French Editorial from the ACHBPT

Inflammation is king in liver resection for hepatocellular carcinoma

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We read with great interest the paper by Miyata *et al.* entitled: *The Impact of Histologic Liver Inflammation on Oncology and the Prognosis of Patients Undergoing Hepatectomy for Hepatocellular Carcinoma* (1). In this single center retrospective study, the authors included 500 patients undergoing curative surgical liver resection for primary hepatocellular carcinoma (HCC) without any neoadjuvant treatment. All liver specimen underwent postoperative pathological analysis to identify fibrosis but also lymphocyte infiltration and hepatocyte necrosis as surrogate marker for hepatic inflammation. Histological hepatic inflammation was graded from A0: no necro-inflammatory reaction, to A3: severe necro-inflammatory reaction. Median follow-up was 47.3 months. Overall, 19.4% of the patients had severe liver inflammation A3 (n=97) and presented with higher postoperative morbidity and reduced overall and recurrence-free survival compared to patients with none to moderate inflammation A0–A2 (n=403). Furthermore, inflammation grade A3 was an independent predictor of HCC recurrence independent of underlying liver disease and fibrosis grade.

The study by Miyata *et al.* contributes to the growing evidence on the importance of hepatic inflammation for tumor environment and oncological outcomes (2). HCC is particularly interesting since it develops under conditions of sustained inflammation (3). Data from animal studies show that upregulation of inflammatory cytokines after liver surgery triggers HCC recurrence (4,5). Interestingly, inflammation also impacts recurrence of HCC after liver transplantation (6). Results from a recent study suggest that treating liver grafts with ex-vivo machine perfusion prior to transplantation reduces recurrence rates by diminishing ischemia-reperfusion injury and inflammasome activation (7).

Based on the results of the study by Miyata *et al.*, we would like to discuss two clinical factors that may impact hepatic inflammation and HCC recurrence in the setting of liver surgery. A first factor is the underlying liver disease. The type of inflammatory signaling differs for example in non-alcoholic fatty liver disease and virus induced hepatitis (8,9). This leads to a different immune surveillance of HCC which can be altered upon treatment and influence recurrence rates (10). For instance, HCV-related HCC has been shown to present high recurrence rates after adjuvant treatment with direct-acting antivirals (11). Of note, the majority of patients in the present study had HCV-related HCC but adjuvant treatments were not included in the analysis. Second, postoperative liver regeneration may also contribute to tumor recurrence (12). For example intraplatelet serotonin, a key player in hepatic regeneration, has been shown to impact early tumor recurrence after liver resection in humans (13). In the present paper only 27% of the patients underwent major hepatectomy and the authors do not specify if portal embolization was performed. An analysis of major hepatectomies with higher regeneration kinetics could further strengthen the authors hypothesis.

The study has several major limitations starting with the retrospective and single-center design. Another major limitation is the absence of potential confounding factors for recurrence in the analysis for example duration of

pedicular clamping and adjuvant treatment. Also, there are no preoperative or peri-operative control biopsies available. Furthermore, the exact recurrence patterns are not investigated in the study. Finally, the pathological grading of inflammation is based on a classification dating back to 1996 (14). In contrast, a recent pilot study showed feasibility of real-time peri-operative determination of hepatic inflammation by video microscopy (15).

In conclusion, the results of the study support the idea of including hepatic inflammation as criterion for HCC risk-stratification with the potential to guide emerging adjuvant and neoadjuvant treatment strategies. Future studies should focus on major hepatectomies in patients with non-alcoholic fatty liver disease and perform an in-depth analysis of perioperative hepatic inflammation.

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