1 INTRODUCTION

Increasing the rate of HCC patients eligible for curative procedures is key to improving the poor prognosis in these patients. This goal can be achieved by promoting surveillance of at-risk populations with chronic liver disease, in particular those with cirrhosis. Patients with very early-stage (BCLC 0) and early-stage (BCLC A) HCC have preserved liver function and solitary lesions or up to three nodules that are <3 cm in diameter. These patients can benefit from resection, transplantation or percutaneous ablation (PA), with a median survival of between 50% and 70% at five years. However, the term « curative» resection or ablation of HCC in patients with cirrhosis is misleading, since tumour relapse is frequent following these procedures. It is therefore highly important to identify predictors of recurrence and promote continued improvement of procedures and therapeutic strategies to decrease this risk.

Early and late recurrence must be considered independently because they are associated with different risk factors. Early recurrence, arbitrarily defined as occurring within two years following a curative procedure, is related to the development of intrahepatic metastases and is linked to tumour burden including large size, an incomplete tumour capsule and vascular invasion. Late recurrence is more likely to be due to a de novo carcinogenic process with risk factors related to the extent of patient’s liver disease (presence of cirrhosis, persistence of the cause of hepatic insult) and high alpha-foetoprotein (AFP) levels. Except for these easy-to-assess characteristics, information obtained by analysis of both tumour and non-tumour biopsy specimens refines the estimates of the risk of recurrence. Figure 1 summarizes
these different prognostic factors and the potential actions that can be taken to optimize curative HCC management (except transplantation) in routine practice, which are developed in the present review. This includes advances in surgical or ablation procedures, control of the cause of liver disease and neoadjuvant/adjuvant approaches currently tested in clinical trials.

2 REFINEMENT OF PROGNOSIS ACCORDING TO PATHOLOGICAL AND MOLECULAR INFORMATION OBTAINED BY TUMOUR BIOPSY

There are three goals to obtaining a tumour biopsy for the therapeutic strategy of HCC: making a diagnosis, assessing the prognosis and predicting the response to therapy.

As recently described by Calderaro et al., distinct morphological phenotypes of HCC have been found to be associated with the different genetic defects and biological pathways that drive tumour progression. Next generation sequencing (NGS) using whole-exome, whole genome and RNA sequencing have highlighted the key mutations in the driver genes involved in liver carcinogenesis: somatic alterations in the TERT promoter (40%-60%), TP53 (15%-40%), CTNNB1 (20%-30%), AXIN1 (5%-15%), ARID1A (5%-18%), ARID2 (4%-15%), RB1 (3%) and CDKN2A (2%-12%). Moreover, integrative analysis of transcriptomic data together with genetic alterations has helped identify major molecular subgroups of HCC, G1 to G6. G1 to G3 subgroups are the 'proliferative' subclasses associated with chromosomal instability and TP53 mutations, whereas the G4 to G6 subgroups are 'non-proliferative' subclasses associated with chromosomal stability. G1 to G2 subgroups are associated with Hepatitis B Virus (HBV) infection and AXIN1 mutations with the G1 subgroup are enriched in stem cell features with a high serum AFP level. G3 subgroups are enriched in FGF19 amplifications and TSC1/2 mutations together with dysregulation of cell cycle genes at the transcriptomic level. The G4 subgroup is associated with a transcriptomic profile close to that of the mature hepatocyte. Finally, G5 to G6 subgroups are strongly associated with the somatic mutations of CTNNB1, coding for β-catenin.

### Key points
- The goal of optimizing curative hepatocellular carcinoma management is to decrease the recurrence rates.
- Histological analysis of a biopsy specimen can further clarify the prognosis.
- Surgical and ablation procedures provide tumour remission in increasing numbers of patients.
- Controlling the cause of liver disease also plays a key role in these patients.
- Neoadjuvant and/or adjuvant approaches and molecular analyses will provide new therapeutic strategies.

Since NGS is not routinely performed, different morphological phenotypes have been identified linked to the different molecular subclasses at the histological level, and can be classified as follows. A CTNNB1 mutated HCC, observed in 20%-30% of resected HCC, is characterized by the activation of the WNT/β-catenin pathway, with strong glutamine synthase immune-histochemical expression and corresponding to the G5 to G6 subgroup. These HCC are morphologically well-differentiated with microtrabecular and/or pseudoglandular architectural patterns, intratumour cholestasis and a lack of immune infiltration. This subclass has not been found to influence prognosis. However, molecular profiling of tumour biopsies from advanced HCC has suggested an altered response to immune checkpoint inhibitors. This could be important for future adjuvant/neoadjuvant strategies (see below).

The second phenotype is the macrotrabecular-massive (MTM) HCC, which is closely associated with the G3 molecular subgroup. This subclass is defined by an architectural pattern composed of large trabeculae (>6 cell-thick) of tumour cells, whatever their cytological aspect (hepatocytic, clear cells, undifferentiated) surrounded by endothelial cells, with empty spaces between these tumour clusters or macrotrabeculae. It is important to note that the prognostic value of this phenotype has been validated in resected liver or biopsy samples of patients undergoing surgery or

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**FIGURE 1** Risk factors for recurrence following HCC curative management (orange) and potential optimization strategies (blue)
ablation showing a poorer prognosis linked to angiogenesis activation and vascular micro-invasion. Thus, detection of any MTM-HCC subtype component in a biopsy sample (10%-20% of patients) eligible for curative treatment may require more intensive therapeutic strategies.

A third subtype is the steato-hepatitic subtype observed in about 10% of HCC, and belonging to the G4 molecular subclass. It is characterized by steatosis, cell ballooning, pericellular fibrosis and inflammatory infiltrate. These tumours are often well-differentiated and develop more frequently in patients with metabolic syndrome. Although steato-hepatitic HCC is rarely associated with microvascular invasion and satellite nodules, no clear-cut relationship with prognosis has been established so far in biopsy samples.

The progenitor subtype, another HCC subtype, can be defined in biopsy samples by the immune-histochemical expression of markers of a biliary lineage such as CK19 and or EpCAM in more than 5% of cells. This subtype may represent 5% of HCC and is associated with TP53 and RPS6KA3 mutations as well as with G1 molecular subclasses. These HCCs express stemness-related markers and have been regularly linked to more aggressive behaviour with increased recurrence and shorter survival.

The immune microenvironment also influences prognosis independent from HCC histological subclass, since tumour infiltrating T lymphocytes were associated with a favourable outcome and a lower risk of relapse after surgery. Finally, screening for microvascular invasion has been performed in biopsy specimens, and two immuno-histochemical markers – PIVKA-II and H4K16 – were identified as a major prognosis factor.

3 | IMPROVEMENT OF CURATIVE PROCEDURES THROUGH TECHNICAL INNOVATION AND ACCURATE PATIENT SELECTION

3.1 | Advances in surgical treatments

The feasibility of liver resection depends on the quality of the parenchyma and the extent of resection, while oncological suitability depends on the biological features of the tumour. Major hepatectomy (resection of 3 or more Couinaud segments) is only feasible in the absence of portal hypertension and with a MELD score <9. Even when these criteria are met, preliminary portal vein embolization is recommended to assess the liver regeneration in patients with cirrhosis in whom right hepatectomy is planned. As growth of the future liver remnant is slower in patients with cirrhosis, chemembolization is often performed first to prevent tumour progression while awaiting the benefit of portal embolization. Recently, simultaneous occlusion of both portal inflow and hepatic venous outflow of the planned resection target showed greater and more rapid growth of the future liver remnant than portal embolization alone, although the concomitant increase in liver function may be somewhat delayed compared to the increase in volume.

Until the most recent EASL guidelines, portal hypertension was considered to be a contraindication to hepatectomy, but these were revised based on several papers showing that resection can be safely performed in the presence of indirect signs of portal hypertension such as platelet count <100 000/µL and/or splenomegaly, as long as liver function remains normal (MELD score <9). It may be possible to further broaden the criteria by incorporating other factors such as an assessment of liver/spleen stiffness. In the absence of clinically detectable ascites, the risk of liver decompensation after minor hepatectomy has been shown to be very low if liver stiffness as measured by elastometry is <12 kPa. Measurements between 12 and 20 kPa make up a ‘grey zone’, and measurement of splenic stiffness and/or volume may increase the accuracy of the noninvasive assessment of resectability.

Several technical improvements and innovations have helped improve the prognosis of patients with HCC. For instance, laparoscopic resection is now extensively used for HCC despite the absence of randomized controlled trials comparing this approach to open surgery. A recent meta-analysis analysed 51 retrospective studies with or without propensity score matching to compare laparoscopic and open resection for HCC in 6812 patients. Laparoscopy was associated with decreased operative blood loss, lower 30-day morbidity and mortality, and a shorter hospital stay, with a similar rate of R0 resection. There was a trend towards lower HCC recurrence and increased long-term survival with laparoscopy. Other innovative technologies, including intra-operative near-infrared (NIR) imaging fluorescence-guided surgery, are highly promising in the field of HCC. Indocyanine Green (ICG), a vital dye that is extensively used to assess liver function, binds to plasma proteins and emits light with a peak wavelength of around 830 nm when illuminated with NIR light. ICG is excreted in bile, and tends to concentrate in HCC enabling intra-operative detection by the NIR camera. While the ultimate role of this technology must be determined, interest is particularly high among laparoscopic surgeons where there is a need for alternative means of tumour detection because of the absence of tactile feedback.

3.2 | Innovation in percutaneous ablations

Innovation in percutaneous ablative techniques including radiofrequency ablation (RFA), microwave ablation (MWA), cryotherapy and irreversible electroporation (IRE) is one of most effective strategies to improve the outcome of patients presenting with the broadened early stages of HCC. Underlying cirrhosis and the presence of comorbidities still limits curative resection in selected patients despite recent developments in hepatobiliary surgery. Furthermore, the worldwide shortage of cadaveric donors makes liver transplantation within 6 months after diagnosis of HCC unrealistic in many more selected patients. Indeed, in most patients with early-stage HCC, ablation is the only opportunity to obtain long tumour progression-free survival that is similar to that reported after resection. Moreover, when feasible, ablation should be considered to be the first line treatment in transplantable patients when bridging treatment is
Monopolar RFA has been the most frequently used technique to optimize the curative management of patients with HCC. Improving the efficacy of tumour ablation. Although real-time and multiplanar ultrasound (US) is the reference guidance method for percutaneous ablative techniques, inconspicuous US targets remain a major cause of technical contraindications to ablation. In patients with unresectable tumours, this usually results in endo-arterial approaches, mainly trans arterial chemoembolization (TACE), which has been associated with a less complete response and shorter survival. Fusion image technologies including the co-registration of real-time US with pretherapeutic CT or MRI 3D-data sets allow US guided ablation of tumours that are normally poorly visible. If necessary, an intravenous contrast bullet injection during the procedure improves US target conspicuity and allows intra-operative delineation of the ablation zones. In practice, percutaneous ablation is not denied in patients because of tumour visibility on US in expert centres that routinely use these tools. Many advanced technologies based on multimodal fused imaging such as cone-beam CT or angiography-CT suite are also now available for more difficult ablative procedures, especially those requiring multiplicator insertions in critical locations. Thus, at present, technical contraindications to percutaneous ablations for liver tumours because of imaging limitations have been almost completely overcome.

Superficial HCC locations have long been considered a contraindication because it was assumed there was a higher risk of bleeding, tumour seeding and collateral damage to neighbouring critical structures such as the diaphragm, digestive tract and gallbladder. The experience acquired worldwide in the last two decades using common intratumourous irradiating ablative methods (monopolar RFA, MWA) has shown that puncturing the target through the non tumorous liver parenchyma and systematic tract ablation is safe for subcapsular tumours in relation to the risk of haemorrhage and tumour seeding. Artificial ascites involving filling the peritoneal cavity with isotonic serum to separate the target from critical adjacent structures are effective in preventing thermal damage. Furthermore, artificial ascites can help improve the visibility of some subdiaphragmatic tumours on ultrasound. However, recent improvements in laparoscopic liver surgery should be considered before choosing ablation of subcapsular HCC because while resection is now more often safe, some reports have suggested that ablation using standard irradiating intratumoural methods such as monopolar RFA may be less effective than in intraparenchymal locations.

Advances in ablative technologies have obviously contributed to optimization of curative management of patients with HCC. Monopolar RFA has been the most frequently used technique for ablative of HCC by far. Two decades ago, monopolar RFA was adopted worldwide rather than ethanol injections and any other chemical methods for the treatment of unresectable tumours presenting with HCC within the Milan criteria. This is because a mean four times fewer procedures was needed to obtain a complete response, resulting in better local recurrence-free and overall survivals. However, up to 25% of local recurrences have been reported after monopolar RFA and systematic pathological examinations of the explanted liver in transplanted patients after first line RFA showed up to 40% of remnant viable tumours at the ablation site. Thus, the efficacy of ablative methods must be improved to increase their ‘curative’ value. Nodules >3 cm and the ‘heat sink effect’ of large neighbouring vessels (>3 in diameter) are the two main predictive factors for incomplete ablation after monopolar RFA. Developments in MWA technologies that heat the tissue faster and at higher temperatures should extend these limits. In clinical practice, despite a trend to induce larger ablation volumes in shorter times, the results of MWA and monopolar RFA are similar for local control of HCC. Cryotherapy has the advantage of clear delineation of the ice ball when CT is used for monitoring. However, only a few centres use this technique for HCC ablation and its limitations seem similar to those reported with monopolar RFA and MWA. Finally, to extend the existing limits of ablative techniques, the type of energy and the number of applicators could be less than the diffusion of energy around and between the applicators. Thus, we developed a classification of ablative technologies according to two modes of energy diffusion. The most common mode including monopolar RFA, MWA and cryotherapy is centrifugal from each applicator, while the other including only multibipolar RFA and IRE is centrifugal between each combination of applicators. The main consequence for clinical application is better prediction of the boundaries of the ablation zone by the centripetal mode compared to the centrifugal mode, which implies a limited diffusion of energy outside of the applicators. Thus, indications for ablation can be extended to larger tumours (up to 8 cm) with centripetal energy devices, even infiltrative tumours with limited portal invasion (Vp1-3). For standard indications (tumour <5 cm), the no-touch approach can be implemented with centripetal methods, especially multibipolar RFA, which involves inserting applicators outside the tumour (extratumourous method). The local recurrence rate in HCC up to 5 cm (including for those <3 cm) is markedly decreased with no-touch multibipolar RFA compared to monopolar RFA. In addition, no-touch ablation allows safe and effective ablation of a wide spectrum of subcapsular tumours. Irreversible electroportation (IRE), which is also a centripetal ablative method, is the only nonthermal technique. IRE is currently a unique option for curative treatment of central HCC abutting the main bile ducts. In addition, because IRE spares the collagenic skeleton and the microvessels of surrounding non tumourous tissue, this technique appears more suitable than other thermal methods in fragile patients with poor liver function and severe comorbidities.
4 | DECREASING RATES OF RECURRENCE

4.1 | Control of underlying liver disease

This step is pivotal because the goal is to preserve liver function and potentially decrease the rates of distant/late recurrences.

4.1.1 | HCV infection

It is not clear whether the benefit of viral clearance is related to a potential impact on the oncological process or a reduction in end-stage liver disease (ESLD)-related risk of death independent from HCC management. Most of the available data for the impact of HCV eradication on the risk of HCC recurrence have been obtained by meta-analyses or meta-regressions performed in the interferon (IFN) era. However, although there was speculation on the potential benefits of IFN on HCC recurrence, based on its antiviral, anti-inflammatory, and anti-angiogenic effects, randomized controlled trials did not demonstrate the efficacy of IFN-based adjuvant therapy in patients undergoing curative HCC procedures.22 Moreover, the controversy on the potential harmful impact of direct antiviral agents (DAAs) on the risk of HCC recurrence has probably not only limited prescriptions in these otherwise priority candidates for antiviral treatment, but also prevented any definite conclusions from being drawn based on rigorous prospective data.23 However, the findings of prospective studies and the latest reports in large American populations24 have challenged these hypotheses and recently provided further support of the safety of DAAs in patients who have achieved effective HCC remission. Finally, it is tempting to speculate that longer follow-up may be required to identify any differences in long-term HCC recurrence (more than 2-3 years). This is probably the time needed for the decreased inflammatory and/or fibrotic processes induced by viral suppression to affect liver carcinogenesis.

Overall, achieving a sustained virological response (SVR) in patients with HCV-related cirrhosis is not clearly associated with a modified risk of short- or medium-term tumour recurrence following a curative procedure. Nevertheless, HCV eradication favours optimal HCC management by preventing deterioration of liver function, leading to improved overall survival, whatever the antiviral regimen. While awaiting confirmation from larger prospective studies with longer follow-up, patients with HCV-related cirrhosis, complicated or not by HCC who are eligible for curative procedures, must be prioritized for access to antiviral treatment.

4.1.2 | HBV infection

Maintained HBV virosuppression in patients with HBV-related cirrhosis has tertiary prophylactic properties in addition to increased overall survival (OS) and decreased HCC occurrence, and is independently associated with a reduced risk of late recurrence after local curative-intent treatment of HCC. At least three meta-analyses including more than 23 000 HBV-related HCC patients, mainly from Asia, showed that nucleoside analogue (NA) therapy significantly reduced the risk of recurrence after surgical resection and improved both disease-free and OS compared to no treatment. In patients with recurrent HCC, the use of HBV antiviral therapy was associated with both preserved liver function at recurrence and an increased proportion of patients eligible for curative HCC treatment.25

4.1.3 | Other causes of chronic liver disease

Scientific evidence of the benefits of controlling non-virological factors involved in underlying chronic liver disease are scarce, but meaningful.26 Abstinence from alcohol consumption and intensive care of diabetes mellitus has been related to an improved prognosis in HCC patients. Conversely, inadequate blood glucose maintenance in diabetic patients is a significant risk factor for recurrent HCC and poor survival after curative RFA therapy.

4.2 | Inclusion of patients eligible for curative procedures in ongoing neoadjuvant/adjuvant trials

The high rates of intrahepatic local HCC recurrence strongly influence patient prognosis, which could be improved by implementation of neoadjuvant and/or adjuvant strategies. However, many adjuvant therapies have failed to improve recurrence-free (RFS) or overall survival (OS), including sorafenib.27 However, the results of these trials are limited by selection biases and tyrosine kinase inhibitors (TKI) side-effects.

Several studies have shown that surgery and particularly ablation procedures may significantly alter the immune microenvironment. Therefore, it could be hypothesized that adding immunotherapy (Io) before and/or after these curative procedures could lead to improved RFS by inhibiting immune related pro-tumour effects.28 In particular, the rationale for combining RFA and immunotherapy is based on boosting the immune response that is triggered by the necrosis induced by percutaneous treatment. Based on positive results in studies evaluating immune checkpoint inhibitors in advanced HCC,29 which reported encouraging results and a fair safety profile, a number of studies are testing the combination of immune checkpoint blockade in addition to curative procedures. Table 1 summarizes ongoing Phase II or III trials testing neoadjuvant and/or adjuvant strategies before/following effective curative procedures (resection or PA). Most studies are designed to include patients with a high risk of relapse (multiple tumours or single >3 cm), with RFS as the main endpoint. All trials are being performed in academic centres worldwide and will recruit several hundred patients thus providing a potential opportunity for patients being managed in routine practice.

5 | PERSPECTIVES

Curative management of HCC patients will continue to improve as progress is made in prognosis, systemic therapy and innovation
in surgical or ablative procedures. Molecular biology will allow personalized intervention strategies, as several non-tumour and tumour molecular prognostic signatures have been validated in both resected liver and biopsy specimens of small HCC, although they must still be prospectively validated for use in clinical practice. Ultimately, combining precision medicine and new drugs with liver resection or percutaneous ablation in neoadjuvant and/or adjuvant approaches might improve patient outcomes in the future.

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**CONFLICT OF INTEREST**
The authors do not have any disclosures to report.

**AUTHOR CONTRIBUTIONS**
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