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Review

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Predictive factors for hepatocellular carcinoma recurrence after curative treatments

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Abstract

Hepatocellular carcinoma (HCC) is the fifth most common neoplasm worldwide. Recurrence of HCC after resection or loco-regional therapies represents an important clinical issue as it affects up to 70% of patients. This can be divided into early or late, if it occurs within or after 24 months after treatment, respectively. While the predictive factors for early recurrence are mainly related to tumour biology (local invasion and intrahepatic metastases), late recurrences are mainly related to de novo tumour formation. Thus, it is important to recognize these factors prior to any treatment in each patient, in order to optimize the treatment strategy and follow-up after treatment. The aim of this review is to summarize the current evidence available regarding predictive factors for the recurrence of HCC, according to the different therapeutic strategies available. In particular, we will discuss the role of new ultrasound-based techniques and biological features, such as tumor-related and circulating biomarkers, in predicting HCC recurrence. Recent advances in imaging-related parameters in computed-tomography scans and magnetic resonance imaging will also be discussed.

Keywords: Liver resection, trans-arterial chemoembolization, radiofrequency ablation, liver stiffness measurement, indocyanine green retention test

INTRODUCTION

Hepatocellular carcinoma (HCC) is the fifth most common tumor and one of the leading causes of cancer mortality worldwide[1,2]. To date, the numbers of HCC has not dropped, despite the introduction of new direct antiviral agents for hepatitis virus C (HCV) eradication[3] to lower the risk of developing HCC in these

patients[3]. HCC remains a widespread tumor due to the persistence of a high prevalence of hepatitis B virus (HBV) infection in African and Asian countries, and from the increasing incidence of non-alcoholic fatty liver disease, alcoholic and non-alcoholic steatohepatitis (ASH/NASH) patients in Western countries.

There are different therapeutic strategies to manage HCC according to both the underlying extent of liver disease and tumor-related factors, as stated by the different guidelines available[2,4-6]. The recommended treatment of choice in these guidelines is mainly an adaptation from the BCLC classification[2,7]. Patients with HCC are classified into five stages by tumor related factors (size, number, vascular invasion, N1, M1), liver function (bilirubin, portal hypertension, liver function preservation) and health status (ECOG)[2]. These guidelines were developed to provide the best treatment to maximize overall survival (OS) according to tumor characteristics listed above. Liver resection (LR) is recommended mainly for single HCCs of any size and in particular, for size > 2 cm, with preserved hepatic function and sufficient residual liver volume. In patients with BCLC 0 and A, or in single tumors 2 to 3 cm in size not suitable for surgery, the treatment of choice is thermal ablation with radiofrequency (RFA) as an alternative to surgical resection. In patients with BCLC B, trans-arterial chemoembolization (TACE) is recommended[2]. Even though treatment choice is tailored for individual patients, HCC recurrence remains the most important concern and can occur irregardless of treatment[8].

In fact, in curative treatments such as liver resection, HCC recurrence developes in up to 70% of patients at 5 years after hepatic resection, both within (early recurrence) or after 24 months (late recurrence)[1,2,9]. Several authors[10-13] have explored the differences between early and late recurrence and investigated the risk factors for each. Predictive factors for early recurrence are well-known[14]. On the other hand, the prediction of late recurrences is limited by poor data; it can also be considered a 'de novo' tumour and thus, has been associated mainly with the degree of fibrosis and extent of portal hypertension (PH)[15-17].

The aim of this review is to summarize the most recent advances in the role of predictive factors for HCC recurrence in patients undergoing curative HCC treatment beyond liver transplantation such as LR, RFA and TACE. Furthermore, when possible, biomarkers and imaging predictors are also differentiated.

LIVER RESECTION

LR is the standard of care of patients with solitary tumors and preserved liver function[4,5]. The major complication after LR is HCC recurrence which reaches an incidence of more than 70% at 5 years[14]. As stated, HCC recurrence can be classified as early or late[11,18]. Early recurrences have well-established predictive factors which are mainly related to tumor biology (i.e., tumor size, tumor number, presence of microsatellites and vascular invasion) and the treatment modality used[14]. In particular, vascular invasion (both macroscopic and microscopic) is one of the most reliable predictors of recurrence and survival and strictly associated with histological differentiation and tumor size[14]. On the other hand, the development of late recurrences is widely considered a de novo HCC affected by the underlying liver status[19,20]. Thus, the presence and degree of PH could play an important role in predicting late recurrences. Indeed, the extent of PH is directly correlated with the risk of developing complications[21-24], including HCC[25]. Recently, several studies have highlighted the role of non-invasive tests such as liver (LSM) and spleen stiffness measurements (SSM) as predictors of late recurrence of HCC[16,17,26]. The predictive factors for early and late HCC recurrence after LR are summarized in Table 1.

Early HCC recurrence

Tumor-related factors

A clear correlation has already been highlighted between tumor size, number and HCC recurrence[27]. These factors remain the best pre-operative prognostic factors such that both the American and European Association for the Study of the Liver endorsed these criteria in their staging systems[2,4]. Indeed, HCC

Table 1. Predictive factors for early and late HCC recurrence after liver resection

	Early recurrence	Late recurrence
Tumor related factors		
Tumor size	[27-29]	[27-29]
Tumor grade	[29-32]	[29]
Macrovascular invasion	[19,33-35]	[19]
Microvascular invasion	[19,36-39]	[19,37]
Satellite nodules	[40]	-
Tumor-free margins	[41-43]	[41,43]
Biomarkers		
AFP	[32,35,44-46]	[27,28]
Immunomarkers	[47-54]	-
ERASL-pre score	[55]	-
REACH score	[56]	-
SVR	[57]	[58-60]
HBV replication	[61]	[15,61]
Alcohol intake		[62,63]
Others		
MicroRNAs	[64,65]	-
Imaging factors	[66-75]	
IGC15	-	[16]
Sarcopenia	[76]	-
NITs		
LSM	-	[16,26,77]
SSM	-	[17]
FIB-4	-	[78]
ALBI > 2	[55,79-82]	[78,83,84]
Platelet/spleen length ratio	-	[17]

HCC: hepatocellular carcinoma; AFP: alpha-fetoprotein; ERASL: early recurrence after surgery for liver tumor; REACH-B: estimates risk of HCC in patients with chronic hepatitis B; SVR: sustained virological response; HBV: hepatitis B virus; IGC15: indocyanine green retention rate at 15 min; NITs: non-invasive tests; LSM: liver stiffness measurement; SSM: spleen stiffness measurement; FIB4: fibrosis-4 index; ALBI: albumin-bilirubin grade

nodules ≥ 5 cm are associated with an increased recurrence rate due to the higher risk of portal vein[28] and micro-vascular invasion (MVI)[36]. Besides, vascular invasion represents another good predictor of tumor recurrence[19,27]. It could be defined as macroscopic, when it is visible on imaging or even on gross examination, and microscopic, when seen only on histological examination. The presence of macrovascular invasion is able to reduce the time to recurrence by 4-fold[19]. Moreover, extension of portal vein thrombosis is directly related to poor prognosis[33,34].

With regard to MVI, it is usually defined as the presence of tumour emboli within the central hepatic vein, the portal vein, or the large capsular vessels[12]. Unfortunately, this evaluation is subject to great variability which affects the true incidence of this condition[37]. The presence of MVI is related to an increased risk of HCC recurrence[19,38,39]. The main limitation of MVI assessment depends on its timing since it is often obtained on resected specimens. MVI can be accurately assessed only on resected specimens, which constitutes a strong limitation to such assessment[29,30,35]. Tumor grade (grade 3/3) and tumor size have also been associated with early HCC recurrence and are strictly related to MVI[29-32].

Several authors have tried to evaluate the usefulness of other pre-operative parameters beyond tumor grade in predicting MVI, such as increased alpha-fetoprotein (AFP), L3-AFP and prothrombin induced by vit K absence-II (PIVKA-II)[30,31,35]. Recently, a low concentration of the autophagy-related marker LC3[85] on HCC and adjacent non-tumor tissues has also been found to be a significant predictor of both early and late HCC recurrence. A further recent study[47] evaluated the role of immunohistochemical markers in a large cohort of resected HCC, concluding that 14 factors showed a prognostic role for predicting recurrence, including

6 clinico-pathological characteristics (clinical stage, differentiation level, capsular invasion, tumor number, tumor diameter, and AFP level) and 8 immunomarkers (CD34, CDKN1A, E-cadherin, HRas, PCNA, p53, TGF-β and VEGF). Other authors[86] evaluated the Epstein-Barr virus-induced gene 3 (*EBI3*) which encodes a secretory glycoprotein which was previously found to be upregulated in different tumors; they found that *EBI3* was a predictor for tumor recurrence. Among the myriad of other tumoral-tissue related markers, a prognostic role was also reported for the Peroxiredoxin 1 (PRDX1)[87]; the divalent metal-ion transporter-1 (DMT1)[88]; the cell cycle factor NIMA-related kinase 2 (NEK2)[89]; among the non-coding tumoral RNAs, the miR-210 and miR-550a-1 were associated with a high risk of recurrence[64], similar to miR-483-3p[65]; low c-Myc protein expression[90]; low MHC class I chain-related gene A (*MICA*)[91]; the long noncoding RNA (lncRNA) expression signature[92]; and the NUF2[93]. However, all these tumoral-tissue related markers have not found clinical application yet.

Circulating biomarkers

Several circulating markers have been identified to be able to predict early HCC recurrence. Certainly, AFP is used not only for diagnosing HCC but also plays a key role in predicting recurrence[44-46] with a cut-off that has recently been lowered from 200 ng/mL to 100 ng/mL[46]. Since the liver is the organ that synthesizes lipoprotein (a) [Lp (a)], reduced levels of this lipoprotein could be a sign of liver dysfunction. Thus, as Lp (a) mirrors hepatic function and the degree of underlying disease, it has recently been found[94] in a cohort of HCC patients that low Lp (a) levels (≤ 20 mg/dL) significantly correlated with low time to recurrence (P = 0.009) and low OS (P = 0.007). Among other circulating markers or composite scores, the albumin-bilirubin (ALBI) score has been validated as a predictor of survival in HCC[79]. Recently, an Asiatic study[80] evaluated the role of ALBI in predicting early recurrence. It was found that an ALBI grade ≥ 2 (P = 0.003) in addition to HBV surface antigen (HBsAg)-positive status (P < 0.001), tumor size ≥ 3.5 cm (P ≤ 0.001), lympho-vascular invasion (P = 0.001), and the presence of satellite lesions (P = 0.009) were the only predictors of early HCC recurrence on multivariate analysis. The same results on ALBI were recently reported by other authors[55,81,82], among whom Chan *et al.*[55] developed the ERASL-pre score, which included male gender, large tumor size, multinodular tumors, high ALBI grade and high serum AFP. More recently, an elevated fibrinogen/albumin ratio was found[95] to be significantly correlated with shorter survival and an increase risk of HCC recurrence. On the same line, the ratio between high-sensitivity C-reactive protein (hsCRP) and albumin was associated with a 1.19-fold increase in the risk of HCC recurrence[96]. In an additional study on hsCRP, it was found to be associated with lymphocyte ratio (HCLR) and positively correlated with large tumor size, TNM stage, MVI, and HCC recurrence[48]. A further composite score is represented by REACH[56] which includes NxS factor, MVI, differentiation, serum albumin, platelet count and indocyanine green retention rate at 15 min and was able to predict the risk of HCC recurrence.

Other simple factors that are able to predict early recurrence of HCC that should be taken into account are the lymphocyte and neutrophil levels computed into the NLR[49], which mirrors a pro-tumor inflammatory environment and the activity of host immunity. In fact, these authors found that patients with pre-operative NLR < 2.5 were at lower risk of recurrence. Thus, others have tried to refine the predictive value of these scores by building a composite score with ALBI and platelet to-lymphocyte ratio[97], which was able to predict the outcome after liver resection, including HCC recurrence. Platelet to-lymphocyte ratio was further associated with NLR with good results[50]. Finally, other immune-biomarkers that have promising results are the lymphocyte-to-monocyte ratio[51], gamma-glutamyl transpeptidase to lymphocyte count ratio[52] and systemic inflammation score[53]. A Chinese group[54] recently demonstrated that IgG4/IgG ratio is an independent indicator of tumor recurrence and a high ratio is associated with a shorter time to recurrence.

Circulating microparticles are novel biomarkers with a potential prognostic role in patients with cancer. Their role in HCC has been investigated by Abbate *et al.*[98] and it was found that the number of circulating HepPar1+ microparticles before resection was higher in patients with early recurrence compared to those

without (P = 0.02). With regard to other cancer biomarkers, platelet derived growth factor-BB has been claimed to be one of the key cytokines in malignant transformation of different cells and recently[99], diminished perioperative platelet derived growth factor-BB has been linked to HCC recurrence. Another potential biomarker concerns serum proteome alterations[100]: PGK1, which is directly involved with carcinogenesis and the intracellular inflammation cascade, was found to be increased in patients with early tumor recurrence. Recently, a glycan-based immunoassay targeting Wisteria floribunda agglutinin-positive human Mac-2 binding protein (WFA^+-M2BP) was evaluated as a noninvasive biomarker of liver fibrosis and predictor of HCC and HCC recurrence, as it was associated with pro-carcinogenic activity in patients with chronic liver disease[101]. In a further study, it was associated with both early (HR = 1.667) and late recurrence (HR = 1.416) with multivariate analysis[102].

In conclusion, some circulating biomarkers have gradually been endorsed in clinical practice in several centers for their simplicity and real-time application based on standard liver tests, and are able to give reliable prognostic information on these patients.

Imaging predictive factors

Pre-operative imaging signatures have been proposed in the last decade for predicting HCC recurrence before resection. With regard to computed-tomography (CT) scan prediction, beyond the classic HCC features associated with HCC recurrence, a HCC texture based study found good correlation with histological grade and thus, the risk of disease recurrence[66].

As for magnetic resonance imaging (MRI), correlation between the preoperative diffusion-weighted imaging and early recurrence has been found[67,68], specifically[67] with minimal apparent diffusion coefficient values. Several studies reported that imaging findings based on peri-tumoral tissue enhancement and hypointensity in the hepatobiliary phase were useful for predicting MVI and early recurrence in HCC[68-70].

A Korean study carried out in 2017[70], which is one of the largest among those stated above, included 197 patients and using gadoxetic acid-enhanced MRI for predicting MVI, highlighted that the combination of at least two of the following - arterial peri-tumoral enhancement, non-smooth tumor margin, and peri-tumoral hypointensity on hepatobiliary phase - was able to predict MVI with > 90% specificity and associated with early recurrence after a single HCC nodule resection. These results have been further confirmed by other groups worldwide[68,69]. To enhance the predictive accuracy of these findings, a recent study[71] used Radiomics on CT-scans for this purpose. Radiomics is a new method for medical image analysis[72], defined as the high-throughput extraction of quantitative metric features that result in the conversion of images into mineable data. These authors[71] found that peri-tumoral radiomics was better in predicting HCC early recurrence than tumoral radiomics[73]. Other authors using radiomics on pre-operative CT-scans found a good correlation with MVI (AUC 0.80)[74]. Beyond texture, using 3D MRI was also possible to evaluate tissue stiffness; a multicenter study[75] recently found that HCCs with subsequent recurrence had higher tumor stiffness.

Finally, an additional prognostic role has also been investigated for fluoro-deoxyglucose (FDG)-positron emission tomoscintigraphy (PET). Indeed, a recent study[103] with FDG-PET before surgery concluded that a larger tumor size and serum AFP were correlated with higher SUV max (≥ 4.9), which was able to distinguish between patients with or without HCC recurrence after resection.

Beyond the standard evaluation of HCC (tumor number, size, location, vascular invasion) however, the above evaluation methods remain as research and are only applied in highly specialized centers.

Resection-related factors

Strong evidence is available on the role of tumor-free margins in HCC[104]. Most previous studies have stated that tumor margins should be at least 1 cm[42,43]. A randomized controlled trial showed however, that in order to improve survival margins should be at least 2 cm[104].

On the other hand, the extent of resection is another key factor to take into account when predicting tumor recurrence. If anatomical resection (whole hepatic segment) allows reduction of risk for intrahepatic metastasis due to microsatellite nodules and segmental neoplastic thrombi, most surgeons would prefer non-anatomical resections instead in order to reduce the risk of post-hepatectomy liver failure[40]. Most studies on this topic are affected by much heterogeneity amongst the patients enrolled, since non-anatomical resections are performed mainly in patients with small HCC nodules and with a higher degree of liver dysfunction. A large series has demonstrated that non-anatomical resection is equally safe in terms of recurrence for HCC nodules less than 2 cm[105]. On the other hand, for larger tumors, anatomical resection is equally able to guarantee a lower rate of early HCC recurrence[8].

Late HCC recurrence

Late HCC recurrence is currently not considered a true recurrence of the primary HCC since it seems to be a "*de novo*" tumor and thus, dependent on the degree of underlying liver cirrhosis[106]. Most studies on this topic highlight predictive factors for late recurrence including the severity of liver cirrhosis, presence of active hepatitis and the degree of PH[11,16,17,26,57,61,77,107]. Indeed, the sole presence of liver cirrhosis itself leads to a doubling of risk for late recurrences[11]. In the specific setting of HBV, Ishak activity > 6, an indocyanine green clearance (ICG-15) > 10% and HBsAg > 250 IU/mL were found to be predictors of late HCC recurrence[15,61]. With regard to HCV etiology, a recent study[58] demonstrated that HCV-eradication was able to reduce the recurrence of HCC, independent of HCC treatment and the HCV-treatment regimen administered. Further confirmation of the importance of viral eradication came from a recent North American study[59] on new direct antiviral agents and regimens, which demonstrated that the risk of HCC recurrence was not increased by this treatment, as previously postulated[60]. Even continuous alcohol intake in patients with Alcohol-related Liver Disease seems to be a HCC risk factor for both the occurrence of primary HCC and late recurrences, since the development of HCC depends both on direct (genotoxic) and indirect factors (cirrhosis development)[62,108]. Indeed, a recent study by Kudo *et al.*[63] found that preoperative excessive alcohol intake was related to decreased disease-free survival rate of HCC recurrence after surgery. Similarly, the presence of obesity at the time of LR has been reported as a risk factor for HCC recurrence[109].

Going back to liver cirrhosis, also in this setting there is an increasing need for non-invasive tests to stratify late HCC recurrences. One of the most frequently used and non-invasive test is the ALBI grade[83], which is an objective and discriminatory method for assessing liver function in HCC, and is gradually replacing the Child-Pugh score. The ALBI has also been found to be a predictor of late HCC recurrence after resection ALBI grades 2 and 3 ($P < 0.001$)[84]. Recently, a composite score[110] for predicting both early and late HCC recurrences in HBV has been developed and validated; this DFT score includes liver function through the use of FIB-4, which is a surrogate marker of liver fibrosis, tumor burden and grade of differentiation. A combination of ALBI and FIB-4 has also been proposed with good accuracy in predicting HCC recurrence[78].

In line with these efforts, Jung *et al.*[26] found that patients with LSM values > 13.4 kilopascal (kPa) were at increased risk for late HCC recurrence with a HR of 1.9. Another research group followed up patients with HCC after treatment and found that a decrease in LSM < 8 kPa suggested a reduced risk of late recurrence[77]. In a subsequent study by Jung *et al.*[16], the LSM value, together with activity grade II-III, the presence of multiple tumours, and ICG R15 achieved good accuracy in predicting late HCC recurrence. Another non-invasive test capable of mirroring the degree of PH is the evaluation of SSM[23,24,111,112], which has been demonstrated to be associated with post-hepatectomy liver failure too[113]. We recently demonstrated[17] in a cohort of compensated advanced chronic liver disease patients undergoing LR for primary HCC, that univariate analyses of late HCC recurrences were associated with esophageal varices, spleen length, platelet/spleen length ratio, LSM and SSM. Multivariate analyses however, showed that SSM was the only predictor of late recurrence (HR = 1.046). Thus, it is possible to conclude that NITs focused on the evaluation of the

Table 2. Predictive factors for HCC recurrence stratified by ethanol percutaneous injection, radiofrequency ablation and trans-arterial chemoembolization

	Ethanol percutaneous injection	Radiofrequency ablation	Trans-arterial chemoembolization
Tumor related factors			
Tumor size	[114,116,118]	[130,131]	[132]
Tumor grade	[121]	[130]	[133]
Macrovascular invasion			[132]
Satellite nodules	[120]		
Intra-tumoral septa	[121,122]		
Tumor-free margins		[131,134]	
Angiogenic factor			[135-138]
Biomarkers		[139]	
AFP	[116,121]	[130]	[140-142]
Immunomarkers			[143,144]
ALBI			[145,146]
HBV replication		[147,148]	
Genetic factors			
MicroRNAs			[149-152]
Imaging factors			[153-163]
Sarcopenia			[76,164]

AFP: alpha-fetoprotein; ALBI: albumin-bilirubin grade; HBV: hepatitis B virus; HCC: hepatocellular carcinoma

degree of liver fibrosis and function and thus, also of PH, are capable of predicting the future development of HCC nodules in patients who have undergone LR for primary HCC.

ETHANOL PERCUTANEOUS INJECTION

Patients with early stage HCC, who are not suitable for resection or transplantation, are ideal candidates for percutaneous ablation. Guidelines for locoregional therapy include patients with a single HCC nodule ≤ 5 cm or up to 3 nodules ≤ 3 cm, even if minor discrepancies exist between different investigators and studies[114]. Percutaneous ethanol injection (PEI) is a percutaneous, ultrasound-guided ablative procedure involving the injection of 95% absolute alcohol which induces coagulative necrosis of the lesion due to protein denaturation, cellular dehydration and chemical occlusion of small tumor vessels[1]. PEI was first described in the early 1980s[115] and had long been the standard in ablation. Indeed, this technique is the most studied type of percutaneous ablation[116]. PEI is also an inexpensive and well-tolerated procedure with few adverse effects, and has been considered the standard against which any new ablation therapy should be compared to[117]. Predictors of HCC recurrence after PEI are summarized in Table 2.

The most important predictor of treatment efficacy and HCC recurrence in this setting is tumor size. Indeed, tumors less than 2 cm in diameter have more than 90% tumor necrosis rate. As the tumor size increases however, the necrosis rate decreases and for tumors 3 to 5 cm in size, this rate is only 50%[114]. Notably, the major limitation of PEI is the high local recurrence rate, particularly for lesions larger than 3 cm[118]. Other potential factors affecting tumor recurrence are the total number of treated lesions, satellite nodules, the presence of a halo and an intra-tumoral heterogeneous echo pattern or intra-tumoral septa and AFP levels > 20 mg/dL[119-121]. When the size of the nodule increases, intra-tumoral septation increases, which is mainly composed of collagen and lipid matrix[122]. A possible explanation is that ethanol diffusion is blocked either by intra-tumoral fibrotic septa and/or the tumor capsule, limiting its curative effect in lesions larger than 2 cm[122,123]. In addition, the OS is modified by the size of the tumor. Patients with Child-Pugh class A function and a solitary HCC smaller than 2 cm have 3- and 5-year OS rates of 70% to 80% and ≥ 50%, respectively. For HCCs 2 to 3 cm in diameter, the 3-year OS rate ranges from 47% to 64%[124,125]. To overcome the limits of conventional PEI in patients with tumors larger than 2 cm that cannot be treated with other procedures, a retractable multipronged injection needle was developed[126]. Chemical ablation with 15%

acetic acid with the use of a multiple-tine infusion device resulted in larger diameters of contiguous tumor coagulation and enabled greater volumes of infusion than the standard technique[126]. However, as this is associated with higher recurrence rates and inferior OS compared to hyper-thermic ablation[127,128], it only plays a secondary role in HCC treatment today, having widely been replaced by more modern techniques such as RFA[129], mainly because it has to be performed repetitively compared to RFA. Furthermore, it is difficult to obtain complete necrosis for tumors larger than 3 cm[114].

RADIOFREQUENCY ABLATION

RFA is a non-surgical, curative treatment for HCC[165] which is designed to destroy the tumor by heating[166]. The heat (above 60 °C) generated by alternating current passing down from the tip of an electrode into the surrounding tissues induces changes in ionic agitation and drives extracellular and intracellular water out of tissues, resulting in their destruction by coagulative necrosis[166,167]. Heat is administered by probes that are inserted through the skin (percutaneously), laparoscopically or with open surgery[168]. In cirrhotic patients treated with RFA for HCC, the 5-year OS reached 74%[169]. Thus, RFA is considered a viable and curative alternative treatment to LR in these patients[170]. Based on current guidelines, RFA is performed on single lesions < 5 cm in diameter or ≤ 3 lesions < 3 cm in largest diameter, Child-Pugh class A or B, and ECOG 0[2]. The high rates of post-procedural recurrence, which might be up to 70% at 5 years, remain a major challenge for long-term survival[130]. Recurrence after RFA for HCC occurs as a result of local tumor progression (LTP) or intrahepatic distant recurrence. LTP occurs along the peripheral margin of the ablative zone when the primary tumor had not been controlled completely after RFA[131]. Several risk factors have been associated with local recurrence including tumor size more than 2 cm, poorly differentiated carcinoma, advanced tumor stage, high AFP levels, and an insufficient safety margin[13]. An ablative margin of at least 5 mm is required to avoid the risk of LTP because microsatellite lesions are frequently present and surround the HCC nodule[134]. The risk of local recurrence is also closely related to the location of the tumor: HCCs next to the portal vein or major hepatic veins were associated with a higher risk for local recurrence (HR = 1.70-2.81) because the patient's blood flow reduces elevation of the tumor's temperature during RFA[171]. Several studies have reported the ability of AFP levels to predict response to ablation: serum AFP increase have been shown to predict a higher risk of HCC recurrence after ablation treatment[130]. The heterogeneity of the studies precludes the formulation of a definite magnitude level, but it is suggested that AFP cut off levels of > 200 and/or > 400 ng/mL are associated with poor outcomes[2]. In contrast to local recurrence, distant intrahepatic recurrence is observed far from the ablation zone and corresponds usually to de novo hepatocarcinogenesis on cirrhosis or metastatic dissemination[172]. Similar to LR, HCC recurrence following RFA occurring early - within 2 years of follow-up - is considered the result of an intrahepatic metastatic process from the primary tumor (related to tumor biology), whereas late recurrence after 2 years would result only from *de novo* carcinogenesis in cirrhosis[170]. The Child-Pugh score is associated with distant HCC recurrence; this would suggest that the severity of liver disease is a risk factor not only for HCC occurrence but also for distant HCC recurrence[173]. The link between HBV replication (high pre-procedural serum viral load ≥ 2000 UI/mL) and the recurrence of HCC after RFA suggests that secondary chemoprevention with nucleos(t)ide analogues could improve the prognosis following percutaneous ablation[147,148,174]. Similarly, several studies found that patients with HCV related cirrhosis who have achieved sustained response to antiviral therapy have a substantially lower rate of HCC recurrence after percutaneous ablation in cirrhotic patients with HCC[175]. The development of non-invasive methods to assess the degree of liver fibrosis including blood marker tests and transient elastography has revolutionized the assessment of liver fibrosis over the last decade[176]. Recent data reported the role of transient elastography in predicting intrahepatic distant recurrence of HCC following RFA[177]. In conclusion, RFA is a potential curative modality for cirrhotic patients with early HCC. Predictors of HCC recurrence after RFA are summarized in Table 2. Additional studies are needed to identify patients with a higher risk of early and late recurrence to improve disease control.

TRANS-ARTERIAL CHEMOEMBOLIZATION

TACE, a direct therapy with a minimally invasive catheter, is the most commonly used interventional radiology technique for the first-line treatment of intermediate stage (BCLC-B) and unresectable HCC[178,179]. The TACE procedure works on the pathophysiological principle that malignant hepatic lesions receive blood supply from the hepatic artery. Thus, the intra-arterial infusion of a cytotoxic agent followed by embolisation of the blood vessels that feed the tumor leads to a direct cytotoxic and ischemic effect on the tumor mass. HCC, indeed, tends to be fed entirely through the arterial supply, unlike the surrounding parenchyma which receives most of its inflow through the portal system. During TACE procedures, a catheter super-selectively places an emulsion of the water-soluble antitumor agent mixed usually with ethiodized oil[180]. The effectiveness of TACE is through providing highly concentrated doses of chemotherapy to the tumor bed, while sparing the surrounding liver parenchyma. Conventional TACE, also known as Lipiodol TACE, consists of catheter delivery of the chemotherapeutic emulsified with Lipiodol, followed by vascular stagnation obtained with embolisation of the particles[181]. During these procedures, the most commonly used chemotherapy drugs are epirubicin, doxorubicin, miriplatin or cisplatin[181]. Besides conventional TACE, other image-guided transcatheter techniques have been developed recently (chemo-lipiodolisation, bland transcatheter embolisation and intra-arterial chemotherapy) but not recommended clinically yet[179]. Recently, drug-eluting beads transcatheter arterial chemoembolization (DEB-TACE) has become a routinely used locoregional treatment for unresectable HCC. DEB-TACE have the same clinical outcomes and reduced procedure-related side effects compared to conventional transcatheter arterial chemoembolization[182,183]. Many potential factors affecting HCC recurrence after TACE treatment have been investigated in the last decades [Table 2].

Tumor-related factors

HCC is a hypervascular tumour such that tumour angiogenesis may be essential to its growth, invasion, or metastasis[184,185]. The changes induced by TACE in the expression of angiogenic and invasiveness factors [basic fibroblast growth factor (b-FGF), vascular endothelial growth factor (VEGF), urokinase-type plasminogen activator (uPA) and mammalian chitinase-like proteins without chitinase activity (YKL-40 -CHI3L1)] have been investigated. These markers work synergically and seem to be overexpressed after TACE as a result of the related ischemic damage, which renders them useful for predicting treatment response to TACE. In fact, when TACE is not adequate, a significant neoangiogenesis reaction happens, as suggested by an increase in VEGF, uPA, b-FGF and YKL-40 following treatment, and affects patient survival[135-138,186]. Moreover, the systemic inflammatory response[187] reflects the state of angiogenesis, DNA damage and tumor invasion[188]. Among these, systemic immune-inflammation index[143], aspartate aminotransferase-lymphocyte ratio index and CRP/Alb ratio[144] are useful non-invasive biological markers with high negative predictive values for HCC OS after TACE. As a matter of fact, tumor size and portal invasion represent the most well-validated HCC prognostic factors after TACE treatment[132]. In 87% of patients, the low-grade tumors (grade 0, 1, or 2) have shown encouraging long-term treatment response (49%; stable disease or local disease progression, 13%; partial response, 38%; complete response) *vs.* 33% of high-grade tumors (grade 3 or 4) (stable disease or disease progression, 67%; partial response, 33%; complete response, 0%) after TACE[133].

Circulating biomarkers and patients' characteristics

Several laboratory markers have been associated with prognostic outcomes in HCC patients undergoing TACE. AFP levels and changes[140-142], low pretreatment platelets[189], low baseline serum 25-hydroxyvitamin (D25-OHD) levels[190], high values of CRP[138], high levels of serum gamma-glutamyl transferase[191] and high levels of bilirubin[132] are all potentially useful biomarkers to predict the poor prognosis in patients with HCC treated with TACE. Moreover, procalcitonin is a precursor of the hormone calcitonin and usually rises in bacterial infections; it was recently proposed as an important prognostic factor for foretelling the prognosis of patients treated with TACE with unresectable HCC[192].

More than a dozen staging systems have been described and some have been put into clinical practice for either HCC prognostication or as treatment guidelines[193]. Amongst them, the Cancer of the Liver Italian Program (CLIP) score (takes into account liver function reserves and tumor characteristics), and the ALBI-CLIP grade (consisting of a formula based on albumin and bilirubin) were good predictors of survival up to 2-years after TACE[145,146]. The CLIP system was superior to the Okuda system for predicting the survival of patients with unresectable HCC treated with TACE[194]. MELD is inferior to the Child-Pugh system in predicting patient survival in those with unresectable HCC after TACE[195]. Instead, the CLIP and MELD systems are superior to the Okuda system in predicting the survival of patients with viral hepatitis and unresectable HCC treated with TACE[196]. A nomogram based on AFP, IGC15, portal vein invasion, tumor capsule, AST and the tumor number has been developed and validated in a precise prognostic model in patients treated with TACE for unresectable HCC[197]. Finally, sarcopenia has also been correlated with disease-free survival and poorer OS in patients with HCC[76]. Recently, the rate of change (< -4.6%) in skeletal muscle mass (ΔL3 SMI) over six months after TACE has been associated with a poor prognosis[164]. Venous ketone bodies, which mirrors muscles status and hepatic reserve function, has been negatively correlated with survival and is thus, a useful predictor of HCC treatment response and prognosis[198].

Molecular and genetics biomarkers

It has been reported that some patients have developed resistance to chemotherapy drugs in which efficacy becomes greatly reduced and toxicity to normal hepatocytes has grown. Therefore, molecular biomarkers capable of predicting treatment response have been studied to improve chemotherapy efficacy.

Many single nucleotide polymorphism (SNP) have been evaluated as an independent prognosis biomarker for HCC after TACE treatment. The main recently studied SNPs were: SNP rs1126497 in the epithelial cell adhesion/activating molecule (*EPCAM*) gene[199], multidrug resistance gene 1 (MDR1) *C1236T* and *C3435T*[200], isocitrate dehydrogenase (*IDH*) gene[201], polypeptide *N*-Acetylgalactosaminyltransferase 14 (GALNT14) "*TT*" genotype[202] and pri-let-7a-1[203]. Moreover, recently a TACE-specific 14-gene signature has been independently related to early disease-free survival and OS in an Asian cohort of HCC patients and further validated in a European cohort[204].

MicroRNAs in circulating blood have also been studied as prognostic markers in HCC[149,150].

Imaging predictive factors

There is a notion that imaging techniques (ultrasound, CT and MRI) might facilitate the visualisation and characterization of HCC nodules clearly and accurately. Additionally, it may also aid in displaying perfusion differences between residual carcinoma and necrotic tissue following TACE ablation. Ultrasound techniques, mainly contrast-enhanced ultrasound, can act as a valuable tool to assess the results of TACE and exhibit mostly optimal effects in the early and very early evaluation of TACE[153,205]. More recently, Xuan *et al.*[138] showed that four contrast-enhanced ultrasound parameters prior to TACE, including time to peak, maximum tumor intensity, washout time, and rise time, were associated with the recurrence and prognosis of HCC after TACE. Time to peak tumor reflected the structure of the blood supply in tumor lesions and was correlated with enhanced tumor metastasis and invasion that can lead to worse survival rates and an unfavourable prognosis[138].

Multi-detector CT is the most commonly used imaging technology for assessing therapeutic response to TACE[154,156]. Patients with hypervascular HCC (defined by an enhancement pattern on the arterial-phase of a CT scan) were more likely to respond to TACE with a reduction in tumor size and increased survival than patients with a less vascular tumor[139]; it is also notable that patients with hypervascular HCCs have a survival benefit from TACE, even if they are classified as non-responders by size criteria[157]. Other criteria such as higher arterial enhancement and grey-level co-occurrence matrix moments (by dynamic CT texture

analysis), lower homogeneity, and smaller tumor size are all significant predictors of complete response after TACE[158].

Recently, in patients with very early and early HCC, the presence of hypovascular hepatic nodules represents a significant risk factor for recurrence and a bad prognosis after treatment; this is a contraindication to the procedure in these patients[159]. Moreover, a CT image analysis method known as the parametric response map approach is more sensitive for finding changes in the response to treatment than the conventional approach based on the recap of statistics assessed on a region of interest. Briefly, parametric response map aligns spatially the longitudinal images before and after treatment and classifies the patient's images into three categories: reduced, unchanged, and increased intensity[160].

MRI has a central role in the identification of focal liver lesions. With technical progress, liver MRI has improved with many imaging modalities now for the diagnosis of HCC[161]. Indeed, gadoxetic acid (Primovist, Bayer Schering Pharma) provides dynamic perfusion imaging and also, evaluation of delayed hepatocyte uptake and biliary excretion which concurs with the precise detection and characterisation of HCC[206]. Gadoxetic acid-enhanced liver MRI is now widely used and plays a crucial role, not just in the initial diagnosis of HCC, but also in the evaluation of therapeutic efficacy and early diagnosis of residual or recurrent tumor after TACE[207]. Indeed, HCCs showing high uptake of gadoxetic acid appear to be susceptible to TACE with increasing HCC free-survival in these patients[162]. Combined diffusion-weighted imaging and choline levels measured at hydrogen-1 magnetic resonance spectroscopy can be used as an early imaging biomarker of treatment response in HCC patients after DEB-TACE[163]. Moreover, in unresectable HCC, baseline early apparent diffusion coefficients $< 0.83 \times 10^{-3}$ mm^2/s is a predictor of treatment response at 1 and 3 months after DEB-TACE and OS with high specificity and sensitivity[155]. Finally, a sophisticated 3D MRI and CT method based on quantitative tumor response (volumetric Response Evaluation Criteria in Solid Tumors and the European Association for Study of the Liver guidelines) were early response markers that can be used to predict survival after initial TACE and allow univocal identification of responders and non-responders in terms of median OS[208].

CONCLUSION

HCC characteristics and the severity of the underlying liver disease are the main considerations in the decision-making process for the best therapeutic strategy for each patient, in order to improve survival and reduce recurrence rates. HCC early recurrence remains related to the aggressiveness of the treated HCC and the technique used. HCC late recurrence, being a "*de novo*" tumor, is mainly predicted by markers of severity of liver fibrosis and the degree of portal hypertension.

Beyond liver disease etiology and the continuous presence of pro-carcinogenetic factors that are etiology-related, the most reliable markers for predicting HCC recurrence after LR are the presence of macro- and micro-vascular invasion, tumor size and the assessment of liver disease severity through the use of LSM. For the same purpose, no definitive data are available in the setting of RFA, even if most studies seem to support a role for LSM. On the other hand, one of the most reliable predictive factors for HCC recurrence after TACE is tumor hypervascularity. The novel circulating, genetic and imaging related markers still need additional validation. Thus, further prospective and well-designed studies are needed to discover new and reliable predictive markers for HCC recurrence after treatments with curative intent.

DECLARATIONS

Authors' contributions

Conceptualized and designed the review: Marasco G, Colecchia A
Wrote, reviewed and edited the manuscript: Marasco G, Ravaioli F, Vestito A, Rossini B, Dajti E, Renzulli M
Provided the tables: Rossini B, Colecchia L, Gjini K

Reviewed and approved the final manuscript as submitted: Marasco G, Colecchia A, Golfieri R, Festi D
All authors read and approved the final manuscript.

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