Editorial

Prognosis of operated hepatocellular carcinoma developed on non-cirrhotic liver

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The incidence of primary liver cancers, and particularly hepatocellular carcinoma (HCC), is increasing throughout the world. The vast majority of HCCs develop on cirrhotic livers (CLs) (CL HCC) or livers chronically infected by hepatotropic viruses, mainly hepatitis B virus (HBV) and hepatitis C virus (HCV) (1). As HCC occurring on non-HBV non-HCV non-CL (NCL) HCC occurs much less frequently, its management is less established than for CL HCC. Consequently, many clinicians might confuse the prognosis and management of NCL HCC with the one of CL HCC. It is however demonstrated that NCL HCCs behave differently than CL HCCs. Their prognostic factors and sensibility to systemic therapy are different, added to the fact that NCLs can undergo major resections allowing curative surgical management or even systemic therapies that are not even possible in CL HCCs due to the failing function of the CL. The established criteria for liver transplantation of CL HCCs, including the famous Milan criteria, have no role in NCL HCC management (2-4). The Barcelona Clinic Liver Cancer (BCLC) strategy for prognosis prediction and treatment recommendation also concerns only CL HCCs; and should not be used for NCL HCCs (5).

It is therefore of the outmost importance to specifically study NCL HCCs. Due to the rarity of this cancer, it is also necessary to merge experiences of large expert liver centers to build strong scientific evidence allowing better management of patients suffering from NCL HCC. Despite the unavoidable bias linked to the retrospective nature of their study, this paper by Maulat *et al.* is an important step, as by grouping 11 French major liver surgery centers, they were able to review the largest series of operated NCL HCC patients so far (n=467), with a median follow-up 30 months (6). The results of this operated series are better than expected in CL HCCs, with a median overall survival (OS) of 88 months and a median recurrence-free survival (RFS) of 28 months. Amongst the preoperative prognostic factors, the number of HCC nodules (>2) and the size of the largest nodule (>10 cm) were determined as significant preoperative prognostic factors for decreased RFS after surgical resection with curative intent. In the population of NCL HCC patients with good RFS prognosis based on these preoperative prognostic factors, the pathology report of the resection specimen was also a very important,

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as microvascular invasion (median RFS: 25 months) or poor/moderate differentiation (median RFS: 33 months) decreased RFS to one-third of the one of patients with well-differentiated NCL HCCs (median RFS: 88 months) (6). These decreased RFSs were correlated to decreased OS. In total 209 patients (44%) developed recurrence in the follow-up period, half of them confined to the liver, and one-third of the recurrences were further managed with curative intent.

These results first confirm the fact that patients with operated NCL HCC should be carefully followed after surgery, as recurrence might occur in half of the patients and as it is likely that early detection of this recurrence might allow a better chance of curative management, especially if it occurs within a healthy liver that can undergo a second resection surgery (7). Secondly, this study allows to preoperatively determine which NCL HCC patients have a higher risk of recurrence after surgery. In this French series, the NCL HCC patients with three or more nodules had a median RFS of 10 months and a 5-year RFS of 5%, meaning that nearly all of them develop recurrence after surgery with curative-intent (6). In the group of patients with an HCC size >10 cm and one or two nodules, the 5-year RFS was also quite poor at 30%. These high-risk patients might be considered for inclusion in future prospective studies on the role of neoadjuvant therapy before liver resection, with maybe a combination of locoregional chemo- or radio-embolization for decreasing the risk of intrahepatic HCC recurrence and systemic immunotherapy for lowering the risk of extrahepatic HCC spread. This study also confirmed that poorly or moderately differentiated NCL HCCs or HCCs with microvascular invasion, information that is often only available postoperatively, are at high-risk of postoperative recurrence. These patients might also be considered in future prospective studies on the role of adjuvant therapies including combination immunotherapies. Finally, as two-thirds of the NCL HCC recurrences are not amenable to curative surgical management, there is also a place for future studies on systemic therapies in these recurrent patients, as their usually normally functioning livers allow them to better tolerate the potential severe side effects of these therapies.

HCC on NCLs is rare and could be considered as a neglected disease with a rising incidence. To improve the management of NCL HCC patients, it is necessary that large expert centers merge their experience in prospective studies evaluating the interests of different therapeutic strategies. This study by Maulat *et al.* allowed to determine a population of NCL HCC patients who might benefit from multimodal management with neoadjuvant or postoperative therapies to improve the overall results. These results should be confirmed by prospective studies, which are difficult to conduct, as NCL HCCs are rare. New therapies, including combination immunotherapies, should be rigorously tested in this particular population (8). However, until now, surgery is the only treatment of NCL HCCs with curative intent, and long-term cancer-free survival can be obtained even with very large tumors (9). In complicated cases or when the expected functional reserve of the future liver remnant (FLR) is insufficient, curative resection might be rendered possible by portal and hepatic vein embolization to induce preoperative FLR hypertrophy (10). As suggested, liver transplantation might also be considered in patients with unresectable NCL HCC without vascular or lymph node involvement (11).

In the Maulat *et al.* retrospective series of 467 patients operated on in France between 2010 and 2018, alcohol consumption and metabolic syndrome were detected as risk factors for HCC in one-third and one-fourth of the cases, respectively (6). With the rising incidence of metabolic syndrome and of metabolic dysfunction-associated steatohepatitis (MASH) throughout the world (12), it is likely that challenges in the management of NCL HCCs will be faced more frequently by liver cancer centers. Therefore, including these patients in prospective studies or registries should be strongly encouraged to improve outcomes in patients with NCL HCCs. Postoperative NCL HCC recurrences are frequent and deserve to be detected early to offer patients a chance on repeated surgical resection.

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