

Prophylactic liver transplantation for high-risk recurrent hepatocellular carcinoma

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Author contributions: Yang PC performed the majority of the writing, prepared the figures and tables; Ho CM designed the outline and coordinated the writing of the paper; Hu RH and Ho MC performed data accusation and writing; Wu YM provided the input in writing the paper; Lee PH assisted with the design and interpretation of this study.

Conflict-of-interest statement: There is no conflict of interest associated with any of the senior authors or other coauthors who contributed to this manuscript.

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Manuscript source: Invited manuscript

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Received: June 27, 2016

Peer-review started: June 27, 2016

First decision: August 18, 2016

Revised: August 24, 2016

Accepted: September 13, 2016

Article in press: September 18, 2016

Published online: November 8, 2016

Abstract

Hepatocellular carcinoma (HCC) is the second most common cause of cancer-related death in the world. Radical treatment of HCC in early stages results in a long disease-free period and improved overall survival. The choice of optimal management strategy for HCC mainly depends on the severity of the underlying liver disease. For patients with decompensated liver cirrhosis and HCC within Milan criteria (MC), liver transplant (LT) is the choice of treatment. However, for patients with good residual liver reserve and HCC within MC, selection of other curative treatments such as liver resection (LR) or radiofrequency ablation may be a reasonable alternative. For patients without cirrhosis, LR can result in an overall survival similar to that provided by LT. Therefore, it is an accepted alternative to LT especially in areas with organ shortage. However, the cumulative 5-year recurrence rate of HCC post LR might be as high as 70%. For initial transplant-eligible (within MC) patients with recurrent HCC post LR, salvage liver transplant (SLT) was first proposed in 2000. However, most patients with recurrent HCC considered for SLT are untransplantable cases due to HCC recurrence beyond MC or comorbidity. Thus, the strategy of opting for SLT results in the loss of the opportunity of LT for these patients. Some authors proposed the concept of "de principe liver transplant" (*i.e.*, prophylactic LT before HCC recurrence) to prevent losing the chance of LT for these potential candidates. Factors associated with the failure of SLT will be dissected and discussed in three parts: Patient, tumor, and underlying liver disease. Regarding patient-related factors, the rate of transplantability depends on patient compliance. Patients without regular follow-up tend to develop HCC recurrence beyond MC at the time of tumor detection. Advancing age is another factor related to severe comorbidities when LT is considered for HCC recurrence, and these elderly candidates become ineligible as time goes by. Regarding tumor-related factors, histopathological features of the resected specimen are used mostly for determining the prognosis of early HCC recurrences. Such

prognostic factors include the presence of microvascular invasion, poor tumor differentiation, the presence of microsatellites, the presence of multiple tumors, and the presence of the gene-expressing signature associated with aggressive HCC. These prognostic factors might be used as a selection tool for SLT or prophylactic LT, while remaining mindful of the fact that most of them are also prognostic factors for post-transplant HCC recurrence. Regarding underlying liver disease-related factors, progression of chronic viral hepatitis and high viral load may contribute to the development of late (*de novo*) HCC recurrence as a consequence of sustained inflammatory reaction. However, correlation between the severity of liver fibrosis and tumor recurrence is still controversial. Some prognostic scoring systems that integrate these three factors have been proposed to predict recurrence patterns after LR for HCC. Theoretically, after excluding patients with high risk of post-transplant HCC recurrence, either by observation of a cancer-free period or by measurement of biological factors (such as alpha fetoprotein), prophylactic LT following curative resection of HCC could be considered for selected patients with high risk of recurrence to provide longer survival.

Key words: Liver transplant; Hepatocellular carcinoma; Salvage; Risk factor; Resection; Microvascular invasion; Recurrence; Prophylactic

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Core tip: In this minireview, we discuss about the strategy of prophylactic liver transplant after liver resection for patients with a high risk of recurrence. Prognostic risk factors and scoring systems for recurrence are also analyzed.

Yang PC, Ho CM, Hu RH, Ho MC, Wu YM, Lee PH. Prophylactic liver transplantation for high-risk recurrent hepatocellular carcinoma. *World J Hepatol* 2016; 8(31): 1309-1317 Available from: URL: <http://www.wjgnet.com/1948-5182/full/v8/i31/1309.htm> DOI: <http://dx.doi.org/10.4254/wjh.v8.i31.1309>

INTRODUCTION

Hepatocellular carcinoma (HCC) is the most common primary liver cancer. It has a high prevalence in Asia and sub-Saharan Africa due to the high incidence of chronic hepatitis B virus (HBV) and hepatitis C virus (HCV) infections in these regions. It is much more common in men than in women. In men, HCC is the second leading cause of cancer-related death in developing countries and worldwide^[1].

It is well established that liver transplant (LT) is the treatment of choice for patients with early HCC and decompensated liver disease^[2]. The most notable criteria for transplant in HCC cases is the Milan criteria (MC)

described by Mazzaferro *et al*^[3] in 1996. In selected patients with a single tumor less than 5 cm in diameter, or no more than 3 tumors each 3 cm or less in diameter, LT can offer a > 70% 5-year survival and a < 10% 5-year recurrence rate^[4]. However, for patients with early HCC and cirrhotic liver with preserved function, the choice between liver resection (LR) and LT has been an issue of debate^[5]. Donor organ shortage is the major problem with using LT for this group of patients^[6]. Primary LR can achieve comparable 5-year overall survival rates (> 70%) with proper patient selection and application of advanced surgical techniques over the last decades^[7-10]. However, the intrahepatic recurrence rate within 5 years of LR in cirrhotic patients is > 70%^[11]. In the era of organ shortage, Majno *et al*^[12] first proposed a treatment strategy that involves performing LR as the first-line treatment for patients with single small HCC and preserved liver function and reserving LT for patients with recurrent HCC within MC. This is the so-called "salvage liver transplant (SLT)" strategy. Most patients with HCC recurrence cannot benefit by this strategy in the real-world clinical setting due to recurrent HCC beyond MC at detection or poor general condition unsuitable for LT. We speculate whether early LT before the development of untransplantable recurrence can save their lives and eradicate the cancer. This concept of prophylactic LT for high-risk recurrent HCC before the development of recurrence is also called "de principe LT"^[13]. Recently, some authors suggested the use of the histopathological features of the specimen of the resected tumor as the selection tool for LT to improve the outcome of cases with high recurrence rate after LR^[13-16]. However, most of these histopathological features are also prognostic factors of post-transplant HCC recurrence. This review will discuss the treatment strategy of LT before HCC recurrence (de principe) and at recurrence (salvage) for initial transplant-eligible patients developing recurrent tumors after LR. Poor prognostic clinicopathological factors associated with early and late HCC recurrence are also reviewed in three parts, "patient", "tumor", and "underlying liver disease". At last, we introduce some scoring systems for predicting HCC recurrence after LR.

LT AT HCC RECURRENCE: SALVAGE LT

LR as the first-line treatment for primary small HCC in compensated cirrhotic liver is widely adopted with an acceptable survival rate but a high recurrence rate. No treatment guidelines exist for recurrent HCC after LR. Salvage curative treatment for recurrent HCC following primary LR includes SLT, repeat LR, and radiofrequency ablation (RFA). In our group, Lee *et al*^[17] first reported in 1995 that the cumulative 5-year survival rates in patients undergoing repeated hepatic resection after the first operation was 65.1%, and according to Ho *et al*^[18], the latest 5-year survival rates after recurrence in patients receiving repeat hepatectomy was 72%,

which is similar to that of patients who have undergone primary resection and have no recurrence. Chan *et al.*^[19] report comparable survival rates and tumor-free survival rates in SLT and repeat LR, but RFA yields poorer outcome than SLT and repeat LR (5-year survival rates in SLT, repeat LR, and RFA: 50.0%, 48.0%, 11.4%, respectively; 5-year tumor-free survival rates in SLT, repeat LR, and RFA: 57.9%, 49.3%, 10.6%, respectively). RFA is associated with poor survival rates but can be considered for patients not suitable for LR. In another series by Yamashita *et al.*^[20] which compared the outcomes between repeat LR and SLT, the perioperative outcomes including the operation time, intraoperative blood loss, the length of hospital stay, and post-operative morbidity, were all significant worse in the SLT group. No significant difference was observed in the overall survival between these two groups, but patients who underwent SLT had better disease-free survival^[20,21]. The difference between the results of these two salvage treatments is similar to the difference between primary LT and initial LR for early HCC in compensated liver. However, in areas without sufficient donors, repeat LR is the only treatment for patients with recurrent HCC and enough remnant liver that can provide an overall survival comparable to SLT. Mise *et al.*^[22] report the result of third or more repeat hepatectomies for recurrent HCC. The 5- and 10-year overall survival rates from the initial hepatectomy are 91.4% and 75.5% respectively, and the 5-year disease-free survival rate after the second hepatectomy is 17.9%.

Comparison of primary LT and SLT for HCC within MC in recent studies revealed similar perioperative course, morbidity, overall survival, and disease-free survival^[16,23-28], while a previous study showed the association of LT after resection and higher operative mortality, an increase of recurrence, and poorer outcomes^[29]. In the systemic review by Chan *et al.*^[30] the median 5-year overall and disease-free survival rates in SLT are 62% and 67%, respectively. In the era of organ shortage, LR should be considered as the primary curative treatment for resectable tumors in compensated livers, and SLT is a safe and effective strategy for initial transplant-eligible patients when recurrent HCC or hepatic function deterioration occur^[12].

The SLT strategy is widely acceptable for patients with previous transplant-eligible HCC. However, some authors also advocate the strategy of performing LR as one of the locoregional therapies for tumor downstaging in patients with initial HCC beyond LT criteria and performing LT after HCC recurrence^[31]. The results of this downstaging strategy showed better survival outcomes as compared with patients with HCC recurrence who undergo LR without SLT. However, for post-LR recurrent HCC beyond MC, the results of SLT are not beneficial and not recommended in a recent report^[22]. Prospective studies are needed to examine the long-term outcomes of extending the criteria of LT for intermediate-advanced HCC either before or after tumor recurrence.

LT BEFORE RECURRENCE: CONCEPT OF PROPHYLACTIC LT

As previous study stated, SLT has been proven effective for patients with recurrent HCC within the criteria of the following: Tumor recurrence within MC, patient adherence to a regular follow-up with imaging to detect early recurrence, and good general patient condition for LT. However, the intention-to-treat analysis by Fuks *et al.*^[32] showed that nearly half of the patients with recurrent HCC following LR did not undergo LT, including one-third due to recurrence beyond MC. Other studies also report that 20% to 80% of the patients considered for SLT are not transplantable due to recurrence beyond transplant criteria or advanced age with significant comorbidity^[8,15,29,33,34]. This means that with the strategy of SLT, we lose the chance of LT in originally transplantable patient. Sala *et al.*^[13] first reported four cases of prophylactic LT, performed based on the expectation of early recurrence according to the gross and microscopic features of the resected specimen, including microvascular invasion and additional nodules. Patients with high risk of recurrence as identified by histopathological findings were enlisted for LT. Scatton *et al.*^[14] predicted the risk of HCC recurrence after LR on the basis of the histological features of the resected specimen (including Edmondson score, vascular invasion, nuclear grade, and architectural growth pattern), which are used as the selection tool for LT. In this series, six patients were enlisted and underwent prophylactic LT without evidence of residual disease. However, the population of this study was heterogeneous, with three of the six patients in this study having HCC beyond MC at resection, and the other three patients having resected HCC within MC. These six patients are all alive without recurrence with mean follow-up of 55 mo.

Tribillon *et al.*^[34] report the largest series of prophylactic LT in intention-to-treat analysis of 63 patients with intermediate or bad pathological factors (microvascular invasion and/or moderate/poor differentiation) in the resected specimen being enlisted for LT prior to recurrence (de principe group). The overall survival of this group was compared to 48 patients with favorable pathological features being enlisted for LT at the time of HCC recurrence (salvage group). The 5-year survival rate since primary LR was significantly better in the de principe group as compared with the salvage group (84.6% vs 74.8%), and the 5-year disease survival rate was also better in the de principe group (79.3% vs 72.3%).

This active attitude of enlisting patients for LT prior to recurrence can treat both potential recurrent HCC and underlying liver disease. However, literature about this strategy is scarce. The most important viewpoint discussed in the literature about this prophylactic strategy is preventing original transplant-eligible patients from developing beyond MC at recurrence and provide longer survival. However, if more stringent follow-ups and increased accuracy of imaging studies lead to

Table 1 Comparison between prophylactic liver transplant and wait-and-see before hepatocellular carcinoma recurrence

The strategy	Prophylactic LT	Wait-and-see
Immunosuppressant exposure	Life-long	Nil
Surgical morbidity and mortality	Present	Nil
Long-term HCC recurrence	Lower ^[32]	Higher ^[11]
Survival benefit (5-year survival rate)	84.6% ^[32]	Around 70% ^[7-10]
Further management after recurrence	Hepatectomy, RFA, TACE, Sorafenib, Yttrium-90	SLT, repeat hepatectomy, RFA, TACE, Sorafenib, Yttrium-90

LT: Liver transplant; RFA: Radiofrequency ablation; TACE: Transcatheter arterial chemoembolization; HCC: Hepatocellular carcinoma.

Table 2 Prognostic factors of early hepatocellular carcinoma recurrence after liver resection and after liver transplantation

Risk factor of HCC recurrence	After liver resection	After liver transplantation
Serological		
AFP	> 400 ng/mL ^[49]	> 1000 ng/mL ^[34,35]
Tumor gross		
Tumor size	> 3 cm ^[30] or > 5 cm ^[37,41,65]	> 6 cm ^[35]
Tumor number	> 3 ^[65]	≥ 4 ^[35]
Satellite nodules	Yes ^[30,63,66]	Yes ^[33]
Tumor microscopic		
Tumor differentiation	Intermediate, or poor differentiation, or undifferentiation ^[30,49,65]	Poor differentiation, or undifferentiation ^[33]
Microvascular invasion	Yes ^[30,37,41,49,64-66]	Yes ^[33,34]
Liver parenchyma		
Severity of cirrhosis	Controversial ^[67-69]	No
Milan criteria	Yes ^[68] (predict recurrence within/beyond MC)	Yes ^[3]

HCC: Hepatocellular carcinoma; AFP: Alpha-fetoprotein; MC: Milan criteria.

early detection of recurrent tumor for these patients, does the result still justify this novel strategy? Salvage treatment after detection of recurrent HCC includes LT, repeat hepatectomy, RFA, transcatheter arterial chemoembolization, sorafenib, and trans-arterial radio-rembolization (Yttrium-90). The choice of these salvage treatment depends on the extent of underlying liver disease, the aggressiveness of tumor at recurrence, and the general condition of the patient. LT has been proven to be correlated with better overall survival and disease-free survival rates with careful patient selection as a curative method, as compared with other salvage treatments previously stated^[17-19]. However, for cases without evidence of recurrence, it is unclear if we should choose prophylactic LT for patients with a high risk of recurrence or just close follow-ups and salvage treatment at recurrence. The accompanying morbidity and mortality with prophylactic LT and the limited number of organs also hinder this aggressive strategy. The comparison of the benefits and risks between prophylactic LT and the wait-and-see strategy followed by salvage treatment is listed in Table 1.

On the other hand, is a higher probability of recurrence after initial hepatectomy equivalent to a shorter disease-free survival after salvage or prophylactic LT? If HCC recurs easily after salvage or prophylactic LT, this strategy became meaningless. Most prognostic factors associated with recurrence after LR are also relevant to post-transplant recurrence, including microvascular invasion of HCC, larger tumor size, higher tumor number, poorer differentiation of the tumor, and higher level of alpha-fetoprotein (AFP)^[35-37] (Table 2). It is difficult to

distinguish patients with higher recurrence after hepatectomy from those with possible post-transplant HCC recurrence. A period of observation should be considered after primary LR to identify the aggressiveness of occult HCC in the absence of specific predicting factors. Further investigation is needed to stratify patients for better application of treatment after hepatectomy.

CLINICOPATHOLOGICAL FACTORS ASSOCIATED WITH HIGH-RISK RECURRENCE

The most important issue in adopting prophylactic LT is the identification of prognostic factors associated with high-risk recurrence. Tumor dissemination from primary tumor before resection and new lesion development in underlying oncogenic cirrhotic parenchyma are two major pathways leading to recurrence^[38-42]. The former is associated with early recurrence within 2 years after primary resection, while the latter is more likely associated with late recurrence^[42-45]. We summarize the recent data in the literature on the clinicopathological factors linked with HCC recurrence.

PATIENT-RELATED FACTORS: DEMOGRAPHIC AND BIOCHEMICAL FACTORS

The age factor associated with recurrence after resection remains controversial. Older age at resection may be

suggestive of long-standing chronic liver disease and higher susceptibility to HCC recurrence over time. Older age (65 years or more) is an independent risk factor for tumor recurrence, as shown in the recent major series by Fan *et al.*^[46] and Pompili *et al.*^[47]. However, in the series of HBV-related HCC by Mathews *et al.*^[48] younger age (40 years or less) was closely associated with more aggressive disease and shorter disease-free survival after resection. The other major series by Hung *et al.*^[49] does not show old age (60 years or more) to be a poor independent factor for tumor recurrence.

Serum AFP level has been conventionally used as a simple and effective tool for routine surveillance of HCC and for monitoring recurrence following treatment^[50]. Elevated serum AFP level at the time of resection has been frequently reported to predict the risk of post-resection recurrence of HCC^[51-56]. Many studies have proposed the relationship between the pretreatment AFP level and tumor-free survival using different cut-off values of AFP level (for example, 20, 100, 400 or 1000 ng/mL)^[44,49,57,58]. Higher pretreatment serum AFP level is associated with shorter disease-free period. Ho *et al.*^[51] proposed the value of 400 ng/mL as the cut-off AFP level to predict untransplantable recurrence after primary curative resection of HCC. However, in another study by Shim *et al.*^[59] the result of a test based on propensity score, included 525 patients who underwent HCC resection and showed no correlation between preoperative serum AFP level and the risk of recurrence. Serum AFP level can also be abnormally high in chronic hepatitis C and advanced cirrhotic liver without HCC^[60]. It is controversial to use serum AFP level as the predictor of HCC recurrence. Instead of predicting the risk of recurrence, the higher level of serum AFP should be considered as the consequence of aggressive tumor features such as microvascular invasion and poorer tumor differentiation, which indicate worse prognosis^[61]. Serum AFP level > 1000 ng/mL is also reported to be associated with higher post-transplant recurrence due to the correlation with more aggressive tumor biology^[35-37].

TUMOR-RELATED FACTORS: HISTOPATHOLOGICAL FACTORS

It is well known that early recurrence after HCC resection is related to tumor dissemination prior to operation^[42]. The histopathological profile obtained from the resected specimen has been used to predict the risk of tumor dissemination and as an objective selection tool for LT in the last decade^[13,14,32,34]. Among these factors, microvascular invasion of the tumor is the most critical factor in disease dissemination. As seen in most cancers, angiogenesis, or new vessel formation, is essential for HCC growth^[62]. In advanced stages of tumor progression, HCC cells develop the ability to invade adjacent blood vessels and potentially begin to metastasize. The presence of microvascular invasion is the hallmark of aggressive tumor behavior

and associated with high recurrence rate after curative resection^[63]. Sumie *et al.*^[64] report 3-year recurrence-free survival rates in HCC with and without microvascular invasion to be 27.7% and 67.5%, respectively. Other poor histopathological features, like the presence of satellite nodules and poor tumor differentiation, are also recognized, along with microvascular invasion, to predict early recurrence^[32,39,43,65-68]. Most of these poor histopathological factors associated with early recurrence after LR are also predictors of recurrence after LT, including larger tumor size, larger tumor number, satellite nodules, poorer tumor differentiation, and microvascular invasion (Table 2). These features are linked to the aggressiveness of the tumor biology and predict the recurrence both after LR and LT. Patients with a tendency of post-LR recurrence may also develop a risk of post-LT recurrence. While considering prophylactic LT for patients with these poor histopathological features, cut-off criteria should be made to exclude those with more aggressive HCC and also potentially easy recurrence after LT.

UNDERLYING LIVER DISEASE-RELATED FACTORS: VIROLOGICAL FACTORS

The preneoplastic status of underlying liver disease is considered to relate with elevated carcinogenesis and *de novo* tumor development in late phase recurrence (2 years after resection)^[42]. The correlation between stage of liver fibrosis and disease-free survival is controversial. Grazi *et al.*^[69] and Taura *et al.*^[70] showed that HCC without cirrhosis has better disease-free survival compared with HCC with cirrhosis after curative resection in Asia, while Beard *et al.*^[71] showed the reverse results for western countries. Instead of the severity of liver cirrhosis, the sustained necroinflammatory reaction resulting from higher hepatitis activity may play a more important role in the development of secondary primary HCC two years after resection. Initial high HBV viral loads > 2000 IU/mL^[72] or 10⁶ copies/mL^[45] at the time of HBV-related HCC resection or one month post resection HBV DNA > 20000 IU/mL^[49] are all proven to be independent risk factors for tumor recurrence. Ongoing HBV replication can induce active hepatitis and subsequent inflammation in oncogenic liver parenchyma leading to *de novo* recurrent HCC. Regarding Hepatitis C, patients with HCV infection tend to have higher hepatitis activity, which is related to elevated carcinogenesis, than patients with HBV infection^[42]. However, the difference in recurrence-free survival is not significant between patients with HBV infection or those with HCV infection^[73,74]. A recent national study of 11950 patients in Japan by Utsunomiya *et al.*^[75] showed that patients without viral hepatitis have a significant lower risk of HCC recurrence than those with HBV or HCV infection.

SCORING SYSTEM

Some authors propose the scoring system that integrated

Table 3 Scoring systems for predicting hepatocellular carcinoma recurrence

Ref.	Basis of scoring system	Prognostic factors	Discriminated scores
Pan <i>et al</i> ^[76]	Glasgow prognostic score	Preoperative CRP > 10 mg/L (1 point) Albumin < 3.5 g/L (1 point)	0, 1, 2
Fuks <i>et al</i> ^[32]	Histological features	Microscopic vascular invasion Presence of satellite nodules Tumor size > 3 cm Poor differentiated tumor Cirrhosis	< 3 factors ≥ 3 factors
Roayaie <i>et al</i> ^[66]	Degree of vascular invasion	Invasion of a vessel with a muscular wall (1 point) Invasion of a vessel ≥ 1 cm from the tumor capsule (1 point)	0, 1, 2
Lee <i>et al</i> ^[68]	Clinical risk score	Initial disease beyond Milan criteria Microsatellites or multiple tumors Lymphovascular invasion (1 point for each factor)	0, 1, 2, 3

Higher scores indicate higher recurrence rate. CRP: C-reactive protein.

clinical, biochemical, and histopathological factors to classify the risk of HCC recurrence after resection^[32,66,68,76] (Table 3). Most scoring systems consist of the extent of tumor invasiveness, while the Glasgow prognostic score originally used in the prediction of outcomes among non-small-cell lung cancer patients^[77] is composed of the serum levels of C-reactive protein (CRP) and albumin. The higher serum level of CRP and lower serum level of albumin present in the systemic inflammatory response is associated with a more active viral hepatitis in the remnant liver parenchyma^[76]. The higher scores in each system indicate shorter disease-free period and poorer outcome. The clinical risk score system by Lee *et al*^[68] uses pathological factors to predict the likelihood of recurrence after LR, and it can be used to identify patients who may lose the chance of SLT at recurrence. Whether this strategy system applies to prophylactic liver transplantation needs further validation.

CONCLUSION

Prophylactic LT is a novel concept for patients with high-risk recurrent HCC after primary resection before recurrence. Microvascular invasion, larger tumor size, larger tumor number, and poor tumor differentiation are all predictors for recurrence after LR and LT, while serum AFP level > 1000 ng/mL is the unique feature for predicting recurrence after LT. The length of observation after prophylactic LT should be established to examine the occult aggressiveness of the HCC resulting in recurrence after LT. It is safe and effective when patients who fulfilled MC at the time of resection are carefully selected. Large prospective studies are required to clarify the long-term results of this strategy.

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