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**Predictors of early and late hepatocellular carcinoma recurrence**

Predictors of HCC recurrence

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## **Abstract**

Hepatocellular carcinoma (HCC) is the most frequent liver neoplasm and its incidence rates are constantly increasing. Despite the availability of potentially curative treatments (liver transplantation, surgical resection, thermal ablation), long-term outcomes are affected by a high recurrence rate (up to 70% of cases 5 years after treatment). A HCC recurrence within 2 years of treatment is defined as "early" and is generally caused by the occult intrahepatic spread of the primary neoplasm and related to the tumor burden. A recurrence that occurs after 2 years of treatment is defined as "late" and is related to a de novo HCC, independent of the primary neoplasm. Early HCC recurrence has a significantly poorer prognosis and outcome than late recurrence. Different pathogenesis corresponds to different predictors of the risk of early or late recurrence. An adequate knowledge of predictive factors and recurrence risk stratification guides the therapeutic strategy and post-treatment surveillance. Patients at high risk of HCC recurrence should be referred to treatments with the lowest recurrence rate and, when standardized, to combined or adjuvant therapy regimens. This review aims to expose the recurrence predictors and examine the differences between predictors of early and late recurrence.

**Key Words:** Hepatocellular carcinoma; Early recurrence; Late recurrence; Predictors; Liver transplant; Liver resection; Thermal ablation.

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**Core Tip:** Hepatocellular carcinoma is burdened by a high rate of both early and late recurrence. The knowledge of the predictive factors of recurrence and its risk stratification should allow to optimize the management of the patient with HCC.

## **INTRODUCTION**

### **Introduction**

Liver **cancers** represent the fifth neoplasm by incidence and the fourth cause of cancer-related death worldwide, with a higher incidence in men than in women <sup>[1]</sup> and an epidemiological distribution that results from the variations of etiological factors for liver disease (with a current reduction in viral hepatitis and an increase in metabolic etiologies)<sup>[2,3]</sup>. Hepatocellular carcinoma (HCC) accounts for about 90% of liver cancer cases, with an increasing incidence of 75% from 1990 to 2015<sup>[1,4]</sup>. The onset of HCC generally follows chronic liver damage resulting in the development of fibrosis and especially liver cirrhosis, although cases of HCC in the absence of liver damage are possible and generally related to **aflatoxin** exposure<sup>[5]</sup>. The main risk factors for HCC are represented by: liver cirrhosis and chronic hepatitis, chronic HBV infection (with or without HDV) or HCV, chronic alcohol abuse, cigarette smoking, metabolic syndrome, diabetes mellitus and obesity<sup>[6-12]</sup>. In particular, 1% to 8% of patients with liver cirrhosis developed HCC annually<sup>[13]</sup>. Low platelet count, severe portal hypertension, certain comorbidities (e.g. obesity, diabetes mellitus), cigarette smoking, concomitant alcohol consumption, older age and male sex are factors closely associated with the development of HCC in patients with liver cirrhosis<sup>[13-17]</sup>. The mortality rate of HCC patients, although improving, still appears to be extraordinarily high<sup>[18]</sup>. An early diagnosis and an appropriate therapeutic approach allow to obtain higher overall and disease-free survival rates. In particular, when diagnosed at an early stage, HCC can be **effectively treated by** liver transplantation (LT) or loco-regional techniques, including liver resection (LR) and radio-frequency ablation (RFA). Optimal treatment choice is based on both tumor burden and residual liver function<sup>[19-21]</sup>. If HCC recurrence rates after liver transplantation accounts for 13% of cases<sup>[22]</sup>, these rates appear significantly higher after loco-regional treatment, reaching 70% of cases at 5 years<sup>[4]</sup>. The recurrence of the neoplasm may reflect both the presence of intrahepatic metastases ("true" or "early" recurrence) and the development of de novo tumors ("late" recurrence). A 2-year cut-off is generally used to define the two entities<sup>[4]</sup>. There are

numerous factors (related to the patient, the tumor and the type of treatment) able to predict the risk of recurrence after loco-regional treatment or liver transplantation. Although many predictors are common to early and late recurrences, other factors may be exclusive for one or the other form due to the different pathogenesis. An adequate recurrence risk stratification would allow to personalise the therapeutic strategy for each patient, optimize the surveillance program and ideally encourage the study, validation and use of adjuvant therapy in high-risk patients.

The aim of this review is to examine the predictors of HCC recurrence after liver transplantation and loco-regional treatment and look over the differences between predictors of early and late recurrence.

### Strategies of HCC radical treatment.

In order to define the most appropriate therapeutic strategy, able to maximize outcomes and reduce the risk of recurrence, HCC requires appropriate staging that takes into account not only cancer-related factors, but also residual liver function. The Barcelona Clinic Liver Cancer (BCLC) staging system is the most used to predict patient prognosis and establish treatment allocation<sup>[4]</sup>. It divides patients into 5 categories (0, A-D) based on tumor characteristics (uni or multifocality, vascular invasion, size and extrahepatic spread) and liver function (assessed by Child Pugh score). "Very early HCC stage" (BCLC 0) is defined as patients with preserved liver function and a carcinoma in situ (single HCC lesion < 2 cm without vascular invasion), whereas an "early stage" (BCLC A) is defined as patients with preserved liver function and a single lesion > 2 cm or 3 Lesions with diameter < 3 cm. Patients at BCLC stage 0 and A are optimal candidates for a radical therapeutic strategy (liver transplant, ablation, surgical resection). Patients in more advanced states (BCLC B-D) are candidates for palliative (chemoembolization, systemic therapy) or supportive treatment<sup>[4,21]</sup>. Due to the excellent long-term outcomes achievable, liver transplantation (LT) is considered the gold standard for the treatment of HCC<sup>[22,23]</sup>. It is indicated as the first-line therapy in

patients with HCC who meet the <sup>6</sup> Milan criteria (single tumor  $\leq 5$  cm or multiple tumors as  $\leq 3$  nodules size  $\leq 3$  cm ) without vascular invasion and/or extrahepatic involvement<sup>[24]</sup> but are not eligible for liver resection<sup>[4]</sup>. Recent evidence also suggests <sup>25</sup> that patients beyond the Milan criteria could be reconsidered for LT after adequate downstaging of the tumor<sup>[25]</sup>. Liver resection (LR) is the treatment of choice in non-cirrhotic HCC patients or in cirrhotic HCC patients with well-preserved liver function, solitary tumors and clinically mild portal hypertension (hepatic vein to portal system gradient, HVPG  $\leq 10$  mmHg)<sup>[4,26]</sup>, with the possibility (not standardized yet) to extend the indication also to multicentric tumors or to  $> 2$  cm ones<sup>[4]</sup>. It is still one of the main local-regional curative-intent treatments, with a 5-year survival between 40% and 70%<sup>[27]</sup>. Thermal ablation with radiofrequency (RFA) or microwaves (MWA) <sup>1</sup> is the standard of care for HCC patients with BCLC 0 and A stage not suitable for surgery (LT or LR) or as an alternative to LR in very early HCC stage with favorable localization also in patients eligible for surgery<sup>[4]</sup>. Thermoablation is also indicated as a neoadjuvant therapy in patients who are candidates for LT (pre-transplant) in order to reduce the risk of recurrence. Selected patients with intermediate HCC - BCLC B (solitary  $> 3$  cm or <sup>1</sup>  $> 3$  nodules  $< 3$  cm or advanced liver failure not clinically decompensated) can be reasonably treated with RFA, even if medium- and long-term outcomes appear worse than patients with HCC BCLC 0 or A<sup>[28]</sup>. <sup>1</sup> Transarterial chemoembolisation (TACE) is the most widely used treatment for unresectable HCC and offers significant overall survival advantages over best supportive care<sup>[4]</sup> although it has no clear curative purposes and cannot be considered a radical approach. In particular, the survival rates after TACE are <sup>1</sup> 70.3% at one year, 51.8% at two years, 40.4% at three years, and 32.4% at five years<sup>[29]</sup>. The rationale of the technique is based on the intermediate HCC intense arterial neo-angiogenic activity and consists in the intra-arterial administration of cytotoxic agents (doxorubicin or platinum derivatives) followed by the embolization of peritumoral vessels inducing a cytotoxic and ischemic effect of the tumor mass. Combination treatments (eg TACE + RFA) and neoadjuvant or adjuvant systemic treatments are currently being studied.

### Early or late recurrence

The recurrence of HCC represents a relevant clinical issue, affecting up to 70% of patients undergoing curative treatment<sup>[4]</sup>. Although many factors are involved in the decision-making process of the best possible treatment (Figure 1), the assessment of baseline risk recurrence significantly influences the choice of treatment type and its timing. Moreover, the treatment of a relapse is generally more complex than the treatment of the first lesion, due to the change in anatomical or functional liver conditions and a more advanced age. Patients at high risk of early recurrence are candidates for close surveillance and potentially adjuvant therapy, which, however, has not yet been standardized<sup>[30,31]</sup>.

The "true" recurrence (mean as secondary to the presence of occult intrahepatic metastases) is generally "early" and accounts for more than 70% of tumor recurrence. It derives from an intrahepatic dissemination of the neoplasm through the portal circulation. A 2-year cut off was used to distinguish it from late recurrence, generally resulting from de novo development of the neoplasm. However, this cut off remains arbitrary and not universally accepted. Yamamoto *et al*<sup>[32]</sup>, for example, identified 17 mo as the best cut off to distinguish early and late recurrence on a cohort of 252 patients with recurrence of HCC after hepatectomy. Previously Hayashi *et al*<sup>[33]</sup> had hypothesized a 1 year cut off, instead. A further shorter observation period has recently been hypothesized by Xing *et al*<sup>[34]</sup> who identify 8 mo as the ideal threshold to define a recurrence of HCC as early or late. Although the temporal criterion is used to distinguish a pathogenesis related to the presence of occult intrahepatic metastases or to a de novo neoplasm, a precise differentiation would require the study of recurrence clonality by genetic/genomic analyzes<sup>[35]</sup>.

The two types of recurrence are two distinct entities associated with different risk factors. Early recurrence is associated with tumor-related factors, where late recurrence is related to the underlying liver disease. They have a substantially different clinical and



biological profile and are burdened by different morbidity and mortality. In fact, an early recurrence represents a significant negative prognostic factor and has a far greater impact on overall survival than a late recurrence<sup>[32,36]</sup>. Overall survival rate reduces as earlier the recurrence is. Xing *et al*<sup>[34]</sup> in fact demonstrated that patients with early recurrence show a median of survival free from cancer equal to 8.4 mo (7.5 - 10.0 mo) compared to a median of 21.3 mo (17.9 - 23.8 mo) for patients with late recurrence. In particular, an early recurrence, mainly determined by the aggressiveness of the primary tumor, is characterized by larger dimensions, higher rates of multifocality and intrahepatic spread, higher probability of vascular invasion and higher levels of alpha-fetoprotein (AFP) compared to a recurrence that develops later<sup>[36]</sup>. Conversely, late recurrence is generally related to aetiology and cirrhotic background, risk factors for hepatocarcinogenesis, and not to the primary tumor<sup>[37]</sup>.

### **Early recurrence predictive factors**

The factors affecting the possibility of early HCC relapse after liver transplantation or loco-regional treatment can be classified into three categories: **those** related to the tumor (size, number of nodules, differentiation, oncological markers), to the patient (e.g.: age, comorbidity, liver function, possible viral load, presence and activity of hepatitis, presence and activity of liver cirrhosis) and treatment (type of treatment, margins, characteristics of resection) (Table 1)<sup>[38,39]</sup>.

#### *Predictors of early recurrence related to HCC characteristics*

Several factors related to the characteristics of HCC are able to predict the risk of early recurrence (Table 1). In fact, the risk of early relapse is closely related to the tumor burden and its aggressiveness, which increases the risk of occult intrahepatic spread, as well as the radicality of the treatment<sup>[40]</sup>.

Pre-operative radiological imaging can already provide first indications about the risk of recurrence. In this regard, the *size* of the tumor represents a relevant



predictor of the risk of early recurrence. Jung *et al*<sup>[36]</sup> showed that a maximum diameter of HCC greater than 3 cm before a curative LR represents an independent risk factor for early recurrence (defined by the Authors as occurring within 1 year of treatment). These results have recently been confirmed by Lee *et al*.<sup>[41]</sup> Zhu *et al* identify a 4.77-fold higher risk of early recurrence after an LR for cancers with a maximum diameter greater than 2.6 cm compared to those with smaller maximum diameter<sup>[42]</sup>. Similarly, the *multifocality* of HCC seems to be another significant risk factor for early recurrence<sup>[41]</sup>. Tumor size and number of lesions represents, together, the aforementioned *Milan Criteria*. As expected, being beyond the Milan criteria represents an independent risk factor for early HCC recurrence<sup>[43]</sup>.

At histological evaluation, the most predictive factors of the risk of early HCC recurrence are the presence of microvascular invasion, the integrity of the capsule and the degree of differentiation. In light of the fact that early recurrence is generally due to intrahepatic dissemination of the neoplasm through the portal circulation, it is not surprising that vascular invasion has been identified many times as an independent predictor of recurrence. If the involvement of the major vessels (eg: portal vein, inferior vena cava) can be evaluated radiologically and often excludes the possibility of loco-regional treatment for radical purposes, *microvascular invasion* needs to be evaluated by histopathological analysis of the intra-operative sample. Microvascular invasion, although dependent upon the operator and influenced by possible sampling errors, represents an independent risk factor for early recurrence<sup>[34,36,38,40,44,45]</sup> affecting approximately one third of HCC cases undergone LR<sup>[37]</sup>. Since a qualitative and/or quantitative classification of microvascular invasion is not yet available, its only presence/absence is generally considered in the histopathological evaluation. However, in this regard, Roayaie *et al*<sup>[46]</sup> proposed a risk system based on histological features of microvascular invasion that includes invasion of a vessel with a muscular wall and invasion of vessels  $\geq 1\text{cm}$  away from the tumor capsule. According to the Authors, this system allow to stratify patients into 3 distinct groups with significantly different risks of recurrence and death. In particular, patients with microvascular invasion and the

aforementioned risk factors show outcomes (tumor recurrence rate, mortality rate) comparable to patients with macroscopic vascular invasion.

The integrity of the HCC capsule would instead represent a protective factor for the risk of recurrence<sup>[42]</sup>. The capsule would act as a barrier to the spread and metastasization of cancer cells. This function is lost in non-capsular HCC or those with ruptured capsule<sup>[34,42]</sup>. Zhu *et al*<sup>[42]</sup> showed that non-capsular HCC was associated with a higher rate of poorer differentiation and vascular invasion than capsular HCC.

Histological differentiation is considered an independent risk factor for early HCC recurrence. It is classified according to the Edmonson-Steiner criteria: 1st and 2nd degree correspond to well differentiated neoplasms, 3rd and 4th degree correspond to poorly differentiated neoplasms. In particular, grades 3 and 4 are related to a significantly increased risk of early recurrence<sup>[36,43]</sup>. In patients without microvascular invasion, the degree of differentiation seems to be the best histological predictor of the risk of early recurrence and overall survival<sup>[47]</sup>.

In light of the growing evidence of the efficacy in predicting the risk of recurrence, histological evaluation will become crucial in choosing the optimal therapeutic strategy for each patient, allowing to implement the stratification of the basal recurrence risk with the post-operative one. Patients at high risk of recurrence should undergo an aggressive surveillance strategy and ideally adjuvant therapy.

Among the predictors of early recurrence, the markers expressed by the neoplasm are certainly the most studied. In particular, *alphafetoprotein* (AFP), a glycoprotein physiologically produced by the liver and fetus, can increase in pathological conditions, such as liver cancer. In addition to the diagnostic phase, it plays an important role as a predictor and monitoring tool also in the context of HCC recurrence. However, although there is almost unanimous agreement on the predictive value of elevated AFP levels for the risk of early HCC recurrence after treatment<sup>[36,40,41,45,48,49]</sup>, there are no standardized cut off pre and post treatment available. Jung *et al*<sup>[36]</sup> for example, showed that high AFP values both pre- and post-hepatectomy are associated to higher risk of early recurrence (which Authors define as

< 1 year after treatment) though without standardizing a threshold value. Using retrospective data analysis, Kim *et al*<sup>[48]</sup> showed that pre-operative AFP values > 10 ng/mL are a predisposing factor of disseminated HCC recurrence within 3 mo after hepatectomy for solitary HCC (OR 5.333; 95%CI, 1.095–25.985). Fang *et al*<sup>[40]</sup> showed instead that preoperative AFP > 400 ng/mL correlates independently with the risk of early recurrence. Recently, AFP levels at 12 wk<sup>29</sup> after achieving sustained virological response (SVR) with direct acting antiviral agents (DAAs) treatment in chronic HCV patients<sup>13</sup> have also been independently associated with risk of HCC recurrence<sup>[50]</sup>.

The protein induced by vitamin K absence or antagonist II (PIVKA-II) is an immature form of prothrombin, a cofactor of vitamin K that is synthesized by the liver when the latter is not produced or antagonized. Evaluation of PIVKA-II has been shown to be useful in diagnosing HCC and in stratifying the risk of recurrence<sup>[38,41,51,52]</sup>. In fact, it acts as a growth factor, promoting cell proliferation and tumor angiogenesis in HCC patients<sup>[52,53]</sup>. The evaluation of the PIVKA-II appears to be complementary to AFP<sup>[54]</sup>. Low values of both AFP and PIVKA-II are associated with a better prognosis compared to elevated levels of AFP and/or PIVKA-II<sup>[55]</sup>. Serial measurements of both proteins allow to obtain a prompt diagnosis of early recurrence. In fact, pre- and post-treatment levels of PIVKA-II are good predictors of early HCC recurrence<sup>[38,41,51]</sup> since they are related to greater aggressiveness of the neoplasm, such as the presence of vascular invasion and intrahepatic metastasis of HCC cells<sup>[52]</sup>. Similarly to what is highlighted for the AFP, also for the PIVKA-II there is no agreement about which cut-off can be useful as a guide for assessing the risk of recurrence. In this regard, Wang *et al*<sup>[51]</sup> showed that in patients with low risk of recurrence (tumor size < 5 cm, single tumor, absence of satellite lesions, absence of vascular invasions, high degree of histological differentiation, BCLC stage 0-A), pre-operative values of PIVKA-II > 375.5 mAU/mL are the strongest independent prognostic factor for the risk of early recurrence (hazard ratio - HR, 2,877; 95%CI 1,524 - 5,429). Furthermore, patients who expressed high levels of PIVKA-II showed<sup>19</sup> lower 1-year time to progression than

patients with low levels (54.8% vs 20.2%). More recently, Hong *et al*<sup>[38]</sup> instead identify a cut-off of 46 mAU/mL for PIVKA-I for predicting an increased risk of early recurrence.

#### *Predictors of early recurrence related to patient characteristics*

Predictors related to patient characteristics are associated more with the risk of late recurrence than with early one. In fact, they represent the substrate for the risk of hepatocarcinogenesis and generally do not correlate with the aggressiveness of the primary tumor, that is strongly associated with early recurrence instead. However, some studies have shown a certain impact of the patient's basal phenotype also on HCC recurrence that occur in the first two years after treatment (Table 1).

In this regard, the presence of liver cirrhosis and the degree of hepatic dysfunction are the factors that most increase the risk of early recurrence after curative treatment<sup>[37,41]</sup>. In the models used for risk stratification in patients undergoing hepatectomy, the degree of hepatic dysfunction is quantified by the Child Pugh score<sup>[56,57]</sup>, the model for end-stage liver disease (MELD)<sup>[41]</sup> or by Albumin-Bilirubin score (ALBI)<sup>[37,58]</sup>. The latter in particular seems to have a better discriminatory power in this setting since it helps to further stratify stage A of the Child-Pugh score, which includes almost all patients undergoing LR<sup>[58]</sup>. Total bilirubin levels, an expression of the degree of hepatic dysfunction, also correlate with the risk of early recurrence<sup>[42]</sup>.

Furthermore, according to Chan *et al*<sup>[37]</sup> male patients undergoing hepatectomy show a higher risk of early recurrence than female patients.

The predictive value on outcomes (mortality and recurrence) of the Neutrophil to Lymphocyte Ratio (NLR) and Platelet to Lymphocyte Ratio (PLR) in HCC patients has been extensively studied. These scores are expression of the systemic inflammatory response, a known preoperative risk factor for HCC outcomes<sup>[49,59,60]</sup>. High PLR has been shown to predict lower overall survival (HR: 1.63, 95%CI: 1.34 - 1.98) and earlier HCC recurrence (HR: 1.52, 95%CI: 1.21 - 1.91)<sup>[59]</sup>. Similar results were also highlighted for NLR<sup>[49,60]</sup>. In addition, both the NLR and PLR were identified as independent risk factors for predicting overall survival and RFS in HCC patients<sup>[59,60]</sup>.



In recent years, a heated scientific debate has been carried out on the hypothesis of an increased risk of HCC incidence and recurrence in chronic HCV patients treated with *direct antiviral agents* (DAAs). Unlike interferon (IFN)-based therapeutic regimens which has been proven to be able in reducing the incidence and recurrence of HCC in case of SVR<sup>[61]</sup>, some data would indicate that after DAA therapy HCC risk may remain high<sup>[4,62]</sup>. In particular, the retrospective analysis of some patient cohorts revealed an unexpectedly high rate of early HCC recurrence in patients undergoing antiviral treatment with DAAs<sup>[62,63]</sup>. It has been hypothesized that the rapid fall in viral load induced by DAAs could lead to an altered immune surveillance, promoting the growth of already existing cancer clones<sup>[4]</sup>. However, the higher number of patients eligible for antiviral treatment with DAAs could influence the apparent raise in early recurrence rates. In fact, due to the manageability and safety profile of these therapeutic regimens, a larger number of patients with advanced liver disease at high risk of HCC (e.g. liver cirrhosis, advanced age, multiple morbidity) have undergone antiviral treatment than those who were candidates to IFN-based schemes. Subsequent prospective studies underlined that, although the rates of early HCC recurrence remain high in patients who have obtained viral clearance by DAAs, these rates are comparable to those reported in the literature for patients not treated with these regimens<sup>[64-66]</sup>. Waziry *et al*<sup>[67]</sup>, in a meta-analysis, concluded that there is no evidence that DAA therapy was associated with higher HCC recurrence and to suggest differentiated surveillance pathways for HCC among patients undergoing or not IFN-free therapeutic regimens. However, the heterogeneity of the studies included in this analysis limits the power of its results. Although there is no conclusive evidence at the moment in favor or against an increased risk of early HCC recurrence in patients undergoing treatment with DAAs, it appears clear that the risk of early HCC recurrence in patients with HCV-related cirrhosis remains high despite viral eradication. The latest guidelines of the European Association for the Study of the Liver (EASL, published in 2018) suggest a more intensive surveillance strategy (3–4-month imaging intervals for the first two years that can be extended to six month intervals thereafter) in this patient setting<sup>[4]</sup>.

However, the updated literature available after the publication of these guidelines almost unanimously confirms that DAAs therapy is not associated with an increase in early HCC recurrence rates and that both <sup>11</sup> recurrence rates and tumor patterns after initiation of antiviral therapy did not differ between patients who received IFN-based or IFN-free therapy<sup>[68-76]</sup>. On the contrary, there is now increasing evidence of a reduction in the risk of early (as well as late) HCC recurrence after viral eradication achieved by DAA<sup>[77-83]</sup>.

#### *Predictors of early recurrence related to HCC treatment*

The choice of treatment of HCC depends on the characteristics of the patient (in particular the residual liver function and the performance status) and the neoplasm ones (size, single or multifocal, vascular invasion, distant metastasis), as well as the indication and eligibility for liver transplant.

In terms of recurrence risk, no conclusive data are available in literature about which type of loco-regional treatment is more advantageous. In the absence of liver cirrhosis, *liver resection* (LR) probably offers the best prognostic prospects, with an early recurrence rate of approximately 10%<sup>[36]</sup>. Including patients with liver cirrhosis, the early recurrence rates of post-hepatectomy HCC reported in the literature range from 25% to 50%<sup>[34,42,45,51,84,85]</sup>. <sup>4</sup> Metachronous HCC, new post-operative lesions, and intrahepatic metastasis from primary HCC are in fact relatively common following hepatectomy<sup>[42]</sup>. In this regard, the resection margins after hepatectomy appear to be closely related to the risk of recurrence. In particular, neoplastic invasion of the resection margins represents a significant predictor of the risk of recurrence<sup>[44]</sup>. A resection margin < 1 cm also seems to be an independent risk factor for early HCC recurrence<sup>[43,86]</sup>. Some evidence also suggests that a non-anatomic hepatic resection (resection or enucleation without regard to sectoral structure) could lead to an increase in early recurrence rate<sup>[45]</sup>. In fact, an anatomic resection (resection of the entire liver parenchymal tissue supplied by the portal venous system draining the HCC tissue, independently of margin length) could hinder cell dissemination, reducing tumor cell

flow throughout the portal circulation and consequently reduce the risk of intrahepatic metastasis and improve RFS. However, the absence of randomized clinical trials comparing anatomical and non-anatomical hepatic resection do not allow to provide conclusive indications<sup>[87]</sup>.

As previously mentioned, a maximum tumor diameter greater than 2.6 cm (according to Zhu<sup>[42]</sup>) or 3 cm (according to Jung<sup>[36]</sup>) before a curative LR is predictive of a high rate of early recurrence. The risk of early HCC recurrence with a diameter greater than 2.6 cm appears 4.77-fold higher than neoplasms with a diameter  $\leq 2.6$  cm<sup>[42]</sup>. Furthermore, high preoperative total bilirubin levels also correlate with an increased risk of recurrence<sup>[42]</sup>. In particular, this risk would be increased by 6% for every 1 mmol/L increase in preoperative bilirubin. Chan *et al*<sup>[37]</sup> in a large multicenter study provide pre- and post-hepatectomy risk stratification models (ERASL-pre and ERASL-post, respectively) able to identify 3 early recurrence risk classes, with a 2-year malignancy free survival rate of 64.8%, 42.5% and 20.7% in low, intermediate or high risk patients, respectively. In these models male gender, large tumor size, multifocal tumor, high ALBI grade and high serum AFP represent the factors closely related to early recurrence after LR. Ideally, these models, once validated, would optimize the therapeutic strategy for patients with high baseline risk of early recurrence after hepatectomy (revaluating the possibility of LT or providing adjuvant therapy) and intensify the surveillance program.

Compared to liver resection, *radiofrequency ablation* (RFA) treatment shows significantly higher recurrence rates<sup>[41,88,89]</sup>. In particular RFA results in shorter overall survival and time to recurrence (5 years overall survival 71.1%, 5 years time to recurrence 63.8%) than LR (5 years overall survival 61.1%, 5 years time to recurrence 71.7%)<sup>[88]</sup>. The HR for death (0.84, 95%CI, 0.74-0.95) and recurrence (0.74, 95%CI, 0.68-0.79) is significantly lower in patients undergoing LR than in those undergoing RFA. Recently, Lee *et al*<sup>[41]</sup>, through a retrospective study comparing the two methods, showed that in patients with BCLC stage A HCC treatment with RFA is associated with a 1.8 times higher probability of HCC recurrence than hepatectomy (95%CI, 1.541 -



2,216) . While confirming higher overall survival rates after LR compared to RFA, other data were unable to demonstrate significant difference in RFS between the two methods<sup>[90]</sup>. Finally, similar to what is shown for the LR, an ablation margin  $\geq 10$  mm away from the tumor lesion guarantees better outcomes and a lower rate of recurrence compared to an ablation margin  $\geq 5$  mm and  $< 10$  mm<sup>[91]</sup>.

### **Predictive factors of late recurrence**

Conventionally, a HCC recurrence is defined as late when it occurs 2 years after treatment of the primary tumor. Different from the early one, late recurrence is generally related to de novo development of the neoplasm and does not depend on the characteristics of the previous tumor. About 90% of late relapses consists in exclusively intrahepatic localization, whereas the remaining cases show both intrahepatic and extrahepatic localizations<sup>[92]</sup>. Therefore the risk factors are mainly the ones related to the underlying liver disease (table 2).

#### *Predictors of late recurrence related to patient characteristics*

Among the predictive factors of late recurrence related to the basal characteristics of the patient, it is easily to understand that the main predictor factor is the presence of *liver cirrhosis*, a fertile substrate for hepatocarcinogenesis<sup>[32,41,43,84,93-96]</sup>. In particular, the presence of liver cirrhosis increases the risk of late HCC recurrence by 3 or 4 times<sup>[41,93]</sup>. In fact, liver cirrhosis is a pre-malignant condition which, due to an accelerated hepatocyte turnover induced by the chronic inflammatory state, promotes the accumulation of gene aberrations and cell transformations. The high rate of gene errors and the subsequent uncontrolled cell proliferation therefore favor the development of HCC<sup>[97]</sup>. However patients with liver cirrhosis undergoing curative treatment for HCC, show a late recurrence rate significantly higher compared to de novo incidence rate in patients with no history of prior HCC<sup>[41]</sup>. This implies that the

presence of liver cirrhosis is not the only factor that elicits the cancer risk in patients with late recurrence.

As highlighted by Lee *et al*, on one hand, and Xu *et al*<sup>[92]</sup> and Yang *et al*<sup>[93]</sup>, on the other, respectively, the *age* and *sex* of the patient also contribute to the late recurrence risk stratification. Older and male patients show an increased risk of late HCC recurrence after curative treatment. The gender difference in the late recurrence rate could be explained by the potential protective role of estrogen for the development of HCC<sup>[98,99]</sup>, resulting in more than 3 times higher probability of late recurrence in men compared to women<sup>[93]</sup>.

The predictive role of *liver stiffness (LSM)* in the risk of HCC occurrence is well documented in the literature<sup>[100,101]</sup>. Since occurrence and late recurrence show similar pathogenesis (de novo hepatocarcinogenesis), it seems reasonable to believe that LSM can also represent a risk factor for late recurrence. In this regard, Jung *et al*<sup>[102]</sup> had already highlighted how the presence of liver cirrhosis assessed by liver stiffness (LSM  $\geq 13.5$  kPa) was associated with an increased overall risk of recurrence. More recently Marasco *et al*<sup>[43]</sup> demonstrated that liver stiffness but even more the *splenic stiffness (SSM)*, surrogate for the degree of portal hypertension) are associated with an increased risk of late HCC recurrence. Late recurrence-free survival was significantly different according to the SSM cut-off of 70 kPa. These data find further evidence in the literature. Fang *et al*<sup>[40]</sup> in fact showed how the *splenic volume* (evaluated through automated volumetry software from preoperative CT images) correlated independently with the probability of HCC recurrence two years after hepatic resection. In particular, for each 1 mL increase in splenic volume, the risk of late recurrence increases by 0.3%. In addition, patients with high splenic volume ( $> 165$  mL) showed a lower 5-year recurrence-free survival (5-years RFS 36%) than patients with low splenic volume ( $< 165$  mL, 5-years RFS 71%). The correlation between stiffness/splenic volume and the risk of late HCC recurrence probably comes from the close association with the severity of liver disease and portal hypertension, both involved in hepatocarcinogenesis. The correlation that some studies showed between the risk of late recurrence and *platelet counts* or the

presence of *esophageal varices*, which are also surrogates of the degree of portal hypertension and severity of liver damage<sup>[43,103,104]</sup>, is therefore easily explained.

In patients with chronic HBV infection, the presence of *viral replication* increases the risk of late recurrence<sup>[105-108]</sup>. In particular, patients undergoing liver resection for HCC with high preoperative HBV-DNA levels show lower median overall survival and RFS compared to those with low viral load<sup>[106]</sup>. Patients with high viremia are characterized by higher Ishak inflammatory and fibrosis scores, favoring hepatocarcinogenesis<sup>[105]</sup>. The liver inflammatory activity induced by the high viral load may lead to necrosis and regeneration of hepatocytes, increasing the rate of gene errors and neoplastic transformation. Recently it has been hypothesized that a high viral load (HBV-DNA > 10<sup>4</sup> copies/mL) is a risk factor also of early recurrence<sup>[109]</sup>. In fact, high preoperative levels of HBV-DNA would increase the risk of microvascular invasion by about 40%<sup>[110]</sup>. In patients with high pre-operative viral load, the initiation of antiviral treatment after surgical resection allow to reduce both early and late HCC recurrence rates<sup>[106,109,110]</sup>. However, a similar effect on late recurrence rates was also found in patients with low pre-operative viral load<sup>[111]</sup>. Despite comparable efficacy in obtaining virological response, recent evidence suggests that the <sup>15</sup>tenofovir disoproxil fumarate (TDF) treatment is associated with a significantly lower risk of both HCC occurrence<sup>[112]</sup> and early and late recurrence<sup>[113]</sup> compared to treatment with entecavir (ETV). In particular, the HCC recurrence rate at 5 years from surgical resection is 33.6% in patients treated with TDF and 44.5% in those treated with ETV<sup>[113]</sup>. Unlike ETV, TDF would induce the synthesis of high serum levels of interferon-lambda 3 (IFN-λ3)<sup>[114]</sup>, which has been shown to exert a strong antitumor activity<sup>[115,116]</sup>. The antitumor effect of IFN-λ3 induced by TDF would therefore be additive to the capacity of breaking down viral replication and turn off necroinflammatory activity, which is common to both nucleoside (EDV) and nucleotide (TDF) analogs.

Increasing evidence is also available on the predictive role of *hepatitis B surface antigen* (HBsAg) levels on the rate of late HCC recurrence. In patients undergoing LR, pre-operative HBsAg levels > 200 IU/mL has shown to be independent predictors of late

recurrence (HR 1,778)<sup>[84,103]</sup>. If the role of the predictor is well defined, there is nevertheless a significant heterogeneity of the cut-offs used. Huang *et al*<sup>[86]</sup> in fact highlighted how, in patients with low viral load, the risk for HCC recurrence significantly increases with HBsAg levels  $\geq 1000$  IU/mL (5-year RFS rate 46.1% in HBsAg  $\geq 1000$  IU/mL group *vs* 34.1% in HBsAg  $< 1000$  IU/mL group). According to Sohn *et al*<sup>[107]</sup> finally, HBsAg levels  $\geq 4000$  IU/mL <sup>27</sup> were associated with late recurrence after curative resection in HBV-related HCC.

#### *Predictors of late recurrence related to HCC treatment*

Several evidences suggest that RFA treatment increases the risk not only of early but also of late recurrence (HR, 1,872; 95%CI, 1,290 - 2,717) compared to LR<sup>[41,88,117-119]</sup>. Furthermore, the overall survival at 3 and 5 years of patients undergoing LR appears significantly higher than patients undergoing RFA<sup>[117,118]</sup>. In particular, the 5-year overall survival rates were 80% *vs* 66%, and 5-year RFS rates were 48% *vs* 18% for LR and RFA groups, respectively<sup>[118]</sup>. <sup>28</sup> Because the choice of treatment is influenced by both tumor- and liver disease-related factors, some Authors hypothesize that the correlation between RFA treatment and the risk of late recurrence could reflect both. In fact, patients undergoing RFA are generally older, have a greater number of comorbidities and a worse degree of liver function than patients undergoing LR. As noted above, these factors are closely related to the risk of both late and early recurrence. Therefore, the higher risk of late recurrence in patients undergone RFA compared to those treated with resection could depend on more severe underlying liver disease.

#### *Predictors of late recurrence related to HCC characteristics*

Different from what expected<sup>[95,96]</sup>, some evidence suggests that factors related to tumor burden (size, multifocality) determine an increase in the risk of late recurrence, as well as early one<sup>[45,93,105]</sup>. Recently, Xu *et al*<sup>[92]</sup> confirmed, in a multicenter retrospective analysis of patients underwent curative LR for HCC, that multifocality, dimensions greater than 5 cm and the presence of satellite nodules or vascular invasion

(macroscopic or microscopic) represents independent risk factors of late recurrence. The presence of multifocal HCC at baseline would increase the risk of a late recurrence after curative treatment by more than 3 times (HR 3,766, 95%CI: 2,287–6,201)<sup>[93]</sup>. In this regard, Cheng *et al*<sup>[94]</sup> also showed that pre-hepatectomy AFP levels > 400 ug/L are related to the risk of late (as well as early) recurrence. Given the dichotomy between "early" and "late", these factors should correlate with an increased probability of occult intrahepatic dissemination (and therefore early recurrence), rather than an increased risk of hepatocarcinogenesis (late recurrence). These data suggest that the dichotomy between early and late recurrence is probably not so clear-cut, and pathogenetic mechanisms and clinical features may overlap. Therefore, the temporal criterion is not able alone to discriminate the pathogenesis and aggressiveness of a recurrence of HCC with certainty.

#### **Liver transplant and HCC recurrence risk**

Liver transplantation (LT) represents the most radical approach for HCC in patients with liver cirrhosis, able to treat simultaneously the neoplasm and the underlying liver disease and to minimize the risk of both early and late recurrence when candidate selection is adequate<sup>[120]</sup>. In fact, a therapeutic strategy that provides for early listing for transplantation and a loco-regional bridging therapy in patients with HCC at high risk of recurrence has proven to be extremely valid and associated with excellent long-term outcome<sup>[121]</sup>. The presence of occult extrahepatic dissemination and the persistence of the cause of liver damage (eg: HBV infection or HBV/HDV coinfection) account for the residual risk of early and late HCC recurrence, respectively. Overall, the estimated HCC recurrence rate in patients undergoing LT is between 12% and 20%<sup>[22,122,123]</sup>.

The most important predictor of the risk of early post-transplant recurrence is certainly the tumor burden. Size and number of lesions closely correlate with this risk, although not in a linear way. In fact, in multifocal HCC, starting from 3 or more lesions,

the increase in the risk of recurrence appears to be attenuated<sup>[124]</sup>. Conversely, this risk is proportional to the size of the tumor. In particular, the recurrence rate increases by 36% for each additional centimeter of HCC diameter<sup>[125]</sup>. The microvascular invasion is another determining factor in the risk of recurrence and HCC-related death<sup>[126,127]</sup>. Its presence increases the risk of recurrence by approximately 2.4 times and significantly reduces the 5-year rates of RFS (44% *vs* 64% in the absence of microvascular invasion)<sup>[126]</sup>. Similarly, the histological finding of poorly differentiated (grade 3 or 4) HCC determines an increased risk of recurrence (39.3% *vs* 13% for grade 1 and 2 tumors) and reduction of 5-years RFS (39.9% *vs* 57.7 %)<sup>[127]</sup>. In this setting, the prognostic role of AFP is also relevant, found to have an inverse relationship with the post-transplant survival rate<sup>[128]</sup>. An increase in AFP greater than 7.5 ng/mL per month is associated with the presence of microvascular invasion and is predictive of post-transplant recurrence<sup>[129]</sup>.

Beyond the characteristics and aggressiveness of the tumor, the etiology of liver disease also affects the rate of recurrence, especially the late one. In particular, the highest recurrence rate was found in patients with chronic HBV infection (18%) compared to other etiologies (11%, 10% and 8% for HCV, alcoholic liver disease and non-alcoholic steatohepatitis - NASH , respectively). In this regard, preliminary evidence suggests that an increase in RFS for HCC patients following LT can be obtained by administering anti-HBV prophylaxis and/or anti-HBV immunoglobulins<sup>[130]</sup>.

Finally, some comorbidities may also influence the risk of recurrence in HCC patients undergoing liver transplantation. In particular, obese patients show a significantly higher frequency of microvascular invasion and recurrence rates and lower RFS than normal weight patients<sup>[131,132]</sup>. This correlation could be explained by a more pronounced tumor neoangiogenesis in obese patients, secondary to the increased expression of vascular endothelial growth factor (VEGF). Furthermore, in obese patients the reduction of adiponectin levels and the simultaneous increase of those of leptin would induce a pro-oncogenic state and stimulate neoplastic proliferation<sup>[131,132]</sup>.



The central theme in managing the risk of recurrence is the selection of patients eligible for liver transplantation. Currently, the strongest evidences identify the Milan criteria as the best strategy to optimize the selection of LT candidates, stratifying the risk of early recurrence, strongly correlated to tumor size and number of focal lesions<sup>[22]</sup>. These criteria suggest the presence of single tumors  $\leq 5$  cm or multiple tumors  $\leq 3$  nodules size  $\leq 3$  cm, without vascular invasion and/or extrahepatic involvement as boundaries for transplant eligibility<sup>[24]</sup>. The application of these criteria guarantees a post-transplant survival rate comparable to that of patients undergoing transplant for non-neoplastic causes<sup>[133]</sup>. On the other hand, patients undergoing organ transplantation beyond the Milan criteria show a significantly higher HCC recurrence rate than patients within these criteria<sup>[22]</sup>.

However, growing evidence suggests that these criteria, developed in 1996, may be excessively restrictive to date, leading to the exclusion of a subgroup of patients who could benefit from transplantation<sup>[120]</sup>. Yao *et al*<sup>[134]</sup> showed that expansion of the tumor size limits (solitary tumor  $\leq 6.5$  cm or  $\leq 3$  nodules with the largest lesion  $\leq 4.5$  cm and total diameter  $\leq 8$  cm - UCSF criteria) does not adversely impact survival post-transplant. Subsequently, the same Authors validated these criteria, confirming a 5-year RFS rate of 81%<sup>[135]</sup>. The extension of the Milan criteria suggested by Yao *et al* could make eligible for LT about the 5-20% of previously excluded patients, guaranteeing comparable long-term survival rates. Also Mazzaferro *et al*<sup>[124]</sup> attempted to overcome the previous limits through the "up-to-seven criteria": HCC with seven as the sum of the size of the largest tumor (in centimeters) and the number of tumors. They showed that, in the absence of microvascular invasion, patients who met these criteria demonstrated survival rates comparable to patients who met the original Milan criteria (5-year overall survival 71.2%). Conversely, the presence of microvascular invasion doubles the likelihood of recurrence and significantly reduces the overall post-transplant survival rates in these patients ("up-to-seven" patients 5-year overall survival 53.6% *vs* "Milan criteria" patients 5-year overall survival 73.3%). Microvascular invasion was observed in 16.6% of patients who met the Milan criteria and in over half of patients beyond the



Up-to-seven criteria<sup>[124]</sup>. Recently Mazzaferro *et al*<sup>[136]</sup> attempted to identify factors associated with HCC-related death of patients who underwent LT and to provide a predictive model of survival. The number of lesions and their size, as well as the levels of AFP, were significantly associated with HCC-specific death. To ensure a HCC-specific post-transplant survival rate of at least 70%, the Authors suggested that the sum of number and size of tumors (in centimeters) should not exceed 7 when level of AFP was < 200 ng/mL, should not exceed 5 when level of AFP was 200-400 ng/mL and should not exceed 4 when level of AFP was 400-1000 ng/mL. Several studies confirmed the predictive value of pre-transplant AFP levels for HCC recurrence<sup>[22,137]</sup>. A similar role has also been demonstrated by PIVKA-II (5-fold increased risk for recurrence after transplantation)<sup>[138]</sup>.

An approach independent of the size of the HCC and the number of lesions has been hypothesized through the "extended Toronto criteria"<sup>[137]</sup>. The latter propose the eligibility for LT when the tumor does not have extrahepatic spread and/or macrovascular invasion, has a low histological grade on pre-operative biopsy and the patient enjoys a high performance status. The post-transplant survival rates in this case were shown to be independent of the patient's status "within" or "beyond" the Milan criteria (5-year overall survival 69% and 78% for patients who met or not the Milan criteria, respectively,  $P = 0.3$ ) and therefore independent of the size of HCC and the number of lesions<sup>[139]</sup>.

Furthermore, growing evidence suggests that an effective and sustained tumor downstaging with locoregional, surgical, or systemic therapies from beyond to within the Milan criteria favorably impact on overall and tumor-free survival<sup>[25,140,141]</sup>. In particular, the success rate of downstaging reported in the literature is higher than 40%<sup>[142]</sup>. Patients eligible for LT who met the Milan criteria after HCC downstaging showed 5-year tumor event-free and overall survival of 76.8% and 77.5% respectively, compared to 18.3% ( $P = 0.003$ ) and 31.2 % ( $P = 0.035$ ) of patients undergone standard of care (non-transplantation therapies)<sup>[25]</sup>. Regardless of the Milan criteria, in patients with

HCC eligible for LT, a pre-transplantation loco-regional therapeutic approach (neoadjuvant, eg: thermal ablation), if feasible, allows to reduce the risk of recurrence<sup>[4]</sup>.

## **CONCLUSION**

HCC is currently a potentially curable disease. However, recurrence rates still appear to be extraordinarily high. Although several factors are involved, the identification of predictive factors for both early and late HCC recurrence could allow to optimize treatment strategies (liver transplant, liver resection, thermal ablation) and surveillance. High-risk patients should be referred to treatments with the lowest recurrence rate (eg, liver transplant<sup>[121]</sup>) and/or combination therapies, as well as intensive surveillance programs. Given the absence of HCC treatment options certainly recurrence-free to date, the combination of multiple treatments or use of adjuvant or neo-adjuvant therapeutic schemes (eg: immunotherapy) could allow to reduce the recurrence rate and improve overall survival<sup>[143]</sup>. Research should therefore aim to the validation of these combined therapeutic strategies, particularly in patients with strong pre- and post-operative predictors of early or late recurrence.

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