

Non-alcoholic fatty liver disease, non-alcoholic steatohepatitis, metabolic syndrome and hepatocellular carcinoma – a composite scenario

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Hepatocellular carcinoma (HCC) is the fifth most common cancer and the second leading cause of cancer-related death worldwide. Solid data suggest that the epidemiology of HCC is changing; while the frequencies of hepatitis B virus (HBV)- and hepatitis C virus (HCV)-related HCC are progressively decreasing owing to the development of nucleo(t)side-based therapies and directly acting antiviral agents, respectively, the frequency of cryptogenic HCC continues to increase (15–30% of cases) (1). The rise of cryptogenic HCC is mainly related to non-alcoholic fatty liver disease (NAFLD) (1,2). NAFLD encompasses a wide spectrum of liver injuries, ranging from steatosis to non-alcoholic steatohepatitis (NASH), which may progress to cirrhosis (1,3).

The clinical counterparts of NAFLD are metabolic disorders. Type 2 diabetes, dyslipidemia, obesity, and arterial hypertension are defined as hallmarks of metabolic syndrome (MS). NAFLD mainly results from liver involvement in the context of MS and is becoming a new epidemic disease. Even though increased short-term mortality in MS patients is mainly due to cardiovascular diseases, the liver disease burden is largely underestimated and an increase in NAFLD-related HCC cases is currently observed by clinicians. However, several issues remain to be elucidated and dedicated guidelines for the management of NAFLD- and MS-related HCC are lacking.

Metabolic disorders, steatosis, and oncogenesis: a blurred picture

Approximately 20% of treated HCC cases are associated with NAFLD and/or with MS (2). In surgical series, the overall proportion of HCC cases associated with NAFLD and/or with MS ranges between 5% and 15% (4,5). In the Humanitas Clinical and Research center, in the period 2014–2017, 120 HCC patients have been scheduled for liver resection. Of these, about 1/4 had NAFLD and/or MS as the only risk factor for HCC. Twelve additional patients (10%) had NAFLD and/or MS in association with other risk factors for HCC.

However, the clinical and pathology evidence of an association among metabolic disorders, NAFLD/NASH and HCC is less robust than epidemiological data. Only half of the patients with MS-related HCC have NAFLD and 1/4 have NASH (4-6). Even among morbidly obese patients, NASH is evident in only 10% of cases (7). In industrialized areas, the prevalence of NAFLD is 30–50%, but it does not correspond to a consistent risk of HCC (3). NASH is more relevant, but its true prevalence is difficult to ascertain; imaging is not contributive, and liver biopsy has low accuracy because NASH has a heterogeneous distribution into the liver (8). Considering metabolic disorders, every single feature of MS, mainly

diabetes and obesity, is associated with increased risk for HCC, but again of limited clinical relevance (1). To make the picture more composite, etiological agents are often combined. HCV infection *per se* can determine or worsen metabolic disorders and NAFLD (9). In such patients, the oncogenic impact of metabolic factors becomes unclear. Further, in cirrhotic patients, NAFLD and NASH can be overlooked because portal hypertension decreases hepatic fat and because fibrosis masks the stigmata of NASH (burned-out NASH) (10).

So far, a contribution of NAFLD or metabolic disorders to liver oncogenesis is plausible, but not fully understood nor determined.

Are we dealing with a different disease? The screening dilemma

NAFLD- and MS-related HCC are often diagnosed at an advanced stage. In comparison with HCV-related HCC, they have a larger size and a higher rate of infiltrative growth (1,2,4,6), which corresponds to a worse prognosis (2). Nevertheless, these HCC should not be considered different from HBV-/HCV-related HCC. The differences at presentation reflect the delayed diagnosis of HCC in metabolic patients due to the lack of a screening program. Pathology discrepancies disappear when diseases at a similar stage are compared (4). The HCC-NAFLD Italian Study Group reported similar survival for NAFLD-related HCC and HCV-related HCC patients when the two groups were balanced according to other prognostic factors (2). Viganò *et al.* reported even better prognosis after liver resection in MS-related HCC compared with HCV-related HCC (4). A lower recurrence rate was observed in the first group, especially considering late recurrences (>2 years after resection). A lower *de novo* carcinogenesis in metabolic patients and the possibility to treat the causal metabolic disorders could explain these findings.

Given that late diagnosis is associated with worse prognosis, the need for a screening program is urgent. The high prevalence of NAFLD and metabolic diseases together with the relatively low risk for tumor make a screening program cost-ineffective. Recent EASL guidelines suggest a more relaxed follow-up in NAFLD patients (every 2–3 years) and a stricter protocol in NASH patients (once a year) (3). However, further efforts are needed; NASH patients are difficult to identify and the HCC risk increases when multiple metabolic diseases are combined (MS) even in the absence of NASH. Epidemiological studies to identify populations in which a strict screening is beneficial should be designed.

Non-cirrhotic liver: friend or foe?

In non-cirrhotic patients, liver surgery is safe with low mortality and liver dysfunction rates. Theoretically, this is the case of most MS- and NAFLD-related HCC (cirrhosis in ~20% of cases). However, a non-cirrhotic liver does not mean a normal liver. The lesson learned from colorectal liver metastases should be kept in mind: chemotherapy-related steatosis and NASH worsen operative outcome. Further, the comorbidities of metabolic patients may have an additional detrimental impact on postoperative recovery. In a recent analysis of a large US database, the presence of MS was associated with higher perioperative complication and mortality rates (a two-fold increase) after liver resection (11). A French study even reported a mortality rate as high as 18% in the presence of NASH (5). The authors suggest to not overestimate those risks. An Italian multicenter trial confirmed that patients with MS-related HCC have high morbidity (44%), severe morbidity (20%) and liver failure rates (13%), higher than the present standards after liver surgery on healthy liver and similar to HCV-related HCC patients, but the mortality rate was very low (1%) (4). So far, two cautionary notes should be stated. First, NAFLD and NASH should be kept in mind, especially when major hepatectomy is planned. The volume of the future remnant liver for a safe resection should be larger than in patients with a true “normal liver”. A more liberal adoption of preoperative portal vein occlusion should be considered. Second, advanced age, comorbidities, and pro-inflammatory status related to insulin resistance should be considered to correctly estimate operative risk.

Provided the increased operative risk of liver surgery in such patients, could liver transplantation be an option? In the report by the Italian study group on HCC-NAFLD, only 1% of patients received transplantation (2). To date, liver surgery still remains the standard. However, NASH patients have a risk of decompensation and progression to cirrhosis (3). NASH-cirrhosis is an increasing indication for transplantation and will be the most common indication in the future (12). Reappraisal of liver transplantation for NASH- and MS-related HCC will be needed both at diagnosis and recurrence, but evidence still needs to be developed.

Reversible damage, reversible risks

Whether steatosis and NASH are reversible remains a relevant clinical question. Lifestyle and dietary changes

improve steatosis of donors in living-donor liver transplant programs (13). Obese patients have a regression of steatosis after bariatric procedures (7). However, there are some doubts concerning the reversibility of steatohepatitis. NASH has been also associated with the administration of irinotecan-based chemotherapy. Viganò *et al.* showed that in chemotherapy-treated patients, NASH does not regress even after a long interval (9 months) (14). However, the patients did not receive any correction of their metabolic disorders. In contrast, Lassailly *et al.* reported a regression of NASH in 85% of obese patients undergoing bariatric surgery (7). Some drugs, namely statins, are thought to impact steatosis and NASH (15). Some preclinical data even reported a protective effect of metformin against HCC development (16). However, evidence for the efficacy of metformin in NASH is scarce and data are insufficient for evidence-based recommendations (3,17). A large number of clinical trials are currently assessing the effectiveness of new therapeutic options. These data suggest an interesting clinical scenario. Patients could be prepared for liver resection by undertaking preoperative specific dietary regimens or lifestyle changes to reverse liver steatosis and reduce operative risks. An adjuvant metabolic protocol after surgery could be applied to preserve liver function and reduce the risk for *de novo* carcinogenesis. Even if appealing, these hypotheses remain to be verified, mostly because of the time span needed for a clinically relevant efficacy.

Looking for guidelines

Validated and shared guidelines drive the management of HCC patients, but these guidelines have been designed and validated in cirrhotic patients. The authors clearly outlined the peculiarities of MS-related or NAFLD-related HCC and advocate dedicated guidelines: the diagnostic criteria of HCC should be validated in non-cirrhotic livers; the candidates for a strict screening program should be identified; the indications for liver resection should be better detailed, as well as indications for liver transplantation; and the management of metabolic comorbidities should be implemented to preserve liver function and to reduce the stimulus to carcinogenesis. New multidisciplinary teams are required and should include nutritionists, endocrinologists, and, in selected cases, bariatric surgeons. Both the tumor and the underlying liver parenchyma and the metabolic status must be considered to achieve a whole patient management.

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Footnote

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