early detection and aggressive management (including repeat surgical resection and salvage transplantation, regional ablation, radiotherapy, etc.) of recurrence. Randomized trials are needed to define the roles of various treatment modalities for recurrence and the benefit of multimodality therapy.

REFERENCES

[1] Ercolani G, Grazi GL, Ravaioli M, *et al*. Liver resection for hepatocellular carcinoma on cirrhosis: univariate and multivariate analysis of risk factors for intrahepatic recurrence. Ann Surg 2003; 237:536-43.

[2] Takayama T, Sekine T, Makuuchi M, *et al*. Adoptive immunotherapy to lower postsurgical recurrence rates of hepatocellular carcinoma: a randomised trial. Lancet 2000;356:802-7

[3] Tang ZY, Ye SL, Liu YK, *et al*. A decade's studies on metastasis of hepatocellular carcinoma. J Cancer Res Clin Oncol 2004; 130:187-96.

[4] Poon RT, Fan ST. Hepatectomy for hepatocellular carcinoma: patient selection and postoperative outcome. Liver Transpl 2004;10:S39-45.

[5] Sakon M, Nagano H, Nakamori S, *et al*. Intrahepatic recurrences of hepatocellular carcinoma after hepatectomy: analysis based on tumor hemodynamics. Arch Surg 2002;137: 94-9

[6] Ng IO, Guan XY, Poon RT, Fan ST, Lee JM. Determination of the molecular relationship between multiple tumour nodules in hepatocellular carcinoma differentiates multicentric origin from intrahepatic metastasis. J Pathol 2003;199:345-53.

[7] Ikeda K, Arase Y, Kobayashi M, *et al.* Significance of multicentric cancer recurrence after potentially curative ablation of hepatocellular carcinoma: a long term cohort study of 892 patients with viral cirrhosis. J Gastroenterol 2003;38:865-76.

[8] Izumi N. Is the incidence of intrahepatic multicentric recurrence of hepatocellular carcinoma more frequent in "the carcinogenic stage" than in liver cirrhosis? J Gastroenterol 2003; 38:918-20.

[9] Morimoto O, Nagano H, Sakon M, *et al*. Diagnosis of intrahepatic metastasis and multicentric carcinogenesis by microsatellite loss of heterozygosity in patients with multiple and recurrent hepatocellular carcinomas. J Hepatol 2003;39:215-21.

[10] Yamamoto T, Kajino K, Kudo M, Sasaki Y, Arakawa Y, Hino O. Determination of the clonal origin of multiple human hepatocellular carcinomas by cloning and polymerase chain reaction of the integrated hepatitis B virus DNA. Hepatology 1999; 29: 1446-52

[11] Imamura H, Matsuyama Y, Tanaka E, *et al*. Risk factors contributing to early and late phase intrahepatic recurrence of hepatocellular carcinoma after hepatectomy. J Hepatol 2003;38:200-7.

[12] Qin LX, Tang ZY. Recent progress in predictive biomarkers for metastatic recurrence of human hepatocellular carcinoma: a review of the literature. J Cancer Res Clin Oncol 2004[Epub ahead of print]

[13] Zhou XD, Tang ZY, Yang BH, *et al*. Experience of 1000 patients who underwent hepatectomy for small hepatocellular carcinoma. Cancer 2001;91:1479-86.

[14] Chang CH, Chau GY, Lui WY, Tsay SH, King KL, Wu CW. Long-term results of hepatic resection for hepatocellular carcinoma originating from the noncirrhotic liver. Arch Surg 2004;139:320-5

[15] Kubo S, Nishiguchi S, Hirohashi K, Tanaka H, Shuto T, Kinoshita H. Randomized clinical trial of long-term outcome after resection of hepatitis C virus-related hepatocellular carcinoma by postoperative interferon therapy. Br J Surg 2002; 89: 418-22

[16] Chen JD, Liu CJ, Lee PH, *et al*. Hepatitis B genotypes correlate with tumor recurrence after curative resection of hepatocellular carcinoma. Clin Gastroenterol Hepatol 2004;2:64-71.

[17] Poon RT, Fan ST, Lo CM, Liu CL, Ng IO, Wong J. Long-term prognosis after resection of hepatocellular carcinoma associated with hepatitis B-related cirrhosis. J Clin Oncol 2000;18:1094-101

[18] Regimbeau JM, Abdalla EK, Vauthey JN, *et al*. Risk factors for early death due to recurrence after liver resection for hepatocellular carcinoma: results of a multicenter study. J Surg Oncol 2004;85:36-41.

[19] Schoniger-Hekele M, Muller C, Kutilek M, Oesterreicher C, Ferenci P, Gangl A. Hepatocellular carcinoma in Central Europe: prognostic features and survival. Gut 2001; 48:103-9

[20] Si MS, Amersi F, Golish SR, *et al.* Prevalence of metastases in hepatocellular carcinoma: risk factors and impact on survival. Am Surg 2003;69:879-85.

[21] Ouchi K, Sugawara T, Fujiya T, *et al*. Prediction of recurrence and extratumor spread of hepatocellular carcinoma following resection. J Surg Oncol 2000;75:241-5

[22] Tangkijvanich P, Anukulkarnkusol N, Suwangool P, *et al*. Clinical characteristics and prognosis of hepatocellular carcinoma: analysis based on serum alpha-fetoprotein levels. J Clin Gastroenterol 2000;31:302-8

[23] Kaibori M, Matsui Y, Yanagida H, Yokoigawa N, Kwon AH, Kamiyama Y. Positive status of alpha-fetoprotein and des-gamma-carboxy prothrombin: Important prognostic factor for recurrent hepatocellular carcinoma. World J Surg 2004 [Epub ahead of print]

[24] Ijichi M, Takayama T, Matsumura M, Shiratori Y, Omata M, Makuuchi M. alpha-Fetoprotein mRNA in the circulation as a predictor of postsurgical recurrence of hepatocellular carcinoma: a prospective study. Hepatology 2002;35:853-60.

[25] Witzigmann H, Geissler F, Benedix F, *et al*. Prospective evaluation of circulating hepatocytes by alpha-fetoprotein messenger RNA in patients with hepatocellular carcinoma. Surgery 2002;131:34-43.

[26] Mou DC, Cai SL, Peng JR, *et al*. Evaluation of MAGE-1 and MAGE-3 as tumour-specific markers to detect blood dissemination of hepatocellular carcinoma cells. Br J Cancer 2002;86:110-6.

[27] Waguri N, Suda T, Nomoto M, *et al*. Sensitive and specific detection of circulating cancer cells in patients with hepatocellular carcinoma; detection of human telomerase reverse transcriptase messenger RNA after immunomagnetic separation. Clin Cancer Res. 2003;9:3004-11.

[28] Pan HW, Ou YH, Peng SY, *et al*. Overexpression of osteopontin is associated with intrahepatic metastasis, early recurrence, and poorer prognosis of surgically resected hepatocellular carcinoma. Cancer 2003; 98:119-27.

[29] Ye QH, Qin LX, Forgues M, *et al*. Predicting hepatitis B virus-positive metastatic hepatocellular carcinoma using gene expression profiling and supervised machine learning. Nature Med 2003; 9: 416-23

[30] Nanashima A, Yano H, Yamaguchi H, *et al*. Immunohistochemical analysis of tumor biological factors in hepatocellular carcinoma: relationship to clinicopathological factors and prognosis after hepatic resection. J Gastroenterol 2004;39:148-54.

[31] Poon RT, Ng IO, Lau C, *et al*. Tumor microvessel density as a predictor of recurrence after resection of hepatocellular carcinoma: a prospective study. J Clin Oncol 2002;20:1775-85.

[32] Sun HC, Tang ZY, Li XM, *et al*. Microvessel density of hepatocellular carcinoma: its relationship with prognosis. J Cancer Res Clin Oncol 1999;125:419-26

[33] Chao Y, Li CP, Chau GY, *et al*. Prognostic significance of vascular endothelial growth factor, basic fibroblast growth factor, and angiogenin in patients with resectable hepatocellular carcinoma after surgery. Ann Surg Oncol 2003;10:355-62.

[34] Poon RT, Fan ST, Wong J. Clinical implications of circulating angiogenic factors in cancer patients. J Clin Oncol 2001;19:1207-25

[35] Poon TP, Lau PY, Cheung ST, Yu WC, Fan ST. Quantitative correlation of serum levels and tumor expression of vascular endothelial growth factor in patients with hepatocellular carcinoma. Cancer Res 2003;63: 3121-6

[36] Jeng KS, Sheen IS, Chen BF, Wu JY. Is the p53 gene mutation of prognostic value in hepatocellular carcinoma after resection? Arch Surg 2000;135:1329-33

[37] Fiorentino M, Altimari A, D'Errico A, *et al*. Acquired expression of p27 is a favorable prognostic indicator in patients with hepatocellular carcinoma. Clin Cancer Res 2000;6:3966-72

[38] Matsumura T, Makino R, Mitamura K. Frequent down-regulation of E-cadherin by genetic and epigenetic changes in the malignant progression of hepatocellular carcinomas. Clin Cancer Res 2001;7:594-9.

[39] Giannelli G, Fransvea E, Bergamini C, Marinosci F, Antonaci S. Laminin-5 chains are expressed differentially in metastatic and nonmetastatic hepatocellular carcinoma. Clin Cancer Res 2003;9:3684-91.

[40] Theret N, Musso O, Turlin B, *et al*. Increased extracellular matrix remodeling is associated with tumor progression in human hepatocellular carcinomas. Hepatology 2001;34:82-8.

[41] Nishida N, Fukuda Y, Komeda T, *et al*. Prognostic impact of multiple allelic losses on metastatic recurrence in hepatocellular carcinoma after curative resection. Oncology 2002;62:141-8.

[42] Qin LX, Tang ZY, Sham JST, Ma ZC, Ye SL, Zhou XD. The association of chromosome 8p deletion and tumor metastasis in human hepatocellular carcinoma. Cancer Res 1999;59:5662-5

[43] Qin LX, Tang ZY, Ye SL, *et al*. Chromosome 8p deletion is associated with metastasis of human hepatocellular carcinoma when high and low metastatic models are compared. J Cancer Res Clin Oncol 2001;127:482-8.

[44] Zhang LH, Qin LX, Ma ZC, *et al*. Allelic Imbalance regions on Chromosomes 8p, 17p and 19p related to metastasis of hepatocellular carcinoma: Comparison between matched primary and metastatic lesions in 22 patients by genome-wide microsatellite analysis. J Cancer Res Clin Oncol 2003;129:279-86

[45] Itano O, Ueda M, Kikuchi K, *et al*. A new predictive factor for hepatocellular carcinoma based on two-dimensional electrophoresis of genomic DNA. Oncogene 2000;19:1676-83

[46] Cheung ST, Chen X, Guan XY, *et al*. Identify metastasis-associated genes in hepatocellular carcinoma through clonality delineation for multinodular tumor. Cancer Res 2002;62:4711-21.

[47] Iizuka N, Oka M, Yamada-Okabe H, *et al*. Oligonucleotide microarray for prediction of early intrahepatic recurrence of hepatocellular carcinoma after curative resection. Lancet 2003;361:923-9.

[48] Ding SJ, Li Y, Shao XX, *et al*. Proteome analysis of hepatocellular carcinoma cell strains, MHCC97-H and MHCC97-L, with different metastasis potentials. Proteomics 2004;4:982-94.

[49] Ding SJ, Li Y, Tan YX, *et al*. From proteomic analysis to clinical significance: overexpression of cytokeratin 19 correlates with hepatocellular carcinoma metastasis. Mol Cell Proteomics 2004;3:73-81.

[50] Welsh JB, Sapinoso LM, Kern SG, *et al*. Large-scale delineation of secreted protein biomarkers overexpressed in cancer tissue and serum. Proc Natl Acad Sci USA 2003;100:3410-5.

[51] Poon RT, Ng IO, Fan ST, *et al*. Clinicopathologic features of long-term survivors and disease-free survivors after resection of hepatocellular carcinoma: a study of a prospective cohort. J Clin Oncol 2001;19:3037-44.

[52] Kudo M, Chung H, Osaki Y. Prognostic staging system for hepatocellular carcinoma (CLIP score): its value and limitations, and a proposal for a new staging system, the Japan Integrated Staging Score (JIS score). J Gastroenterol 2003;38:207-15.

[53] Omagari K, Honda S, Kadokawa Y, *et al.* Preliminary analysis of a newly proposed prognostic scoring system (SLiDe score) for hepatocellular carcinoma. J Gastroenterol Hepatol 2004l;19:805-11.

[54] Chan ES, Chow PK, Tai B, Machin D, Soo K. Neoadjuvant and adjuvant therapy for operable hepatocellular carcinoma. Cochrane Database Syst Rev 2000;CD001199

[55] Little SA, Fong Y. Hepatocellular carcinoma: current surgical management. Semin Oncol 2001;28:474-486

[56] Schwartz JD, Schwartz M, Mandeli J, Sung M. Neoadjuvant and adjuvant therapy for resectable hepatocellular carcinoma: review of the randomised clinical trials. Lancet Oncol 2002;3:593-603.

[57] Mathurin P, Raynard B, Dharancy S, *et al*. Meta-analysis: evaluation of adjuvant therapy after curative liver resection for hepatocellular carcinoma. Aliment Pharmacol Ther 2003;17:1247-61.

[58] Sun HC, Tang ZY. Preventive treatments for recurrence after curative resection of hepatocellular carcinoma - A literature review of randomized control trials. World J Gastroenterol 2003; 9: 635-40

[59] Yoshida T, Sakon M, Umeshita K, *et al*. Appraisal of transarterial immunoembolization for hepatocellular carcinoma: a clinicopathologic study. J Clin Gastroenterol 2001;32:59-65

[60] Sato Y, Ichida T, Ito S, Hatakeyama K. Preoperative administration of 5-FU and interferon beta may prevent recurrence of hepatitis B and C virus. Am J Gastroenterol 2002;97:215-216

[61] Lau WY, Leung TW, Ho SKW, *et al*. Adjuvant intra-arterial lipiodol iodine-131 for resectable hepatocellular carcinoma: a prospective randomised trial. Lancet 1999; 353: 797-801

[62] Boucher E, Corbinais S, Rolland Y, *et al*. Adjuvant intra-arterial injection of iodine-131-labeled lipiodol after resection of hepatocellular carcinoma. Hepatology 2003;38:1237-41.

[63] Izumi R, Shimizu K, Iyobe T, *et al*. Postoperative adjuvant hepatic arterial infusion of Lipiodol containing anticancer drugs in patients with hepatocellular carcinoma. Hepatology 1994;20: 295-301

[64] Lai ECS, 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: 183-8

[65] Ono T, Yamanoi A, Nazmy El Assal O, Kohno H, Nagasue N. Adjuvant chemotherapy after resection of hepatocellular carcinoma causes deterioration of long-term prognosis in cirrhotic patients: metaanalysis of three randomized controlled trials. Cancer 2001; 91: 2378-85

[66] Huang YH, Wu JC, Lui WY, *et al.* Prospective case-controlled trial of adjuvant chemotherapy after resection of hepatocellular carcinoma. World J Surg 2000;24:551-5

[67] Kwok PC, Lam TW, Lam PW, *et al*. Randomized controlled trial to compare the dose of adjuvant chemotherapy after curative resection of hepatocellular carcinoma. J Gastroenterol Hepatol 2003;18:450-5.

[68] Zhou J, Tang ZY, Fan J, *et al*. Capecitabine inhibits postoperative recurrence and metastasis after liver cancer resection in nude mice with relation to the expression of platelet-derived endothelial cell growth factor. Clin Cancer Res 2003;9:6030-7.

[69] Kubo S, Nishiguchi S, Hirohashi K, *et al*. Effects of long-term postoperative interferon-alpha therapy on intrahepatic recurrence after resection of hepatitis C virus-related hepatocellular carcinoma. A randomized controlled trial. Ann Intern Med 2001; 134: 963-7

[70] Ikeda K, Arase Y, Saitoh S, *et al*. Interferon beta prevents recurrence of hepatocellular carcinoma after complete resection or ablation of the primary tumor-A prospective randomized study of hepatitis C virus-related liver cancer. Hepatology 2000;32: 228-32

[71] Lin SM, Lin CJ, Hsu CW, *et al*. Prospective randomized controlled study of interferon-alpha in preventing hepatocellular carcinoma recurrence after medical ablation therapy for primary tumors. Cancer 2004;100:376-82.

[72] Suou T, Mitsuda A, Koda M, *et al*. Interferon alpha inhibits intrahepatic recurrence in hepatocellular carcinoma with chronic hepatitis C: a pilot study. Hepatol Res 2001;20:301-311

[73] Camma C, Giunta M, Andreone P, Craxi A. Interferon and prevention of hepatocellular carcinoma in viral cirrhosis: an evidence-based approach. J Hepatol 2001;34: 593-602

[74] Ikeda K, Kobayashi M, Saitoh S, *et al*. Recurrence rate and prognosis of patients with hepatocellular carcinoma that developed after elimination of hepatitis C virus RNA by interferon therapy. A closed cohort study including matched control patients. Oncology. 2003;65:204-10.

[75] Wang L, Tang ZY, Qin LX, *et al.* 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

[76] Kuang M, Peng BG, Lu MD, *et al*. Phase II randomized trial of autologous formalin-fixed tumor vaccine for postsurgical recurrence of hepatocellular carcinoma. Clin Cancer Res 2004;10:1574-9.

[77] Kojima S, Okuno M, Matsushima-Nishiwaki R, Friedman SL, Moriwaki H. Acyclic retinoid in the chemoprevention of hepatocellular carcinoma. Int J Oncol 2004;24:797-805.

[78] Okuno M, Kojima S, Akita K, *et al.* Retinoids in liver fibrosis and cancer. Front Biosci 2002;7:d204-18.

[79] Muto Y, Moriwaki H, Ninomiya M, *et al*. Prevention of second primary tumors by an acyclic retinoid, polyprenoic acid, in patients with hepatocellular carcinoma. Hepatoma Prevention Study Group. N Engl J Med 1996;334:1561-7.

[80] Muto Y, Saito A. Prevention of second primary tumors by an acyclic retinoid in patients with hepatocellular carcinoma. N Engl J Med 1999; 340: 1046-7

[81] Okuno M, Kojima S, Matsushima-Nishiwaki R, *et al*. Retinoids in cancer chemoprevention. Curr Cancer Drug Targets 2004;4:285-98.

[82] Chen WT, Chau GY, Lui WY, *et al*. Recurrent hepatocellular carcinoma after hepatic resection: prognostic factors and long-term outcome. Eur J Surg Oncol 2004;30:414-20.

[83] Minagawa M, Makuuchi M, Takayama T, Kokudo N. Selection criteria for repeat hepatectomy in patients with recurrent hepatocellular carcinoma. Ann Surg. 2003;238:703-10.

[84] Shimozawa N, Hanazaki K. Long term prognosis after hepatic resection for small hepatocellular carcinoma. J Am Coll Surg 2004;198:356-65.

[85] Matsuda M, Fujii H, Kono H, Matsumoto Y. Surgical treatment of recurrent hepatocellular carcinoma based on the mode of recurrence: repeat hepatic resection or ablation are good choices for patients with recurrent multicentric cancer. J Hepatobiliary Pancreat Surg. 2001;8:353-9.

[86] Sugimachi K, Maehara S, Tanaka S, Shimada M, Sugimachi K. Repeat hepatectomy is the most useful treatment for recurrent hepatocellular carcinoma. J Hepatobiliary Pancreat Surg 2001;8:410-6.

[87] Tanabe G, Ueno S, Maemura M, *et al*. Favorable quality of life after repeat hepatic resection for recurrent hepatocellular carcinoma. Hepatogastroenterology 2001;48:506-10.

[88] Poon RT, Fan ST, O'Suilleabhain CB, Wong J. Aggressive management of patients with extrahepatic and intrahepatic recurrences of hepatocellular carcinoma by combined resection and locoregional therapy. J Am Coll Surg 2002;195:311-8.

[89] Momoi H, Shimahara Y, Terajima H, *et al*. Management of adrenal metastasis from hepatocellular carcinoma. Surg Today 2002;32:1035-41.

[90] Majno PE, Sarasin FP, Mentha G, Hadengue A. Primary liver resection and salvage transplantation or primary liver transplantation in patients with single, small hepatocellular carcinoma and preserved liver function: an outcome-oriented decision analysis. Hepatology 2000;31:899-906.

[91] Hess D, Humar A, Sielaff TD. Living related liver transplantation for recurrent hepatocellular carcinoma in a normal liver. Clin Transplant 2002;16:240-2.

[92] Jonas S, Steinmuller T, Settmacher U, Langrehr J, Muller A, Neuhaus P. Liver transplantation for recurrent hepatocellular carcinoma in Europe. J Hepatobiliary Pancreat Surg 2001;8:422-6.

[93] Poon RT, Fan ST, Lo CM, Liu CL, Wong J. Long-term survival and pattern of recurrence after resection of small hepatocellular carcinoma in patients with preserved liver function: implications for a strategy of salvage transplantation. Ann Surg 2002;235:373-82.

[94] Maruyama M, Asano T, Kenmochi T, *et al*. Radiofrequency ablation therapy for bone metastasis from hepatocellular carcinoma: case report. Anticancer Res 2003;23:2987-9.

[95] Zeng ZC, Tang ZY, Yang BH, *et al.* Radiation therapy for the locoregional lymph node metastases from hepatocellular carcinoma, phase I clinical trial. Hepatogastroenterology 2004;51:201-7.

[96] Maeda T, Itasaka H, Takenaka K, *et al*. Low-dose cisplatin plus oral tegafur and uracil for the treatment of lung metastases of hepatocellular carcinoma. Hepatogastroenterology 2003;50:1583-6.

[97] Chung YH, Song IH, Song BC, *et al.* Combined therapy consisting of intraarterial cisplatin infusion and systemic interferon-alpha for hepatocellular carcinoma patients with major portal vein thrombosis or distant metastasis. Cancer 2000;88:1986-91.

Received: August 3, 2004 Accepted: September 9, 2004