



The growing threat of non-alcoholic fatty liver disease-related hepatocellular carcinoma

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Non-alcoholic fatty liver disease (NAFLD) is the fastest growing cause of hepatocellular carcinoma (HCC) worldwide (1). It is anticipated that the burden of NAFLD-related HCC will continue to increase in tandem with the global obesity epidemic (2,3). This has become a global issue of concern, as liver cancer is associated with significant morbidity and mortality, and is currently the third leading cause of cancer death (4).

In this review, Geh *et al.* provided a comprehensive overview of NAFLD-related HCC and its diagnosis, treatment and surveillance (5). The authors described the distinct clinical characteristics of NAFLD-HCC patients, as well as the impact of specific treatments on NAFLD-HCC patients. They described how patients with NAFLD-HCC tend to be older, with greater likelihood of having obesity, type 2 diabetes mellitus (DM), cardiovascular disease, and cerebrovascular disease, and lower likelihood of having cirrhosis. These are in line with a recent systematic review and meta-analysis of 61 studies (94,636 patients) which corroborated these findings, and determined that NAFLD-HCC patients were more likely to have uninodular lesions and larger tumour diameters (6). However, this meta-analysis did not find a difference in Barcelona clinic liver cancer (BCLC) stage and overall survival between NAFLD-HCC and non-NAFLD HCC patients, although there were a limited number of included studies that described the comparative survival between etiologies of liver disease (6).

As NAFLD-related HCC patients are generally older

with more comorbidities, this may affect fitness for surgery and influence peri-operative outcomes. Geh and colleagues described how the data for short-term outcomes in NAFLD-related HCC patients who undergo surgical resection are variable, and NAFLD-HCC patients who undergo liver transplantation were found to be at increased risk of short-term complications. In contrast, long-term outcomes were comparable to those with HCC of other etiologies. A recent large meta-analysis determined that 1-year overall survival after surgical resection for HCC in general is high at 90%, although 5-year survival is substantially poorer at 55%, but there were limited data for NAFLD-related HCC (7). Another meta-analysis determined that surgical resection was associated with lower overall survival compared to liver transplantation, likely because liver transplant treats both the tumour and the surrounding cirrhotic micro-environment, but survival was similar between HCC patients with uninodular lesions who underwent surgical resection and liver transplantation (8,9). Patient selection, pre-operative planning and attention to peri-operative care are key to achieving good short and long-term surgical outcomes, and are even more important in the setting of NAFLD-related HCC where patients are more likely to be overweight or obese with multiple cardiovascular comorbidities (5,10,11).

A multi-pronged strategy is required to improve outcomes for patients with NAFLD-related HCC. There is an urgent need to improve HCC surveillance in

NAFLD individuals. Currently, as Geh and colleagues have highlighted, surveillance in NAFLD individuals is suboptimal—only 33% of NAFLD-HCC patients had HCC surveillance prior to diagnosis of HCC (6). There is no consensus on the best strategy for surveillance in NAFLD patients without cirrhosis. Geh and colleagues discuss how it is not cost-effective to conduct routine surveillance for all patients with NAFLD without cirrhosis, although some major society guidelines recommend HCC surveillance for NAFLD patients with cirrhosis or advanced fibrosis with ultrasound (US) with or without alpha-fetoprotein every 6 months (12). Further research needs to be done to develop risk models or risk scores to identify NAFLD patients at high risk of developing HCC for enrolment into surveillance programmes (13). In addition, limited visualization on US is associated with decreased sensitivity and higher likelihood of false negatives in HCC surveillance (14). Obesity, which is common among NAFLD individuals, is a well-known risk factor for limited visualization on US (15). A possible alternative imaging modality for HCC surveillance is abbreviated magnetic resonance imaging (aMRI), which has been shown in a recent prospective study to be superior to US for visualization in patients with NAFLD cirrhosis, especially those who are obese (16). More studies are required to evaluate the benefit of alternative imaging such as aMRI when US is deemed inadequate.

NAFLD-related HCC is now a global public health challenge. Understanding the unique characteristics and challenges of managing patients with NAFLD-related HCC are essential to the development of better strategies for early detection and treatment.

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