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TOPIC HIGHLIGHT

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Prognostic factors for hepatocellular carcinoma recurrence

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Abstract

The recurrence of hepatocellular carcinoma, the sixth most common neoplasm and the third leading cause of cancer-related mortality worldwide, represents an important clinical problem, since it may occur after both surgical and medical treatment. The recurrence rate involves 2 phases: an early phase and a late phase. The early phase usually occurs within 2 years after resection; it is mainly related to local invasion and intrahepatic metastases and, therefore, to the intrinsic biology of the tumor. On the other hand, the late phase occurs more than 2 years after surgery and is mainly related to *de novo* tumor formation as a consequence of the carcinogenic cirrhotic environment. Since recent studies have reported that early and late recurrences may have different risk factors, it is clinically important to recognize these factors in the individual patient as soon as possible. The aim of this review was, therefore, to identify predicting factors for the recurrence of hepatocellular carcinoma, by means of invasive and non-invasive methods, according to the different therapeutic strategies available. In particular the role of emerging techniques (*e.g.*, transient elastography) and biological features of hepatocellular carcinoma in predicting recurrence have been discussed. In particular, invasive methods were differentiated from non-invasive ones for research purposes, taking into consideration the emerging role of the genetic signature of hepatocellular carcinoma in order to better allocate treatment strategies and surveillance follow-up in patients with this type of tumor.

Key words: Percutaneous ethanol injection; Percutaneous radiofrequency ablation; Transarterial chemoembolization; Hepatic resection; Orthotopic liver transplant; Liver biopsy; Liver stiffness measurement; Hepatocellular carcinoma

Core tip: Hepatocellular carcinoma (HCC) recurrence represents an important clinical challenge due to its negative impact on overall patient survival. The predictors of HCC recurrence, based mainly on HCC radiological features (*i.e.*, number and size of HCC nodules), have enabled early diagnosis thereby drastically reducing the HCC recurrence rate and, hence, patient survival. However, other more efficacious predictors are needed in order to further reduce the HCC recurrence rate. This review describes the more clinically useful predictors of the different imaging techniques and the molecular features of HCC recurrence according to the available therapeutic strategies.

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INTRODUCTION

Hepatocellular carcinoma (HCC) represents the sixth most common neoplasm and the third leading cause of cancer-related mortality worldwide[1]. Its occurrence has a clear geographical distribution, having the highest incidence in East Asia, sub-Saharan Africa and Melanesia, where about 85% of all cases occur, due to the high prevalence of hepatitis B virus (HBV) infection. On the other hand, the incidence of hepatitis C virus (HCV) and alcohol-related HCC is rising in developed countries[2].

To date, different diagnostic and therapeutic strategies are available for the overall management of HCC, all of them present in different guidelines published by various international scientific societies[3-5].

From a clinical point of view, the critical problem is represented by the recurrence of HCC which can be early or late, and can occur practically after every type of treatment.

In fact, it has been documented that the recurrence rate of HCC involves 2 phases. The early phase usually occurs within 2 years after resection, and is mainly related to aggressive pathological factors, such as high tumor grade, local invasion and intrahepatic metastases and therefore to the intrinsic biology of the tumor; on the other hand, the late phase occurs more than 2 years after surgery and is mainly related to *de novo* tumor formation as a consequence of the carcinogenic cirrhotic environment[6].

There are several treatment strategies available for HCC. The choice of the best treatment is guided by a prognostic classification [Barcelona clinic liver cancer (BCLC) classification][1] (Figure 1) which divides patients into 5 different stages, according to pre-established prognostic variables, which take into consideration tumor status, liver function and performance status[3].

Resection is the first-line therapy in patients with solitary tumor and well-preserved liver function. However, its major complication is the recurrence of HCC, reaching an incidence of more than 70% at 5 years[7]. Vascular invasion (both macroscopic and microscopic) is the strongest predictor of recurrence and survival, directly associated with histological differentiation and tumor size[7].

The aim of this review was to identify predicting factors for the recurrence of HCC (early or late recurrence) according to the different therapeutic strategies available. Furthermore, we differentiated the invasive methods from the non-invasive ones for research purposes, taking into consideration the emerging role of the genetic signature of HCC in order to better allocate treatment strategies and surveillance follow-up in patients with HCC.

It was not our aim to discuss the role of clinical predictors (*i.e.*, disease severity, age, gender, etiology, *etc.*) or of serum markers (alfa-fetoprotein, des-γ-carboxy prothrombin, *etc.*) as prognostic factors for the recurrence of HCC, see specific reviews[8-10] for a more detailed discussion.

PREDICTING FACTORS OF RECURRENCE AFTER HCC TREATMENT

Percutaneous treatments

During the past few decades, several minimally invasive ablation techniques have been developed to treat unresectable HCC. Percutaneous ethanol injection (PEI) was introduced as the seminal ablation technique for HCC in the 1980s[11]. In 1990, the first use of percutaneous radiofrequency ablation (RFA) for HCC was published followed by percutaneous microwave (MW) ablation in 1994[12]. More recently other hot- and frost-based extracorporeal techniques as well as high-intensity focused US ablation, laser ablation and cryoablation have also been introduced into clinical practice[12]. However, in this review, we will discuss only PEI and RFA since, according to the recent guidelines of the European association for the study of the liver (EASL), only these two therapies are considered standard therapies for HCC non suitable for surgery[13].

Furthermore, it is necessary to remember that treatment efficacy after ablative therapy is represented by a complete necrosis of the lesion (defined as complete response, CR) at imaging techniques according to the recently modified RECIST (mRECIST) assessment for HCC[14].

However, it is known that imaging techniques understate the histopathological findings, mainly for tumors larger than 3 cm; in fact, in these cases, where successful RFA was diagnosed at imaging techniques, necrosis is present in only 50% of the patients[15]. Therefore, it is not easy to recognize when recurrence is due to incomplete necrosis and, consequently, to the presence of a residual tumor, or when it is due to true local recurrence.

In our review, we considered CR as assessed by imaging techniques after percutaneous treatment according to the EASL guidelines[13], and tumor recurrence as the appearance of new nodules during patient follow-up.

PEI

PEI is a percutaneous ultrasound-guided ablative technique involving the injection of an ethanol solution of 95% absolute alcohol which induces coagulative necrosis of the lesion as a result of cellular dehydration, protein denaturation and chemical occlusion of small tumor vessels[11].

It represents a well-established technique for the treatment of nodular-type HCC in early BCLC stages, achieving complete necrosis in 90% of tumors < 2 cm in diameter, 70% in those of 2-3 cm and 50% in those between 3 and 5 cm[12,16].

The major limitation of PEI is the high (local) recurrence rate, in particular in the presence of lesions larger than 3 cm[17]. Tumor size ⩾ 3 cm and the presence of peritumoral capsule in lesions < 3 cm, which could limit adequate ethanol diffusion, represent significant risk factors associated with early local recurrence rate at 12 and 24 mo[17].

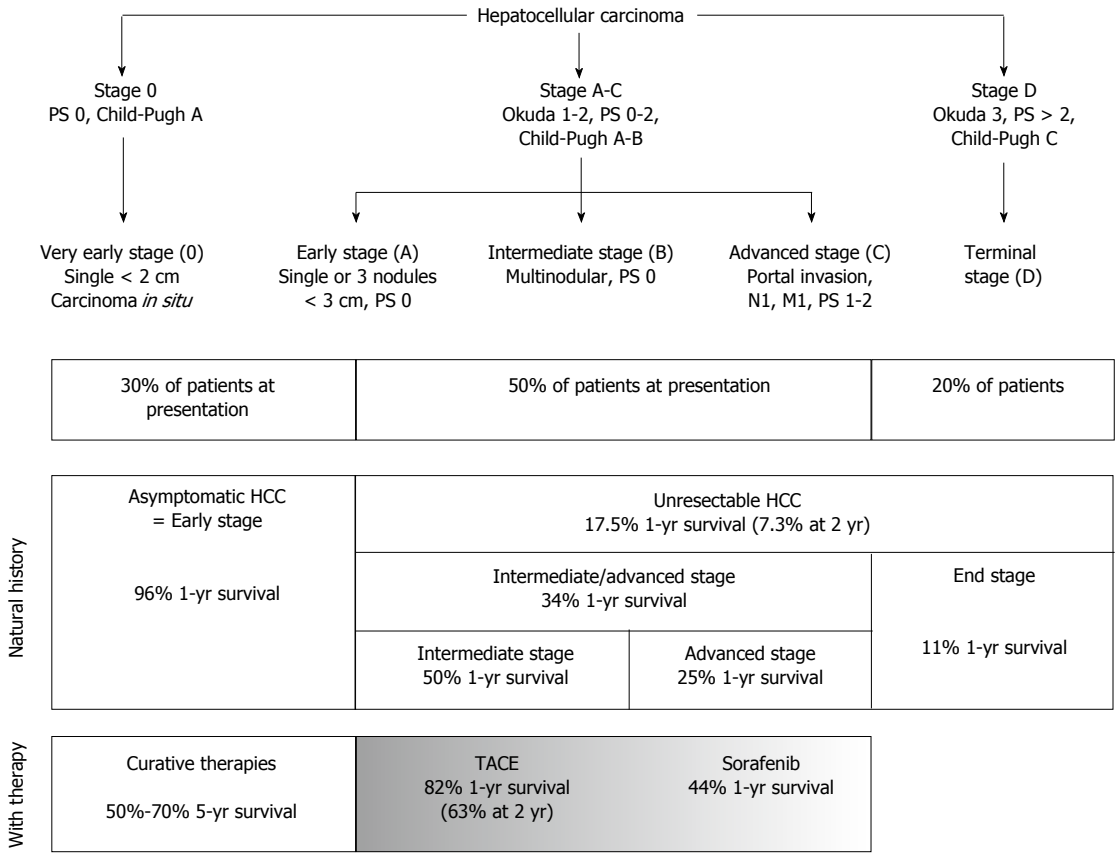

Figure 1 The Barcelona clinic liver cancer algorithm for the management of hepatocellular carcinoma, adapted from Bolondi *et al*[140]. HCC: Hepatocellular carcinoma; TACE: Transarterial chemoembolization.

Other potential factors affecting tumor recurrence are represented by intratumoral septa, satellite nodules, total number of treated lesions, the presence of a halo and an intratumoral heterogeneous echo pattern and serum alpha-fetoprotein levels > 20 mg/dL[18-20]. The latter seems to be independently associated with new nodular recurrence[20].

The most limiting factor affecting the efficacy of PEI is tumor size, as confirmed by studies which compared the efficacy of PEI to RFA in terms of recurrence rate[21-23]. When the tumor nodule increases in size, it develops intratumoral septation, which is composed of collagen and lipid matrix and is rare in small tumors[24]. A possible explanation is that ethanol diffusion is blocked either by the intratumoral fibrotic septa and/or the tumor capsule, limiting its curative capacity in lesions larger than 2 cm[24]. In fact the peritumoral capsule and intratumoral septa frequently harbor cancer cells within matrices which are not easily penetrated and are completely destroyed by 95% ethanol[24]. Therefore, viable tumor cells persist and display time-dependent local recurrence. Large HCCs without capsule formation could manifest recurrence from the intraseptal harboring of cancer cells and this may explain why capsule formation affects the recurrence rate in small HCCs and not in large HCCs.

To improve the efficacy of the conventional ethanol ablation technique in patients with tumors larger than 2 cm not treatable with other techniques, a retractable multipronged injection needle was developed[25]. This new ablation technique using the multipronged needle delivery system (multipronged ethanol ablation) has recently been proposed in a human study to treat larger HCCs in a single session. With this new device, PEI reached a rate of sustained complete response of 90% in tumors up to 5 cm. The complication rate was 2%, similar to that of conventional PEI[26]; the diameter of the main tumor ($\leqslant$ 3.0 cm *vs* > 3.0 cm, $P = 0.002$), ethanol volume per tumor ($\leqslant$ 30 mL *vs* > 30 mL, $P = 0.021$), and ethanol volume per patient ($\leqslant$ 40 mL *vs* > 40 mL, $P = 0.032$) were significantly related to the occurrence of complications, but only ethanol volume per patient was an independent risk factor in the multivariate analysis[27].

Percutaneous RFA

Radiofrequency ablation is a percutaneous thermal ablative technique which induces coagulative necrosis of the tumor using heat, producing a safety ring in the surrounding peritumoral tissue at the same time. Local ablation is considered the standard of care for patients with BCLC 0-A stage, not suitable for surgery[3]. For HCCs $\leqslant$ 2 cm, in the setting of a multi-disciplinary evaluation, RFA can be considered the first-line treatment when performed in expert centers[4]. The efficacy of RFA is clearly superior to that of PEI for tumors larger 2 cm[5] and is

considered to be an acceptable alternative to resection for HCCs < 3 cm in Child Pugh A cirrhosis patients[28].

As far as comparison between RFA and surgical resection is concerned, in a recent meta-analysis which evaluated HCCs < 5 cm, it was highlighted that surgical resection was better than RFA only for HCCs > 3 cm and < 5 cm both for disease-free survival and for overall survival[29]. Furthermore, assessing the cost effectiveness of RFA and surgical resection for early HCC, the authors found that, for early HCCs (< 2 cm), RFA was more cost effective than resection while, for single larger early stage HCCs, surgical resection remained the best strategy[29].

Short-term outcomes after treatment are excellent, with overall survival rates of 100% and 98% at 1 and 2 years, respectively.

However long-term observation has shown a high recurrence rate (> 70 % at 5 years), owing to the underlying liver cirrhosis. Moreover, early recurrence, local or distant, is present, although with a notable difference between their percentages. In fact, in a recent long-term 10-year-follow-up study, early local recurrence was present in approximately 3% of the patients and early distant recurrence in approximately 70% of the patients[30].

Several different risk factors for the two types of recurrence have been observed; local recurrence assessed by imaging techniques [computed tomography (CT) and magnetic resonance (MR)] was observed mainly in larger HCCs, close to vessels, localized near the diaphragm[31], having a poor degree of differentiation, with ablative margins less than 1 cm and non-encapsulated tumors.

As far as distant intrahepatic recurrence is concerned, predictive factors are considered to be the number (> 2) of nodules, and HCC lesions with gradual enhancement in early arterial time as evaluated by CEUS[32,33].

Moreover, incomplete necrosis has been observed for lesions larger than 3 cm and in the presence of large peritumoral vessels (≥ 3 mm of diameter) due to the convective heat loss mediated by high perfusion of the peritumoral tissue[32].

In fact, a tumor size > 2-3 cm represents the best predictor of early (after 1 or 2 years) local and distant recurrence after treatment[33-36].

On the other hand, in the presence of HCCs ≤ 2 cm, RFA has better overall and disease-free survival rates when compared to hepatic resection[37-39]. with the advantage of a significantly lower rate of major complications, thus leading to the consideration of RFA as the treatment of choice for patients with a single HCC ≤ 2 cm, even when surgical resection is possible[4,40]. However, RFA is not free from potential complications, due to potential neoplastic seeding[41] and peritumoral structural damage, in particular in the presence of HCC nodules adjacent to large vessels, extrahepatic organs or the liver capsule[42,43].

At the same time, the HCC nodule position within the liver also seems to influence the local recurrence rate; in fact, proximity to large vessels and the diaphragm significantly increases the risk of local recurrence as does large tumor size (HR = 2.609, 3.128, 1.716 respectively)[33].

Transarterial chemoembolization

Transarterial chemoembolization (TACE) consists of the intra-arterial infusion of chemotherapeutic agents, such as doxorubicin or cisplatin with or without a viscous emulsion (lipiodol), followed by embolization of the blood vessel with gelatin sponge particles or other embolic agents, resulting in a combined cytotoxic and ischemic effect. It represents the treatment of choice in patients at an intermediate BCLC stage, those with compensated disease, those with multifocal HCCs who are not candidates for resection and those without signs of vascular invasion or extrahepatic diffusion[3]; thus, the best candidates for TACE are asymptomatic Child-Pugh class A patients, although those with a Child-Pugh score of B7 or ECOG PS 1 can also be considered[4]. Transarterial chemoembolization is not indicated in patients with jaundice, untreatable ascites, main or branch portal vein thrombosis, hepatofugal portal blood flow or HCC nodules larger than 10 cm. Transarterial chemoembolization can be utilized in patients with early stage HCC if surgical or ablative techniques are not applicable due to technical conditions and/or comorbidities[4].

The recommendation for TACE as the standard of care for intermediate-stage HCC is based on the demonstration of improved survival in comparison to the best supportive care or suboptimal therapies in a meta-analysis of six randomized control trials[34]. However, there was considerable heterogeneity between the individual study designs of the six trials, and the differences included patient populations and TACE techniques. More specifically, the older trials of the meta-analyses included lobar or whole liver embolization (*i.e.*, the injection of a mixture of Lipiodol, a chemotherapeutic agent, and an embolizing material into either the main lobar artery or the hepatic artery itself) whereas, more recently, selective treatments have been used (*i.e.*, the injection of agents into the segmental or subsegmental branches feeding the tumors) with apparently better survival results[35-37].

Furthermore, a recent study[38] has confirmed that selective/superselective TACE was more successful than lobar procedures in achieving complete histological necrosis, and TACE was more effective in 3- to 5-cm tumors than in smaller ones. In fact, a significant direct relationship was observed between tumor diameter and mean tumor necrosis level (59.6% for lesions < 2 cm, 68.4% for lesions of 2.1-3 cm, and 76.2% for lesions > 3 cm). Histological necrosis was maximal for tumors > 3 cm: 91.8% after selective/superselective TACE and 66.5% after lobar procedures.

After initial success, treated tumors tend to be revascularized, as a result of neoangiogenesis, thus influencing tumour recurrence. In a recent paper, the cumulative recurrence rates at 1, 3 and 5 years were 22%, 64% and 79%, respectively[39]. Potential factors affecting HCC recurrence after complete response with TACE treatment are multifocal disease[39,40], age > 60 years[39]. and the pattern of lipiodol accumulation, detected by CT immediately after TACE, reflecting the local response to

Table 1 Risk factors predicting hepatocellular carcinoma recurrence after non-surgical treatments

Treatment	Risk factors	Ref.
Percutaneous ethanol injection	Tumor size > 2-3 cm	[17,21-23]
	Multinodularity	[18,19]
	Peritumoral capsule	[17,24]
Percutaneous radiofrequency ablation	Tumor size > 2-3 cm	[31,33]
	Position of nodule near large vessels or diaphragm	[31]
Transarterial chemoembolization	Multifocality	[39,40]
	Partial necrosis	[44]
	Age > 60	[39]
	Pattern of lipiodol accumulation (partial or heterogeneous)	[41,42]

treatment[41,42]. Regarding the latter aspect, lipiodol distribution involving the entire tumor area and the surrounding peritumoral tissue is representative of a good local response and is thus associated with better disease-free survival; on the other hand, partial lipiodol accumulation or heterogeneous uptake are associated with a higher rate of local recurrence.

Transarterial chemoembolization has also been proposed as a neoadjuvant treatment or for a down-staging strategy before liver transplantation (LT), resulting as a safe and efficacious procedure with a high rate of histological response although the benefit in terms of disease-free survival is not clear[43]. However, most importantly, the percentage of histological necrosis after TACE results in a strong predictive factor of recurrence; in fact, partial necrosis has been demonstrated to be the only risk factor for tumor recurrence at multivariate analysis in patients who have undergone liver transplantation after a bridging TACE treatment[44]. Since partial necrosis is considered a risk factor for tumor recurrence after liver transplantation, patients and procedures should be selected carefully, bearing in mind the side effects of incomplete necrosis of the nodules.

A new technique which provides the controlled release of therapeutic agents inside the tumor lesion, with minimal systemic exposure (drug-eluting beads TACE, DEB-TACE), has demonstrated good results in terms of reduced systemic toxicity and increased local tumor control, in particular in advanced disease[45].

The risk factors for predicting HCC recurrence after non-surgical treatments are summarized in Table 1.

Liver resection

Despite improving results in non-surgical approaches, partial hepatectomy still represents a cornerstone for the potentially curative treatment of HCC. Unfortunately, tumor recurrence remains the main obstacle in achieving better results in long-term survival with an expected 5-year intra-hepatic recurrence rate of up to 70%. Recurrent tumors could originate from either intra-hepatic metastasis from the primary tumor or multi-centric occurrence arising from persistent fibrosis and hepatitis-related carcinogenicity in the remnant liver. As a result of clinical and molecular studies conducted in the late nineties and early 2000s, HCC recurrence after hepatic resection is currently divided into early recurrence (within 1 or 2 years after surgery) and late recurrence (greater than these temporal end-points)[46-48]. Early recurrences are considered to result from intra-hepatic metastasis of the primary HCC, and are mainly affected by adverse tumor features whereas late recurrences should be considered as *de novo* HCCs and are mainly affected by the underlying liver status[46-48]. Among the various tumor factors involved in determining the prognosis after resection for HCC, tumor size, multifocal disease, and the presence of vascular invasion or of poor histological differentiation, have been reported to be able to predict early recurrence[49-56]. The presence of cirrhosis represents a risk factor for *de novo* HCC when compared to patients having chronic hepatitis without cirrhosis and, among cirrhotic patients, it has been reported that some cirrhotic characteristics, such as previous surgery either alone or together with increased aspartate aminotransferase (AST) levels and Ishak activity can determine a high-risk profile for the development of late recurrence[46].

Early tumor recurrence: The relationship between tumor size, number and recurrence is rather clear[49]. Briefly, and in accordance with the American Joint Committee on Cancer staging system, HCC nodules $\geqslant$ 5 cm in diameter are associated with an increased recurrence rate[50,51] due to the higher risk of intrahepatic metastases, and the portal vein[50] and micro-vascular invasion (MVI)[51] observed in the presence of larger tumors, in particular in those without tumor capsules[52]. These two morphologic features are not only associated with recurrence and patient survival, but can also determine the optimal therapeutic strategy to adopt[3,5]; thus, even in the presence of a more defined prognosis of resected HCCs, tumor size and number remain the best, and easily available, preoperative prognostic factors after surgery.

Vascular invasion represents one of the best predictors of tumor recurrence after HCC resection and is usually identified as either macroscopic, when invasion of the vessel is visible on radiologic imaging or on gross examination, and microscopic, when invasion is visible only on microscopy[49,53]. The presence of macro-vascular invasion is a strong predictor of a poor prognosis after a hepatectomy, with a median time-to-recurrence of 6.7 mo corresponding to approximately a 4-fold decrease in time-to-recurrence with respect to tumors without macro-vascular invasion[53]. However, this aspect should not be considered as a contraindication to surgery[54-56]. A large multi-centric study in 2013, showed that a hepatectomy for tumors with radiologically evident and histologically proven macro-vascular invasion (portal vein, hepatic vein, inferior vena cava) can achieve 5-year disease-free survival of 18% and 5-year survival up to 38%[54], confirming previous single-center studies which suggested surgery as the best therapeutic choice for these tumor stages[55,56]. Even if the expected prognosis is evidently in-

ferior to that of tumors without macro-vascular invasion (overall survival up to 60%-70%), the finding of median survival of approximately 36 mo suggests that the surgical approach is fundamental since international guidelines suggest Sorafenib for this tumor stage which is accompanied by a median survival of approximately 6-12 mo[3,5].

In the absence of macroscopic tumor spread, the histological presence of microscopic vascular invasion represents one of the best predictors of tumor recurrence after HCC resection. Micro-vascular invasion is usually defined as the presence of tumor emboli within the central hepatic vein, the portal vein, or the large capsular vessels[46]. The presence of MVI is related to a hazard ratio of 1.8 and a 1.4-fold decrease of time-to-recurrence[53]; however, great heterogeneity can be found in the literature, mainly as a consequence of inter/intra-observer variability in reporting the grading of micro-vascular invasion[57]. A risk score evaluating the histological pattern of micro-vascular invasion has been proposed for the prediction of outcome after hepatic resection, obtaining good results in terms of correlation with recurrence and survival[53]. In particular, the histological evidence of invasion of a vessel with a muscular wall and invasion of a vessel which is more than 1cm from the tumor capsule was found to be related to both recurrence and survival after HCC resection (hazard ratios 1.8 for recurrence and 2.1 for survival). A strong limitation of MVI as a prognostic factor is that it can be accurately assessed only on resected specimens[58-64]. Some attempts have been made with the aim of preoperatively predicting the presence of MVI. Tumor grading obtained through tumor biopsy, tumor size, increased alpha-fetoprotein (AFP), L3-AFP and PIVKA-Ⅱ have all been investigated as potential surrogates[58-61]; artificial neural networks have been proposed[62] and there is recent evidence that MR could predict MVI by diffusion-weighted imaging[63-64]. Tumor grade is another strong predictor of early recurrence[45,49,65] but its impact in determining such an inauspicious event is masked by its close relationship to MVI[58,59,65]. Overall, poorly differentiated tumors bring a 2-fold increased risk of early recurrence when compared to well-moderately differentiated tumors[65].

In most hepatectomies for HCC, some of the surrounding non-tumorous liver tissue is resected in order to prevent recurrences caused by microsatellite nodules and/or cancer cell thrombi surrounding the main tumor. The role of a tumor-free margin in HCC was largely investigated in the past, and there is a large consensus among surgeons that the minimal margin-free width should be at least 1 cm[66]. However, recent evidence from a randomized controlled trial showed that a resection margin of 2 cm efficaciously decreased recurrence rate and improved survival outcomes when compared with a gross resection margin of 1 cm[67]. In particular, a wider resection margin can lead to a 1.3-fold reduction of the 1- and 2-year recurrence-rates[67]. In addition to the margin-free width, the type of surgery has also been thought to influence tumor recurrence. Resection procedures for HCC can be divided into anatomic and non-anatomic ones. The systematic removal of a hepatic segment, confined by tumor-bearing portal tributaries, namely anatomic resection (AR), has been suggested because it should be more effective for the eradication of the intrahepatic metastases of HCC caused by microsatellite nodules and/or cancer cell thrombi surrounding the main tumor. On the contrary, most surgeons prefer to leave a greater portion of the parenchyma of this functional unit, such as in non-anatomic resection (NAR), in order to reduce postoperative liver failure in patients with cirrhosis[68]. It remains unclear whether hepatectomy for hepatocellular carcinoma should be performed as an AR or an NAR because no randomized controlled trials are currently available on this topic. A recent systematic meta-regression suggested that patient survival and disease-free survival (DFS) after AR seem to be superior to NAR because the poorer liver function reserve in the NAR group significantly affects prognosis[68]. In fact, patients in the NAR group were characterized by a higher prevalence of cirrhosis (relative risk: 1.27), more advanced hepatic dysfunction (relative risk: 0.90 for Child-Pugh class A) and smaller tumor size (weighted mean difference 0.36 cm) as compared to patients in the AR group. These differences explain the heterogeneity which can be found in the literature regarding this topic. The prognostic role of AR *vs* NAR is probably not independent of other aspects but relative to the tumor characteristics. In the largest published series from Eguchi in 2008, the benefit of AR over NAR, in terms of recurrence-free and disease-free survival, was not observed in HCCs less than 2 cm[69]. It can thus be suggested that, when an anatomic approach cannot be pursued due to inadequate remnant liver volume, NAR for small HCCs will not affect tumor recurrence. This is because tumor size is known to be strictly related to tumor differentiation and the presence of micro-vascular invasion[59,60,62]. These findings have been confirmed in a very recent report which suggested that NAR could be safely pursued in patients with HCCs without MVI or in those having tumors less than 2 cm in size, without affecting tumor recurrence[70]. On the contrary, for larger tumors or in the presence of adverse pathological features, AR provided better early recurrence-free survival.

Late tumor recurrence: Late recurrences represent *de novo* HCCs and, similarly to primary tumors, are affected by the underlying liver status. One of the first published studies regarding this topic showed that cirrhotic patients bring a 2.4-fold risk of developing a late recurrence when compared to non-cirrhotic patients[46]. An Ishak activity > 6 (HR 4.6), surgery for multinodularity, indocyanin green clearance (ICG-15) > 10%, HBV-DNA > 106 IU were also found to be predictors of late tumor relapse in hepatitis-B patients[71]. Regarding cirrhotic patients, it has been reported that surgery for multiple tumors with AST > 2N in male patients over 65 years of age has an unfavorable outcome in terms of late recurrence[65]. Interestingly, this latter study highlighted the fact that, even

if resected patients overcome early recurrence, their risk of late recurrence still remains higher than the expected HCC occurrence of the general cirrhotic population, suggesting that previous HCC itself represents a risk factor for a new tumor[65].

The distinction between early and late recurrence is of particular importance in view of possible and available adjuvant therapies. Sorafenib, due to its anti-angiogenetic property, should be theoretically utilized for preventing early recurrence. The "Sorafenib as Adjuvant Treatment in the Prevention Of Recurrence of Hepatocellular Carcinoma" (STORM) trial is currently ongoing[72]; therefore, to date, there is no evidence of the benefit of this approach. Conversely, since late recurrence represents a *de novo* tumor, there is room to propose anti-viral therapies. Interferon has the potential of the chemoprevention of HCV-related cirrhosis, and it has been demonstrated that it can help in reducing the late-recurrence rate[73] after surgery as has already been suggested for other therapies[74].

Liver transplantation

Transplantation is definitely the optimal therapy in the treatment of HCC since it can remove both the tumor and the underlying liver disease which causes it. Unfortunately, this surgical approach is strongly limited mainly by the chronic shortage of liver donors, but also by some patients characteristics, such as age and presence of co-morbidities. Consequently, during the last two decades, transplant policy regarding HCC patients has moved toward identification of those patients who will achieve an acceptable outcome in terms of tumor recurrence and survival. In fact, early experiences of transplantation for HCC were associated with poor outcomes, reflecting the fact that the patients selected had advanced disease[75,76]. The first benchmark in the prediction of tumor recurrence is represented by the study of Mazzaferro and colleagues in 1996 which defined the criteria for transplant eligibility (Milan criteria) as the presence of a tumor 5 cm or less in diameter in patients with a single HCC and no more than three tumor nodules, each 3 cm or less in diameter, in those patients with multiple tumors, and in the absence of macroscopic tumoral vascular invasion[77]. Patients with tumor features surpassing these thresholds have a significantly higher recurrence rate (relative risk around 1.5) and lower survival (relative risk around 2.0) in comparison to patients who fulfill the Milan criteria[77]. Even if this study was conducted on a small population (48 patients), this seminal paper indicated how tumor burden can guide the therapeutic choice, and it opened the way for all subsequent studies on the topic of liver transplantation for HCC. Regarding tumor characteristics, such as tumor size, number, vascular invasion and differentiation, considerations made for recurrence after liver resection also remain consistent in the present case. Observations from the early nineties identified macro-vascular invasion and lymph node metastasis as significant negative predictors[78]. Subsequent experiences have confirmed that both macro-vascular and micro-vascular invasion lead to a worse outcome, correlating with an increased incidence of post-transplantation tumor recurrence[79]. In addition, tumor size (cut-off: 5 cm)[80], the presence of bilobar disease[81], the total number of lesions[82] and/or tumor grade[83] can influence tumor recurrence and, ultimately, patient survival. Elevated serum alpha-fetoprotein levels have also been observed to play a role[79]. There are, however, other interesting topics which deserve a dedicated discussion in the field of predictors of HCC recurrence, in particular the role of neo-adjuvant therapies and that of immunosuppression.

Of particular interest is the role of downstaging and the response to bridge therapies. Downstaging refers to the therapeutic procedures adopted in those HCC patients ineligible for liver transplantation according to transplantability criteria (often the Milan criteria) by reducing the tumor burden and consequently fulfilling such criteria. Bridge therapy refers to the therapeutic procedures adopted in patients listed for LT to prevent exclusion from the waiting-list due to tumor progression. The response to downstaging and/or bridge therapies could be considered as a surrogate marker of tumor biology; a favourable response to those therapies could select those patients who have a less aggressive tumor and, consequently, a better outcome after transplantation even in stages which are ineligible according to the transplantability criteria. Several authors have focused on the results of different down-staging protocols[84]. Successful down-staging was defined as fulfilling the Milan criteria[77], the University of San Francisco criteria[85] or the Milan criteria with a simultaneous drop in serum AFP below 400 ng/mL, or a 30%-50% decrease in the size of the HCC nodule(s)[86,87]. Overall, patients successfully down-staged so as to satisfy the Milan criteria achieved survival after transplant similar to that of patients transplanted within such criteria, with 79%-100% alive at 3 years and 54.6%-94% at 5 years[88]. In addition, recurrence rates in down-staged patients were comparable with published rates for those already within the Milan criteria[88]. Findings of such comparable outcomes strongly support the hypothesis of selection of HCCs having favorable tumor biology. Conversely, unfavorable tumor characteristics can also be found in HCCs already within the transplantability criteria, and the current observations can easily be applied to patients undergoing bridge therapies. In this regard, the first evidence, in 2004, showed that HCC recipients, having partial necrosis at pathological examination as a consequence of bridge therapies, have a significantly increased risk of tumor recurrence (relative risk around 9.6)[44]. A subsequent similar study found that tumor recurrence was primarily influenced by control of the disease through continued TACE while on the waiting list[87]. Five-year recurrence-free survival was 94.5% in patients who were progression-free while undergoing TACE during the waiting time whereas it was 35.4% in patients who progressed before LT after an initial response to TACE[87]. More recent evidence has suggested that the 3-mo radiological assessment after initial bridge therapies is a reasonable predictor of both waiting-list

Table 2 Risk factors predicting hepatocellular carcinoma recurrence after surgical treatments

Treatment	Recurrence	Risk factors	Ref.
Liver resection	Early	Tumor size ⩾ 5 cm	[50,51]
		High histological grade (G4)	[58-61]
		Microvascular invasion	[53]
		Resection technique	[67-70]
		Genetic profile	[123]
	Late	Stage of liver disease	[46,51]
		Multinodularity	[51]
		Age	[65]
		Gender (male)	[65]
		AST > × 2 normal values	[65]
		Genetic profile	[124]
Orthotopic liver transplant		Milan criteria	[77]
		Vascular invasion	[78]
		Bilobar nodules	[81]
		Tumor grade	[83]
		Tumor size > 5 cm	[80]
		Total number of lesions	[82]

AST: Aspartate aminotransferase.

removal and survival after transplantation[89,90]. Thus, response to bridge therapy and down-staging protocols can represent a surrogate marker of tumor aggressiveness and, ultimately, of recurrence after LT.

A potential role of immunosuppression has also been advocated in determining tumor recurrence. In 2002, the first indications came from a study reporting an increase in 5-year recurrence-free survival in patients treated with smaller cumulative doses of cyclosporine in the first year following transplant for HCC[91]. These data were subsequently tested on tacrolimus levels but, despite these findings, there is still no definitive link between calcineurin inhibitors (CNIs) and recurrent HCC following transplantation[92]. More interesting is the potential antitumoral effect of mTOR inhibitors. Sirolimus possesses both immunosuppressive and anti-neoplastic properties. In a preclinical model, sirolimus inhibits metastatic tumor growth and decreases neo-vascularization in the liver[93]. There is still a lack of convincing evidence to suggest mTOR inhibitors as standard therapy in HCC-transplanted patients, but a meta-analysis of the current literature available suggests a lower recurrence rate in sirolimus patients (4.9%-12.9%) as compared to CNIs (17.3%-38.7%), with a 5-year recurrence-free survival of 79%-80% *vs* 54%-60%, respectively (OR: 0.30)[94]. Additional prospective and randomized controlled studies in this field are warranted but, at present, given the good tolerance observed for sirolimus, its use in preventing HCC recurrence can be a reasonable approach.

The risk factors predicting HCC recurrence after surgical treatment are summarized in Table 2.

INVASIVE METHODS FOR HCC RECURRENCE PREDICTION

Liver biopsy (percutaneous and surgical biopsy)

In cirrhotic patients with HCC, the outcome after surgical procedures is heavily influenced not only by the number and size of nodules but also by the tumor biology and vascular invasion. The former (HCC morphological characteristics) are provided by imaging techniques while the latter can be obtained only by evaluating histological material.

Knowledge of preoperative tumor grade is crucial in the management of HCC because it can influence recurrence and survival after orthotopic liver transplantation (OLT)[95-97]. Needle core biopsy (NCB) is the only preoperative method for obtaining histological specimens for the assessment of the histological grading of the tumor. However, only a few conflicting studies have evaluated the accuracy of NCB in comparison to surgical specimens (which are considered the histological gold standard)[58,59,98], being more accurate both in our[58] and D'Amico's study[98] (overall sensitivity 65%) than in Pawlik's study[59] and it was related to tumor size. In fact, in our study, sensitivity increased to 80% in HCCs < 5 cm, to 86% in HCCs < 3 cm, and to 100% in HCCs < 2 cm while it decreased in HCCs > 6.5 cm.

Furthermore, the close relationship between tumor grade and microvascular invasion has also been observed in several studies[58,58,95].

In recent years, other histological factors, such as EpCAM, p53 protein mutation/over expression and keratin 19 (k19) have been assessed on histopathological specimens in order to obtain additional prognostic information. Of these factors, k19 has been more extensively tested on both surgical and bioptic specimens[99-103]. k19, which is considered a marker for cholangiocytes, hepatic progenitor cells and early hepatoblasts[104,105], has been associated with more aggressive HCCs.

It has been speculated that the reason for this major aggressive behavior could be due to potential stem cell features, such as proliferation and differentiation[106]. In fact, it has been shown that HCCs with k19 positivity expression had a worse prognosis after surgical resection[99]. In fact, in subjects with HCC, k19 expression showed a correlation not only with morphological tumor parameters (increased tumor size, poor grade differentiation, microvascular invasion) in both surgical specimens and in samples obtained by fine needle biopsy[100,107] but also with overall survival and recurrence rate[100,107].

Furthermore, CT scans have shown that k19 was more frequently expressed in hypovascular HCCs, indicating a major risk of early recurrence[108].

The percentage of HCCs with a k19 positivity expression (> 5% of the cells positive) ranged from 4[99] to 16%,[100] having a greater concentration in advanced HCC [8 out of 35 (23%) of the patients in BCLC stage B] than in early HCC [1 out of 24 (4%) patients in BCLC stage A][100]. Furthermore, k19 was significantly more frequent in non-cirrhotic patients than in cirrhotic patients (45% *vs* 9%)[100].

A recent interesting paper[109] showed that k19 evaluation could permit better outcome stratification for the different types of HCCs. In fact, k19$^+$ HCC (defined as cancer of the hepatocellular phenotype with the

stem/progenitor cell immunophenotype) and cHCC-CC (combined hepatocellular and cholangiocarcinoma) had outcomes which were between those of classic HCC and intrahepatic cholangiocarcinoma, $CK19^+$ HCC being closer to HCC and cHCC-CC being closer to cholangiocarcinoma.

Therefore, k19 immunoreactivity could be of additional value in the prognosis of HCC. However, although the evaluation of k19 expression is an easy and economical method, it is only present in a low percentage of patients, mainly in those with advanced HCC. Larger prospective studies are needed mainly in patients with early HCC.

Unfortunately, NCB is not routinely performed in clinical practice because of seeding; however the possibility that NCB of a tumor nodule might produce implantation of tumor cells along the trajectory of the puncture has been studied in a meta-analysis[110] showing an incidence of seeding of approximately 2.7%. However, in a more recent series, seeding was close to 0%, depending on the caliber of the needle and the technique used[111,112]. When this procedure is accompanied by a percutaneous treatment, such as radiofrequency, this rate is even lower and is practically null when the coaxial technique is employed[113].

Regarding the NCB material, other than histological grading and microvascular invasion, the possibility of also obtaining genetic profile signature characteristics has recently been explored. The aim was to integrate more information regarding tumor biology useful for better characterizing the tumor and accurately predicting its recurrence.

Other than morphological parameters, gene expression profiling using microarray technologies to understand the complex biological systems of the tumor has also been used[114]. With genetic profiling, it has been possible to identify four signature classes according to prediction signature, phenotype, function and molecular target[115]. Prediction signature includes the signatures generated from the gene expression itself, microRNA[116,117], DNA copy numbers and epigenetic regulations[115]. Some of these signature have frequently been ill-defined since they were generated in patients at different stages and with underlying liver disease of different etiologies, although the concordance of these signatures on a patient-by-patient basis is still unknown. Furthermore, according to the type of recurrence, different gene profiling was used which was more complex and more exact in predicting late recurrence. The seminal study by Hoshida *et al*[118] showed that a gene profile from a 186-gene signature, obtained from the fixed tissue of the surrounding non-tumoral liver tissue, was highly correlated with survival in a training set of tissue samples from 82 Japanese patients; the signature was validated in tissues from an independent group of 225 patients from the United States and Europe. Importantly, it was also observed in this study that late recurrence was predicted from gene profiling of tissue obtained from non-tumoral surrounding tissue and not from tissue obtained from the resected primary tumor supporting the concept that late recurrence of HCC represents a new primary tumor in patients at risk. The same authors demonstrated that gene profiling from both tumoral and non-tumoral tissue was complementary in refining the prognosis of subjects undergoing liver resection for HCC[119]. Furthermore, they showed that gene expression signatures were similar when the sample of tissue was obtained from the center or from the periphery of the tumor; this observation is important because it could be a prerequisite for considering preoperative profiling using tumor tissue fine-needle biopsy, especially in small tumors.

Nevertheless, there is a growing list of studies which propose gene profiling models using a wide degree of genes in their models, but only a few studies have been validated externally[118-122]. Moreover, the lack of external validation in the majority of the studies, too often associated with complicated models of gene signature, did not permit wide use of gene profiling in clinical practice. Recently aimed at simplifying the gene profiling models, an easy-to-use 5 gene score has been proposed, based on the combined expression level of HN1, RAN, RAMP3, KRT19 and TAF9, which has been validated in Europe and the US and is capable of predicting early recurrence and overall survival. Its prognostic accuracy is improved if it is associated with the Hoshida gene profiling model for non-tumoral tissue[123].

The next challenge of these genetic tests will be to verify their usefulness in clinical decision making before any treatment. The integration of genetic profiling into clinical staging (BCLC) could modify our current therapeutic decision making; in fact, indications for liver transplantation or for liver resection could be modified. The Milan criteria could be extended to tumors larger than 5 cm but with benign genetic profiling; in contrast, HCCs with a bad prognostic molecular model, even within the Milan criteria, could be excluded from OLT or subjected to more aggressive neo-adjuvant treatment.

Furthermore, it is important to remember that the totality of the studies carried out to predict the recurrence of HCC using genetic tests were carried out on surgical specimens; thus, the major limitation for the clinical use of a molecular diagnosis could be related to the need for preoperative samples. However, two distinct studies may shed hope for the future; the first showed that tissue obtained from the center or periphery of the tumor had the same genetic profiling[119] and the second, a recent study, showed that genetic profiling can also be carried out on tissue obtained by needle biopsy performed to predict HCC occurrence in cirrhotic patients[124].

Specific studies are obviously necessary to verify mainly the possibility of performing needle biopsy in a real life clinical setting (patients with ascites, impaired coagulation, difficult position, *etc*.).

NON-INVASIVE METHODS FOR HCC RECURRENCE PREDICTION

Ultrasonography

Some ultrasonographic features of tumors could help in

Table 3 Morphological characteristics predicting hepatocellular carcinoma recurrence by means of imaging techniques

Imaging technique	Predictors of HCC recurrence	Ref.
US	Poorly defined margins	[33]
	Infiltrative pattern	[20,33]
	Portal infiltration	[20,33]
	Peripheral hypoechoic band	[20,33]
	Heterogeneous echo pattern	[20]
	Contrast enhancement pattern	[32,125]
CT scan	Heterogeneous enhancement pattern	[126,128]
MRI	Contrast washout pattern at dynamic MRI	[63]
	Signal pattern on hepatobiliary phase	[132]
^{18}F-FDG PET	Maximum SUV by tumor	[129]
	Tumor SUV/non-tumoral tissue SUV ratio	[130]

HCC: Hepatocellular carcinoma; US: Ultrasounds; CT: Computed tomography; MRI: Magnetic resonance imaging; PET: Positron emission tomography; SUV: Standardized uptake value.

predicting tumor behavior after ablative procedures, such as RFA. In fact, the presence of poorly defined margins, infiltrative patterns, hyperechoic echo-texture and portal infiltration at ultrasound examination are correlated with both early and late intrahepatic recurrence after RFA[33]. Moreover, the presence of a peripheral hypoechoic band around the tumor and an intratumoral heterogeneous echo pattern are predictors of local recurrence after PEI[20].

Contrast-enhanced ultrasound provides additional prognostic information. For example, a gradual contrast enhancement in the early arterial phase accurately predicts distant recurrence risk after RFA because it may reflect the complex hemodynamic changes during HCC progression; the gradual increase of intratumoral signal intensity could be related to the rapid drainage of the arterial contrast agent through the portal vein branches or hepatic sinusoids, thus reflecting the high risk of tumor invasion of the portal tracts and the diffusion of metastatic cells through the portal circulation[32].

Intraoperative contrast-enhanced ultrasonography (CEIOUS) accurately predicts the presence of microvascular portal vein invasion during hepatic surgery[125]. A thunderbolt vasculature pattern at CEIOUS examination is significantly correlated with tumor stage, histological differentiation, portal vein invasion and, therefore, with recurrence-free survival ($P = 0.0193$).

CT scan

During contrast-enhanced ultrasound examination, a gradual contrast enhancement in the early arterial phase accurately predicts distant recurrence risk after RFA because it may reflect the complex hemodynamic changes during HCC progression; the gradual increase of intra-tumoral signal intensity could be related to the rapid drainage of the arterial contrast agent through the portal vein branches or hepatic sinusoids, thus reflecting the high risk of tumor invasion of the portal tracts and the diffusion of metastatic cells through the portal circulation[126]. A recent study shows that an increase in lesion density on CT carried out immediately after and 1 wk after TACE (median lesion density was 625 HU immediately after and 431 HU 1 wk after) is a predictor of a low rate of local recurrence[127].

Moreover, during the arterial phase of dynamic CT, a heterogeneous enhancement pattern with irregular ring-like structures accurately predicts cumulative recurrence after RFA due to its good correlation to poorly differentiated histological grade[128].

^{18}F-FDG positron emission tomography

A preoperative (^{18}F)-fluorodeoxyglucose (^{18}F-FDG) positron emission tomography (PET) scan is a useful tool not only for detecting tumors but also for studying tumor behavior and aggressiveness. In fact, it may accurately predict microvascular invasion[129] as well as the histological differentiation of tumors and early recurrence (< 1 year) after surgery[130]. The maximum standardized uptake value (SUV) of ^{18}F-FDG by the tumor and the ratio tumor SUV/non-tumoral tissue SUV (TNR) are strongly correlated with tumor differentiation ($P < 0.001$). Moreover, a SUV tumor $\geqslant 4$, and a TNR value $\geqslant 2$ represent predictors of early recurrence[130].

^{18}F-FDG uptake on PET is also a reliable preoperative predictor of tumor recurrence after OLT in patients with HCC, triggered by its elevated association with tumor differentiation and microvascular invasion[131].

MRI

Poor differentiation grade and microvascular invasion seem to be significantly associated with the presence of contrast washout demonstrated on dynamic contrast-enhanced magnetic resonance imaging[63]; on the other hand, gadoxetic acid-enhanced MR images could accurately predict histological differentiation grade while the iso- to hyperintensity signal in the hepatobiliary phase may represent a useful imaging biomarker to indicate a longer time to recurrence after surgery[132].

The characteristics for predicting HCC recurrence by means of imaging techniques are summarized in Table 3.

Liver stiffness measurement

As previously stated, late recurrence after curative liver resection for HCC depends mainly on the severity of the underlying liver disease[6]. It could thus be important to have non-invasive predictors of the severity of liver disease.

Liver stiffness measurement, a new method used for assessing the stage of liver disease, has been considered to be not only an accurate non-invasive method for evaluating the presence of liver cirrhosis[133], but also for predicting its natural history. In fact, some longitudinal studies have shown that liver stiffness can predict overall survival and HCC development in patients with both HCV and HBV chronic liver disease[134-136]. It has moreover been demonstrated that the risk of developing HCC increases with increased liver stiffness[135,136]. In fact,

for baseline liver stiffness measurement (LSM) values > 25 kPa in HCV patients, the risk of HCC development increased 46 fold as compared to those with an LSM value less than 10 kPa[135] while, in HBV patients, when the baseline LSM value was > 23 kPa, the risk of HCC development increased nearly 6.6 fold as compared to patients with a baseline LSM value less than 8 kPa[136]. Furthermore, LSM was useful in predicting postoperative outcome in patients with HCC who had undergone liver resection[137,138].

According to these experiences, Jung *et al*[139] have recently demonstrated that the preoperative values of liver stiffness can predict HCC recurrence after curative HCC resection. In fact, the Authors found that a preoperative LSM > 13.4 kPa had a nearly 2 fold increase in the risk of HCC recurrence as compared to those with an LSM < 13.4 kPa. Together with satellite nodules, LSM was the only variable related to late recurrence (more than 2 years) at multivariate analysis, confirming the pathogenetic role of the "field effect" for late recurrence and the usefulness of LSM in diagnosing the severity of underlying liver disease.

In conclusion, the recurrence of HCC represents an important clinical challenge for both hepatologists and surgeons, due to its negative impact on the overall survival of the patient. The criteria selected, based mainly on HCC radiological features (*i.e.*, number and size of the HCC nodules) adopted in the last twenty years, have drastically reduced the HCC recurrence rate and hence patient survival; however, other more efficacious predictors are needed to further reduce the HCC recurrence rate. The possibility of defining the characteristics of the tumor utilizing biological features and genetic profile analysis could open new horizons for better staging the tumor itself and for predicting its recurrence. This opportunity will allow better selection of patients in order to have a treatment strategy tailored to the individual patient and the possibility of choosing the most effective clinical and therapeutic follow-up.

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