Editorial

What should be the best approach post-liver resection in non-viral non-cirrhotic hepatocellular carcinoma?

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Hepatocellular carcinoma (HCC) is the sixtieth most prevalent cancer and the third cause of cancer-related mortality worldwide (1). HCC occurs in the context of liver disease, with around 85% of liver cancers developing in the set of liver cirrhosis (2). However, the proportion of non-cirrhotic HCC is not transversal across the etiologies of liver disease, with HCC occurring in patients with metabolic-associated steatotic liver disease (MASLD) being five times more likely to occur in non-cirrhotic livers. Indeed, 2 out of 5 MASLD-associated HCC patients are non-cirrhotic. With the changing landscape of etiologies of advanced liver disease we are assisting in the last decade, with a decline in hepatitis B or C virus liver disease and an increase in MASLD, we can foresee an increase in the burden of non-cirrhotic HCC (3). However, our accumulated knowledge on the prognosis and treatment strategies for HCC relies mostly from cirrhotic patients, which does not allow truly evidence-based decisions in the set of non-cirrhotic HCC.

To fill that gap in knowledge, Maulat *et al.* performed a multicenter retrospective study under the aegis of the French Association of Hepato-Biliary Surgery and Liver Transplantation, in which 467 patients with non-cirrhotic HCC, without underlying viral hepatitis or hereditary metabolic disorders, submitted to hepatic resection were evaluated (4). Most of those patients had either MASLD or metabolic and alcohol related liver disease (MetALD). Only patients without advanced liver fibrosis, who were F0 to F2 of the METAVIR classification, were included.

The first relevant finding of this study was that the median age was almost 70 years old. This goes in alignment with other epidemiological studies that show that non-cirrhotic MASLD-associated HCC is exceptionally rare in patients under 65 years old (5). The older age of these patients has major implications in their treatment, since most are beyond the age to be candidates for liver transplantation, and frequently have comorbidities that jeopardize oncological surgical and medical treatment (6).

Regarding the background stage of liver disease, half of the patients did not have any liver fibrosis (F0), almost one third had very mild fibrosis (F1) and only one fifth moderate fibrosis (F2). Although a high proportion of absence of fibrosis or very mild fibrosis has been described in other similar cohorts (7,8), it is in conflict with the fact that liver fibrosis is an important risk factor for HCC development, either in the cirrhotic or non-cirrhotic range (6). This paradox may be explained by the fact that even if the risk of developing HCC increases with worsening fibrosis, the population of non-fibrotic MASLD is much larger than the fibrotic one (3).

Liver fibrosis seems to induce an imbalance in the hepatic stellate cells population, biased toward a higher proportion of the myofibroblastic population that produce collagen I, which when in excess in the extracellular matrix, leads to activation of procarcinogenic pathways such as transcriptional coactivator with PDZ-binding motif (TAZ) pathway, through increased stiffness and aberrant cycles of mechanosensing and mechanoresponses. Also, collagen deposition may represent a barrier to immune cell influx

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and immune cancer surveillance (9). With liver fibrosis, conversely, the underrepresentation of the quiescent hepatic stellate cells phenotype, results in hepatocyte deprivation of hepatocyte growth factor (HGF), a survival factor for hepatocytes, with subsequent increase in hepatocyte apoptosis (9). Those dying hepatocytes induce a progenitor proliferative response, which may result in an increased carcinogenic risk (10). As such, different pathways may promote hepatocarcinogenesis in non-cirrhotic, non-fibrotic MASLD patients. For example, steatosis by itself may be steatogenic through oxidative-stress cell injury and DNA damage (10). Also, compared to cirrhotic patients, non-cirrhotic SLD-associated HCC patients tend to have less frequently diabetes mellitus and metabolic disturbances, suggesting a higher influence of genetic polymorphisms such as in PNPLA3, TM6SF2, MBOAT7, and HSD17B13 which are known to be associated with non-metabolic SLD and HCC development, and may also represent different carcinogenic pathways (6). Lastly, in non-fibrotic livers, HCC may also derive from the degeneration of benign hepatic adenomas, and represent a different disease (11). As such, different pathogenesis and carcinogenic pathways might translate in different prognosis and response to therapy.

Previous literature tells us that the overall survival in cirrhotic and non-cirrhotic MASLD-associated HCC is similar (5). This similar survival is despite the fact that non-cirrhotic patients tend to have more frequently single, larger tumors. Non-cirrhotic patients more frequently are offered liver resection but less frequently liver transplantation (12). However, after liver resection, some studies suggested that non-cirrhotic patients present lower tumor recurrence and longer disease-free and overall survival (13).

In this French cohort (4), non-cirrhotic HCC patients submitted to liver resection presented a 5-year recurrence-free survival of just 34.5% and a 5-year overall survival of 59%. Those results seem similar to what have been described in the whole HCC population, however it is of note that the median tumor size was 9 cm, which is much higher than the recommended size for resection in cirrhotic patients.

The high recurrence rate after HCC resection may be related to both tumor-related risk factors that have already subclinical spread in the liver or outside the liver, or by the fact that liver disease by itself, particularly in the set of liver cirrhosis, is a premalignant condition, which places the patient at risk of *de novo* hepatocarcinogenesis. After the IMBRAVE50 study (14), adjuvant immunotherapy post liver resection for HCC is recommended in patients who present HCC features of high risk for recurrence, such as tumor size higher than 5 cm, more than 3 tumors, vascular invasion and poor tumor differentiation, which resulted in a 12% absolute decreased risk of 12 months recurrence. Interestingly, it does not take into account liver disease features of high risk of *de novo* carcinogenesis, such as liver fibrosis and genetic background.

Regarding the non-cirrhotic HCC, can we extrapolate the same high-risk tumor-features as in the cirrhotic patients? Maulat *et al.*'s study found that having more than two tumors (unlike the IMBRAVE50 which considers more than 3), and tumors higher than 10 cm (unlike 5 cm for the IMBRAVE50) associates with high risk of recurrence, with less than half the patients with no more than two tumors smaller than 10 cm recurring in 5 years, as compared to 70% if more than 10 cm and 95% if more than two tumors (4). Patients resected for no more than two tumors lower than 10 cm, who presented well differentiated tumors, and without vascular invasion performed particularly well, with only 37.5% 5-year recurrence.

The one million dollars question is why resection of larger tumors in non-cirrhotic patients performs better than in the cirrhotic patient. First of all, extended liver resection is more frequently tolerated by non-cirrhotic patients, which present higher liver function/mass reserve. Furthermore, it might be related to the fact that the absence of fibrosis might confer lower resistance to expansive tumor growth (6), and represent less advanced tumors in the tumorigenic process with higher differentiation, lower cumulative mutations burden, and lower vascular invasion. On the other hand, different carcinogenic pathways in non-cirrhotic patients might translate into different tumor behavior, less prone to local and distant spread. Lastly, multifocal carcinogenesis might be less frequent in non-cirrhotic patients (13), such as it could be expected for hepatic adenoma-derived HCC.

The results from this French cohort should make us rethink the indications for adjuvant therapy post-resection in non-cirrhotic HCC, which might include a lower burden of number of tumors, but be more permissive regarding tumor size. A more personalized stratification for adjuvant therapy in non-cirrhotic HCC patients seems particularly important since it is an older population, with higher comorbidity and hence more prone to adverse reactions to immunotherapy. Furthermore, it is still to be answered whether immune therapy might be less effective in non-viral liver disease patients. We should not propose a considerable high-risk therapy if it would add no benefit, but we also should not exclude for therapy patients with a

lower burden in tumor number by a wrong assumption of risk extrapolated from the cirrhotic population.

Clinical trials in HCC should include and be stratified for the absence of liver cirrhosis or fibrosis, since different pathways can result in a similar HCC phenotype, but a different HCC behavior.

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