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• REVIEW •

The prognostic significance of clinical and pathological features in hepatocellular carcinoma

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Abstract

The prognosis of patients with HCC still remains dismal. The life expectancy of HCC patients is hard to predict because of the high possibility of postoperative recurrence. Many factors, such as patient's general conditions, macroscopic tumor morphology, as well as tumor hitopathology features, have been proven of prognostic significance. Female HCC patient often has a better prognosis than male patient, which might be due to the receptor of sex hormones. Younger patients often have tumors with higher invasiveness and metastatic potentials, and their survival and prognosis are worse than the older ones. Co-existing hepatitis status and hepatic functional reserve have been confirmed as risk factors for recurrence. Serum alpha-fetoprotein (AFP) is useful not only for diagnosis, but also as a prognostic indicator for HCC patients. AFP mRNA has been proposed as a predictive marker of HCC cells disseminated into the circulation and for metastatic recurrence. Many pathologic features, such as tumor size, number, capsule state, cell differentiation, venous invasion, intrahepatic spreading, and advanced pTNM stage, are the best-established risk factors for recurrence and important aspects affecting the prognosis of patients with HCC. Marked inflammatory cell infiltration in the tumor could predict a better prognosis. Clinical stage is still the most important factor influencing on the prognosis. Extratumor spreading and lymph nodal metastasis are independent predictors for poor outcome. Some new predictive systems have recently been proposed. Different strategies of treatment might have significant different effects on the patients' prognosis. To date, surgical resection is still the only potentially curative treatment for HCC, including localized postoperative recurrences. Extent of resection, blood transfusion, occlusion of porta hepatis, and blood loss affect the survival and prognosis of HCC patients. Regional therapies provide alternative ways to improve the prognosis of HCC patients who have no opportunity to receive surgical treatment or postoperative recurrence. The combination of these treatment modalities is hopeful to further improve the prognosis. The efficacies of neoadjuvant (preoperative) or adjuvant (postoperative) chemotherapy or chemoembolization in preventing recurrence and on the HCC prognosis still remain great controversy, and deserves further evaluation. Biotherapy, including IFN-alpha therapy, will play more important role in preventing recurrence and metastasis of HCC after operation.

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INTRODUCTION

The outcome for patients with hepatocellular carcinoma (HCC) still remains dismal, although it has been proven much in the past few decades, a definitive subset is cured by surgery only, and encouraging long-term survival of patients have been obtained in some clinical centers. The high possibility of intrahepatic and/or extrahepatic recurrence postoperatively remains one major obstacle for further improving the survival and prognosis of HCC patients. The life expectancy of HCC patients is hard to predict, making it difficult to decide the patient's prognosis. 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,), tumor pathohistology features, as well as effective treatment and adjuvant therapies, have been proven of prognostic significance. In recent years, as the understanding of tumor biology and the development of molecular biology techniques, many molecular factors (biomarkers) have been shown related to prognosis[1-11]. In this review, we will focus on the prognostic significance of clinical and pathological features of HCC.

PATIENTS'SEX AND AGE

Sex and sex hormone related factors

Many reports indicate that female HCC patient more frequently has a well-encapsulated, less invasive tumor, and longer survival, lower recurrent rate, and better prognosis than male patient. These might be due to the receptor of sex hormones[5,12]. Both androgen receptor (AR) and estrogen receptor (ER) are found closely related to the prognosis of HCC patients. The 5-year survival rates of AR negative, ER negative, ER positive, or AR positive HCC patients were 55%,

24%, 10%, and 0%, respectively. ER positive HCC has less malignant biologic behavior and a better prognosis than ER negative ones, with higher percentages of single nodule, complete encapsulation, and lower PCNA labeled index. And the ER positive rate of small HCC (62.5%) is higher than that of large HCC (30.4%). The presence of variant liver ER transcripts in the tumor is the strongest negative predictor of survival in inoperable HCC, with spontaneous survival significantly worse than that of patients with wild-type ER. HBsAg-positive patients with variant receptors have a even worse survival[12]. But there is still controversy with the relationship between the better prognosis of female HCC patients and the sex hormone receptors.

Age

Younger HCC patients often have tumors with higher invasiveness and metastatic potentials, higher recurrence possibility, and their survival and prognosis are worse than the older ones. However, Chedid found male, older patients often had poorly differentiated tumors, and poorer survivals, and age younger than 45 years was a good prognostic factor[13]. In authors' institute, no significant difference between the younger and older patients was found[14].

CO-EXISTING HEPATITIS STATUS AND LIVER CIRRHOSIS

Co-existing hepatitis status and liver cirrhosis are other important factors influencing the prognosis of HCC patients. The inflammatory activity and hepatic reserve have been confirmed as risk factors for recurrence. Longer disease-free survival (DFS) is found in patients without active hepatitis, and suppression of co-existing hepatitis is necessary to achieve better DFS[15]. The postoperative overall and disease-free survival rates of patients without hepatitis viral infection (N-HCC) are better than those hepatitis B virus-related HCC (B-HCC) and HBV-HCV double infection HCC(D-HCC)patients. The postoperative long-term survival rate of patients seronegative for HBsAg is greater than that of patients seropositive for HBsAg[16]. This is due to N-HCC cases have a good liver function reservation, and have no synchronous and metachronous multicentric occurrence[17]. D-HCC often has a higher surgical complication rate and hospital mortality, and recurred earlier after hepatectomy[18].

A high viral load is an independent risk factor for recurrence. The HBeAg, wild-type HBV are more likely to be found in patients with a high viral load, while precore mutant-type HBV is useful for estimating a patient's prognosis after resection of B-HCC[19]. Patients infected with genotype 1b of HCV may have a relatively high risk of ongoing hepatocarcinogenesis and more aggressive progression of associated liver dysfunction, resulting in a poorer outcome than with other genotypes[20, 21].

Functional reserve of the remnant cirrhotic liver is another independent prognostic factor. Hepatic functional damage immediately after hepatectomy is a significant risk factor for early intrahepatic recurrence[22]. 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, are important predictive markers for DFS of HCC patients[23-25]. According to the scoring of hepatitis activity index (HAI), the histologic activity of hepatitis was closely related to the HCC recurrence, the HCC patients with middle hepatitis activity (HAI score of 6-9) in the non-tumor liver tissue had a higher 2-year intrahepatic recurrent rate[26]. Recurrence hardly could be avoided in the patients with liver dysfunction[27,28]. The serum albumin level of patients was also an independent risk factor of early recurrence, while liver cirrhosis and serum bilirubin were independent prognostic factors for late recurrence after HCC resection[29]. Patients with Karnofsky index <80%, serum bilirubin >50micromol/l, serum alkaline phosphatase at least twice the upper limit of normal range, and prothrombin time <70% of normal level have been found to have a poor prognosis[14,30].

TUMOR MAKERS

Serum alpha-fetoprotein (AFP) is useful not only for diagnosis, but also as a prognostic indicator for HCC patients. Patients with high AFP levels at diagnosis tended to have greater tumor size, bilobar involvement, massive or diffuse types, and portal vein thrombosis. The median survival rates with normal AFP (<20IU/mL), or with moderately elevated AFP (20-399IU/mL) (6-7 months) were significantly longer than that with markedly elevated AFP (> or =400IU/mL) (3months)[31]. Nonetheless, a correlation could not be established between increased AFP and Okuda's stages, degree of tumor differentiation, or extrahepatic metastasis.

AFP mRNA has been proposed as a predictive marker of HCC cells disseminated into the circulation and for metastatic recurrence in many reports[32-37], but its clinical significance remains controversial[38-40]. The patients with positive AFP mRNA in peripheral blood were found to have a higher possibility of extrahepatic metastasis than those negative. Some of them could change to negative after adjacent treatment, whose overall and disease-free survival rates are much better than those with permanent positive AFP mRNA. So, AFP mRNA in peripheral blood of HCC patients in perioperative period might be a predictive marker for the early intrahepatic recurrence and distant metastasis after HCC resection[32,33]. In a recent report, circulating AFP mRNA was transiently detected in cirrhosis with no predictive value for HCC development.

Lens culinaris agglutinin A-reactive fraction of alpha-fetoprotein (AFP-L3) is found to be a useful indicator of distant metastasis and a poor prognosis for HCC. Patients with AFP-L3-positive had worse liver function and larger tumors compared to the negative group. They also had more advanced cancer with poor tumor histology compared to the negative group. Distant metastasis was diagnosed significantly more often in the positive group than that in the negative group[41].

Although DCP was not an independent prognostic factor, its measurement was effective in predicting HCC recurrence and had the advantage that it can be assessed before operation[42]. However, albumin mRNA in peripheral blood has no confirmed value for predicting circulating spread of HCC cells.

PATHOLOGICAL FEATURES OF TUMOR

Many pathologic factors of tumor itself, such as tumor size, number, capsule state, cell differentiation, venous invasion, presence of satellite nodules, and advanced pTNM stage, are the best-established risk factors for recurrence and important aspects affecting the prognosis of patients with HCC[43-46]. Assal *et al*. proposed an invasiveness scoring system to predict recurrence and survival after curative HCC resection, which consists of six variables including portal venous invasion, intrahepatic spreading, hepatic venous invasion, membrane invaded, and no tumor capsule, or capsule invaded. According to this system, HCC could be divided into three groups: low invasiveness HCC (A): 0-1 score, middle invasiveness (B): 2-4, and high invasiveness HCC (C): 5-11 scores. The recurrent rate increased as the score became higher. The prognosis of Group B and C patients were much worse than Group A[47].

Tumor size

Many studies have confirmed that tumor size is one independent

prognostic factor[46,50]. Both of the 5-year overall survival (OS) and disease-free survival (DFS) rates of small HCC(tumor largest diameter≤5cm) are better than that of large HCC (tumor diameter >5cm)[3,4-8,14,48].

Tumor number and capsule status

The prognosis of patient with single tumor nodule is much better than those with multiple nodules. However, there was still a different result, no significant difference between their overall and DFS rates could be found[49].

The patients with well-encapsulated HCC have a better prognosis than those with poor encapsulated. However, well-encapsulated and nonnecrotic HCCs have a significantly higher tumor pressure (TP) and great pressure gradient (TP-PVP), both of them are found to associate with venous invasion or intrahepatic metastasis[50].

Venous invasion and intra-or extrahepatic spreading

Venous invasion and intrahepatic metastasis (IM) might strongly reflect the invasiveness of HCC. They are also important independent factors for poor prognosis[45, 49, 51,52]. In Authors' institute, the 5-year survival rate of the HCC patients without portal vein thrombi (PVT) (63.9%) after operation is much higher than that of patients with PVT (40.8%). Ouchi K, *et al*. defined portal vein invasion (Vp) and IM as the extratumor spread, and found it was the only significant variable influencing recurrence in multivariate analysis. As a predictive factor for recurrence after resection of HCC, the extratumor spreads was found to be more accurate than is any single invasiveness parameter such as Vp or IM[53]. The patients with macroscopic portal vein invasion, microscopic vascular invasion, intrahepatic metastasis, poor differentiation, pleomorphism, sarcomatous change, vascular lake, and angiographic condensed pooling were more frequently found to have extremely poor prognosis[54]. The prognosis of patients with lymph nodal metastasis from HCC is generally poor, even if hepatic resection with regional LN dissection is performed[52,55].

Inflammatory cell infiltration

Marked inflammatory cell infiltration in the tumor could predict a better prognosis, which could attribute to the anti-tumor effect induced by cellular immunity of CD8+ and CD4+ T lymphocytes. Wada found the patients with HCCs less than 3 cm in diameter with marked inflammatory cell infiltration had a much lower recurrence rate after resection (9.1%) (compared with 47.7% in the controls), and a higher 5-year survival rate (100%) (compared with 65.1% in the controls). The tumor invasion into the portal vein in the vicinity of the tumor was much lower. Varying degrees of piecemeal necrosis of cancer nests produced by infiltrating lymphocytes were observed in all patients with marked inflammatory cell infiltration in the tumor[56].

CLINICAL STAGING

It is well known that clinical stage is the most important factor influencing on the prognosis of HCC patients. The most common used staging system is UICC's TNM (tumor, nodes, metastases). Okuda system is also used in some regions. Based on the current TNM staging system for human HCC, a new T staging system has been proposed to correlate the staging group with patient outcome after curative liver resection. In this new system, T1 is defined as no vascular invasion, small size (< or = 5cm), and solitary tumor; T2 as the presence of one of the following factors: size greater than 5cm, vascular invasion, or multiple tumors; T3 as the presence of two of the above three factors; and T4, the presence of all three factors. The new T staging system shows good correlation between the staging group and patient outcome. But this modified TNM system is not superior to the UICCpTNM system in predicting survival of HCC patients[43]. Portal vein invasion (Vp) and intrahepatic metastasis (IM) strongly reflect the invasiveness of HCC, and are predictive factors for recurrence and prognosis after resection of HCC[53]. Lymph nodal metastasis is one independent predictor for poor outcome[55].

A new score system, the Cancer of the Liver Italian Program (CLIP) score, recently is proposed, which includes the parameters involved in the Child-Pugh stage, plus macroscopic tumor morphology, AFP levels, and the presence or absence of portal thrombosis. The CLIP score is able to predict survival better than the Okuda or TNM staging system, accurately identify patients with different prognoses, particularly in the early phases of HCC[57]. Besides, Schoniger-Hekele developed a multivariate Cox proportional hazard model (Vienna survival model for HCC=VISUM-HCC) predicting survival, and found patients with serum bilirubin > 2mg/dl, portal vein thrombosis, prothrombin time <70%, AFP> 180mg/l, tumour mass >50%, and enlarged lymph nodes were independent predictors of survival. Applying the VISUM-HCC survival model to patients in Okuda stage 2 identified subgroups with an excellent and very poor prognosis for which different treatment modalities should be offered[52].

TREATMENT STRATEGIES RELATED

Effective treatment is important for prolonging the survival and improving the prognosis of HCC patients. Different strategies of treatment might have significant different effects on the patients' prognosis.

At present, surgery is still the only potentially curative treatment for HCC, including either partial hepatectomy or total hepatectomy with orthotopic liver transplantation (OLT). Although the survival rates of selected patients for transplantation and partial hepatectomy are comparable, the use of OLT is limited by the difficulty of obtaining donor livers, the expensive cost (particularly in developing countries)[58]. So, surgical resection is still the most important way to obtain long-term survivals. In recent years, regional cancer therapies, such as transcatheter arterial chemoembolization (TACE), and vary kinds of liver tumor ablation therapies (including percutaneous ethanol injection-PEI, percutaneous microwave coagulation therapy-PMCT, radiofrequency ablation-RF, etc.) have been developed. These regional therapies are hopeful in further improving the prognosis of HCC patients who have no opportunity to receive surgical treatment or postoperative recurrence. The combination of these treatment modalities is hopeful to further improve the prognosis of HCC patients[59,60].

OPERATION RELATED

Many operation-related factors, such as extent of resection, blood transfusion, occlusion time of porta hepatis, blood loss, affect the survival and prognosis of HCC patients.

Surgical margin

The significance of the extent of surgical resection remains controversial. Some reports indicated it had no significant influence on the OS and DFS rates. No significant difference between the major hepatectomy (2 segments or more) and a minor hepatectomy group (one segment or less) could be observed in patient OS and DFS. So, a major hepatectomy is therefore not recommended for patients with solitary small HCC[61,62]. However, many other reports emphasized the importance of surgical margin in the prognosis of HCC patients. Anatomical resection appeared to have a beneficial effect on recurrence-free survival after hepatectomy for HCC. If the liver

functional reserve is good, the extent of surgical resection should be big enough to increase the DFS[63,64]. Some reports indicated that surgical margin might have some effect on the survival rate of patients with small HCC, while no obvious influence on the overall survival of HCC patients[65]. However, in China, co-existing liver cirrhosis is found in most of the HCC patients, which limits the extent of surgical resection. If major liver resection is performed in the patients with severe liver cirrhosis, the patients could be died of the poor remnant liver function. And more, when tumor locates in the porta hepatis or is closed to the important vessels (blood vessels and bile duct), it is impossible to have the surgical margin >1cm. In authors' institute, no significant difference in the survival rates between the HCC patients received different extensions of liver resection was found. So, it is not necessary to try to have an extended surgical margin for the patients with obvious liver cirrhosis.

Blood transfusion

Many reports indicate perioperative blood transfusion enhances the risk of intrahepatic recurrence of HCC, and is a significant independent factor that influence cumulative survival rate of patients[48,66]. Cox regression analysis for recurrence revealed that blood transfusion was the most significant prognostic indicator for recurrence in stage I-II patients but not in stage III-IV patients[67].

ADJUVANT THERAPIES

Adjuvant therapies are hoped to decrease or elimination of intrahepatic recurrence of HCC after liver resection and satisfactory OS. However, in 2000, Chen *et al*. reviewed all of the eight truly randomized and quasi-randomised clinical trials (totaling 548 patients) (RLT) 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 (+/- embolization), chemo- and immunotherapy interventions were tested. Seven of the eight 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[68]. Little and Fong also thought as yet there were no evidence demonstrated benefit from the various neoadjuvant and adjuvant therapies investigated[58].

Preoperative adjuvant therapy (neoadjuvant therapy)

The value of preoperative TACE on the prognosis still remains great controversy. Many reports indicated that it could increase the possibility of recurrence and lung metastasis, showed no contribution to prognosis, should be avoided for the resectable HCC, particularly in patients with advanced cirrhosis of the liver[69,70]. Partial tumor necrosis caused by preoperative TACE might facilitate postoperative disease recurrence. The possible reason is that the remaining tumor cells might become more aggressive, and less firmly attached, more likely to be dislodged into the bloodstream during hepatic resection [71]. And more, preoperative TACE for resectable HCC results in delayed surgery and operational difficulty, without any benefit. It might also increase the possibility of liver failure in those with severe liver cirrhosis[32]. Preoperative TACE should only be performed to reduce tumor bulk in patients with HCC with borderline resectability, and increased the resectability. Peng *et al*. found preoperative TACE might only benefit patients with tumors >8cm but not those with tumors 2 to 8cm[72]. Yoshida found preoperative TACE could not improve DFS after liver resection, but preoperative transarterial immunoembolization (TIE), a newly developed arterial embolization technique using OK-432 and fibrinogen, seemed to be more effective than conventional TAE against extracapsular invasion and intrahepatic metastasis, could improve the disease-free survival[73]. However, Wu *et al*. found effective preoperative TACE might be one of the best methods for resectable HCCs including small HCCs for improving disease-free survival after hepatectomy[74].

Preoperative portal vein embolization could improve prognosis after right hepatectomy for HCC in patients with impaired hepatic function, but cannot prevent tumor recurrence after HCC resection[75]. Main portal branch transection combined with major liver resection and neoadjuvant and adjuvant locoregional immunochemotherapy could increase the resectability rate and the overall survival and DFS[76]. Preoperative administration of 5-FU and interferon LFN-beta may prevent recurrence of co-existing hepatitis B and C virus infections[77].

Postoperative adjuvant therapy

Effective postoperative adjuvant treatment might also be helpful in further improving the prognosis of HCC patients[78].

The effectiveness of postoperative chemotherapy and chemoembolization on the prognosis of HCC patients still remains controversial. Some reports indicated TACE or hepatic arterial infusion chemotherapy (HAIC) was an effective in preventing recurrence after radical hepatectomy for HCC, it could suppress residual liver recurrence from intrahepatic micrometastases rather than multicentric carcinogenesis[79-82]. This was confirmed by one RCT[83]. However, another RCT indicated that TACE after radical resection for HCC could increase the possibility of extrahepatic metastasis, and the prognosis would be even worse[84]. And more recently, Ono *et al*. summarized three RCTs of postoperative chemotherapy, and found postoperative chemotherapy was associated with significantly worse disease-free and overall survival rates, enhanced the cancer recurrence in the remnant liver is enhanced and deteriorated the long-term outcome in patients with cirrhosis[85].

According to authors' institute data, postoperative adjuvant TACE or HACE or combined IFN-alpha therapy, or autologous lymphocytes activated vitro with recombinant interleukin-2 (LAK) therapies could decrease significantly the 3-year recurrent rate of patients received radical liver resection for HCC[3,86,87]. Postoperative TACE is useful for prevention and treatment of HCC recurrence, particularly in treating the postoperative residual tumor[88,89].

Biotherapy plays more and more important role in the prevention of recurrence and metastasis of HCC after operation[33]. Adoptive immunotherapy can lower recurrence and improve recurrence-free outcomes of HCC[78].

Postoperative IFN-alpha therapy can decrease recurrence after resection of hepatitis C virus-related HCC[90]. This result was further confirmed by two pilot RCTs[91,92]. A similar effect was obtained by preoperative IFN-alpha therapy, it might due to IFN can prevent the recurrence of hepatitis B and C virus, and decrease the incidence of HCC in patients with HCV[48,93]. We found high-dose and long-term therapy with IFN-alpha dose-dependently inhibited tumor growth and recurrence after resection of HCC. The result of RCT carried in authors' institute also showed that IFN-alpha therapy could decrease the postoperative recurrence rate of HCC and prolong the DFS after HCC resection. This might be attributed to antiangiogenesis effect of IFN-alpha[94].

Recently, one RCT indicated that a single 1850 MBq dose of intra-arterial ^{131}I-lipiodol given after curative resection significantly decreased the rate of recurrence and increased the 3-year overall survival rate from 46.3% to 86.4%[95].

TIME OF RECURRENCE

Recent studies have shown that the prognosis of recurrent HCC after resection was dependent on the time of recurrence. Based on the time of recurrence, Poon *et al*. classified the intrahepatic recurrences into early (</= 1 year) and late (> 1 year) recurrences, and found that early and late intrahepatic recurrences were associated with different risk factors and prognostic factors. By multivariate analysis, preoperative tumor rupture and venous invasion were independent risk factors for early recurrence, whereas cirrhosis was the only significant risk factor for late recurrence. The prognosis for patients with early recurrence was worse than that of patients with late recurrence. Independent prognostic factors for early recurrence were serum albumin level and initial tumor pTNM classification, whereas only serum bilirubin level was found to be an independent prognostic factor for late recurrence. Early recurrences appear to arise mainly from intrahepatic metastases, whereas late recurrences are more likely to be multicentric in origin[29]. Prognosis was determined by the interval to recurrence, number of recurrent tumors, any concurrent extrahepatic recurrence, and type of treatment[24, 30,45].

SUMMARY AND PERSPECTIVE

In summary, the prognosis of patients with HCC is still dismal. In addition to clinical stage, age, sex, hepatitis activity in the nontumorous liver, treatment strategies, and perioperative transfusion also appear to have some prognostic significance. Pathologic factors indicative of tumor invasiveness such as venous invasion, presence of satellite nodules, large tumor size, and advanced pTNM stage, are the best-established risk factors for recurrence.

Effective treatment is important for prolonging the survival and improving the prognosis of HCC patients. Different strategies of treatment might have significant different effects on the patients' prognosis. To date, surgical resection is still the only potentially curative treatment for HCC, including localized postoperative recurrences. There is a lack of convincing evidence for the efficacy of neoadjuvant or adjuvant chemotherapy in preventing recurrence, which deserves further evaluation. Regional therapies, such as TACE, PEI, RF, etc, are alterative modalities for the nonresectable HCC and nonresectable recurrences. Combination of regional therapy modalities, may offer additional benefit. Biotherapy, particularly IFN-alpha therapy, will play more important role in the preventing recurrence.

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