

NAFLD— which patients should have hepatocellular carcinoma surveillance?

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Studies linking non-alcoholic fatty liver disease (NAFLD), non-alcoholic steatohepatitis (NASH) and cryptogenic cirrhosis to the development of hepatocellular carcinoma (HCC) began to emerge 15 years ago (1,2). A number of large registry or cohort studies have subsequently confirmed these observations in the United States (3,4), Europe (5) and the Asia Pacific (6,7). The increasing prevalence of obesity worldwide underpins this global pattern of change, with the predicted higher prevalence of NAFLD in coming years a cause for major concern (8). The characteristics and natural history of HCC on the background of NAFLD are slowly emerging, as are concerns that HCC risk in some individuals with the metabolic syndrome may be independent of the presence of cirrhosis. Presently, HCC surveillance—with bi-annual ultrasound scan (USS)—is recommended in all patients with cirrhosis who are fit to treat (9). Extending this recommendation to NAFLD patients without cirrhosis would have major cost implications and would need careful consideration.

Recently, Piscaglia *et al.* have published their multicentre prospective observational study, characterising the clinical patterns of NAFLD associated HCC as compared to HCV-related HCC in secondary referral centres in Italy (10). Over a 3-year period, from January 2010 until December 2013, 756 patients diagnosed with HCC as per EASL-EORTC guidelines (9) were studied, including 145 patients with NAFLD associated HCC and 611 with HCV-

associated HCC. In summary, compared to HCV-HCC patients, the NAFLD-HCC patients in this multicentre cohort were younger (67.8 versus 71.1 years), were more likely to drink at least some alcohol (<30 g/L per day), were more likely to be male (79% versus 61%), and were significantly less likely to have cirrhosis (54% had cirrhosis versus 97%). As has been previously shown (5), patients with NAFLD associated HCC were more likely to present at an advanced tumour stage, attributed to lack of surveillance in patients with NAFLD compared to those with known HCV cirrhosis. Although survival was poorer in the NAFLD-HCC patients, after adjusting for factors known to be associated with survival in patients with HCC, this was confirmed consequent to later stage presentation rather than the underlying disease. The group concluded that greater efforts should be made ‘to identify patients with NAFLD who require more stringent surveillance in order to offer the most timely and effective treatment’. This is undoubtedly a major challenge that needs to be addressed, but some of the observations made by Piscaglia *et al.* were contradictory to those previously reported. These and the potential reasons for differences should be considered.

In other published cohorts, NAFLD-HCC tends to present at a more advanced age compared to HCV-HCC rather than an earlier one (4,5,11). In our own consecutive series of 628 patients with HCC in Northern England, where NAFLD is the commonest cause of HCC, the

median age for HCV-HCC was 60 years, compared to 71 for HCC-NAFLD (5). Similarly, in other series, NAFLD-HCC was not more common in men than HCV-related HCC—sex distribution between the two etiologies was similar, in the region of 79–80% in both etiologies. Alcohol intake in other reported cohorts was in fact commoner in HCV patients compared to NAFLD patients. Most importantly, in our own series HCC in the absence of cirrhosis was commoner than in other etiologies, but accounted for only 22.8% of cases (5) rather than 46%. So why these differences?

Firstly, it appears that there are differences in the HCV related HCC cases. In our own cohort, HCV most typically arose consequent to intravenous drug use, where co-existing alcohol consumption was also common. Metabolic risks, particularly type 2 diabetes, were also highly prevalent in our own HCV-HCC cases. These factors most likely account for some of the differences between the HCV-HCC cases in the different series, with a combination of synergistic factors accelerating the course to end stage liver disease and HCC, presenting typically in men at a younger age in the UK (5,11), as compared to Italy where HCV infection is traditionally regarded as nosocomial or healthcare related.

The frequency of HCC arising in the absence of cirrhosis in such a large proportion of the Italian patients is a particular concern, owing not only to the increasing morbidity and mortality, but also the cost implications of surveillance in this ever increasing at risk population with NAFLD. The average BMI in NAFLD-HCC was relatively low in the Italian series compared to our own (29 versus 32), with younger age at presentation—possibly hinting at a different course for NAFLD in Italy versus UK. Rather than supporting a more aggressive disease, however, the cases in Italy were generally less advanced at presentation. The Barcelona Clinic for Liver Cancer (BCLC) stage in NAFLD cases in the Italian centres was A–B in 62% of the cases, with a median overall survival of 25.5 months. In our own series only 30% were classed as A–B, with a median overall survival of 11.4 months. A genetic predisposition to NAFLD progression is well recognised and there may well be differences in disease biology when comparing patients with different genetic and environmental backgrounds. It may be, however, that the Italian cases simply presented at an earlier stage in the course of their disease. It is also possible that there was selection bias in the Italian series, with only those fit enough to be considered for treatment referred to secondary centres, i.e., the younger and fitter

Italians with relatively preserved liver function were referred to the centres. Typically, those with preserved liver function would be patients without cirrhosis. This potential bias was not present in our own series, where referral to a specialist multidisciplinary team was mandatory irrespective of stage or treatment opportunity.

Regardless of the differences in the characteristics of NAFLD-HCC patients between different cohorts and case series, the biology of which will most likely emerge with continued research, some features are consistent and not in any doubt. NAFLD-HCC patients—even those with cirrhosis—are less likely to be in surveillance programmes. They are more likely to present with more advanced HCC. Consequently, they are less likely to be fit for therapy and their survival from the time of presentation is relatively poor.

The major challenge, as pointed out by Piscaglia *et al.*, is how to identify the patients who need surveillance, in order to detect cancers at an earlier stage. Our own series indicate that cirrhosis remains the single most important risk factor predicting HCC development. In prospective series in patients with metabolic risk factors, the incidence or risk to an individual of either cirrhosis or HCC is actually very small (12). The incidence of HCC in the presence of simple steatosis is not well defined, but is rare and possibly coincidental (13). Given the huge numbers of patients globally with metabolic risks, an effective test would have to be extremely cheap and minimally invasive—e.g., a blood test at the time of annual diabetic review—given the cost implications and potential harm caused by screening (14). As so many NAFLD-HCC patients present synchronously with NASH cirrhosis and cancer, the major focus presently should be on identifying those patients with the most significant disease, i.e., those who have NASH, NASH with fibrosis, and NASH cirrhosis. These are the patients most at risk. Prospective follow-up studies, as are ongoing in Europe as part of the FLIP, EPOS and LITMUS consortia, will hopefully identify factors that further stratify HCC risk, potentially in addition to sex, BMI, age and polymorphisms such as PNPLA3 (15), facilitating the development of risk scores to guide future surveillance strategies.

Piscaglia *et al.* also refer, however, to the need for ‘more stringent’ surveillance in those at risk—alluding to the fact that even for known individuals at risk, abdominal USS is user dependent with relatively poor sensitivity and specificity in obese individuals. Again, it is the collaborative prospective studies that are ongoing that will hopefully transform the future of surveillance, with cost effective serum based tests.

Until we have validated tools to stratify risk, as well as sensitive and cost effective surveillance tests suited to these patients, we propose that only NAFLD patients who have either advanced fibrosis or cirrhosis should be offered surveillance, as per current guidelines (9).

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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