Editorial

Is there a real survival benefit of surveillance for hepatocellular carcinoma in cirrhotic patients?

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Surveillance with abdominal ultrasound (US) of patients with chronic liver disease who are at risk of developing a hepatocellular carcinoma (HCC), has progressively emerged as a consolidated practice for achieving early diagnosis and improving treatment of liver cancer, despite the lack of robust evidence-based data. Surveillance is recommended by the international societies from both hemispheres (1-3), where however recommendations from Far East voice some nuances with respect to the need for adding serum alfa fetoprotein (AFP) to US and of adopting accelerated intervals of screening for patients at very high risk of HCC, like those with viral hepatitis and multiple co-morbidities. A recent meta-analysis form the US confirms indeed a benefit in adding serum AFP to US (4). In the western world, a 6-month interval is considered more than adequate for screening patients with compensated cirrhosis of any aetiology, as several meta-analyses have reported appreciable survival benefits in those patients who had a small tumor detected with US surveillance that ultimately could access curative treatment with liver transplantation, hepatic resection or local ablation (5,6).

This notwithstanding, the argument of cost effectiveness of US screening in patients with cirrhosis has repeatedly come across the community of hepatologists, gaining special attention in the USA where HCC is the most rapidly growing cause of cancer death. In that country, the uptake of surveillance unfortunately is globally suboptimal when compared to Europe and Far East, and, importantly, both uptake and effectiveness of screening are further challenged by the growing role of HCC associated to the epidemic of overweight and metabolic syndrome, two conditions that limit the application and diagnostic accuracy of abdominal US. Last but not least, while the European Association for the Study of the Liver recommends that US surveillance of patients with cirrhosis should be carried out by expert personals only, questions have been raised about the consolidated practice in the USA to have US screening of patients with liver disease performed by technicians, only.

While all these facts challenge cost-effectiveness of US surveillance of patients with cirrhosis, in the USA the controversy has recently been fueled by a study reporting a high rate (25%) of false positive or indeterminate results of screening with US and AFP causing the harm of additional investigations that obscured the clinical benefits of surveillance. Noticeably, in that study non-guideline concordant management of indeterminate US results accounted for nearly one third of cases with this pattern of surveillance-related downstream harm (7). While this study clearly pinpointed the need for optimizing the procedures of surveillance in cirrhosis without questioning its benefits, the retrospective study by Moon and associates recently published in Gastroenterology, seems to blow at the heart US surveillance in cirrhosis, as it in fact questions the ability of screening to prevent cancer related mortality in this patient population. In a case-control study conducted in the US Veterans Affairs (VA) hospitals, 238 patients with cirrhosis who died of HCC between 2013 and 2015 and had been in VA care with a diagnosis of cirrhosis for at least

4 years before the diagnosis of liver cancer, were matched for relevant demographic and clinical features to 238 patients with cirrhosis who did not die of HCC and had been in VA care for a similar length of time as cases. Per protocol, all patients had to have a MELD score less than 20 to comply with AASLD recommendations for screening, whereas, as expected for the VA population, index cases and controls (all males) were burdened by such co-morbidities as overweight, diabetes, hypertension not to speak of alcohol use disorders that were ascertained in 48% and 61% of the participants, respectively. Not surprisingly, therefore, most patients with a potentially curable tumour that was detected during screening (71% <5 cm in size and 51% within Milan criteria), ultimately did not access any radical treatment: 2.1% were treated with resection only, 13% with radio frequency ablation and none received liver transplantation. Conversely, in half of the HCC population tumour disease was palliated with a variety of procedures, most frequently trans arterial chemo-embolization (42%) known to provide marginal survival benefits, only. After adjusting for demographic and clinical confounders, no significant differences could be found between cases and controls in the proportions of patients who underwent screening with US alone (52.9% *vs.* 54.2%), AFP alone (74.8% *vs.* 73.5%), US plus AFP (81.1% *vs.* 79.4%), or US and AFP (46.6% *vs.* 48.3%) within 4 years before the index date, a finding that suggested lack of survival benefits for patients undertaking surveillance.

To reconcile the negative findings of this study with dozens of cohort studies which instead did report survival benefits of US surveillance in cirrhotic patients, the authors advocated the importance of the case control design of their study that was meant to neutralize both lead-time and length-time biases thought to account for the survival benefits observed in previous cohort studies of surveillance. While this is a well taken point, we still believe that the pros of the design of the VA study were completely obscured by the role that frequently occurring severe co-morbidities had in preventing patients with a potentially curable tumour from accessing radical therapies, making therefore the peculiar demography of the VA population an additional risk factor of mortality of the HCC cohort. While the authors acknowledge that it would be useful to replicate this case-control study in a different health care system whose records would allow to minimize the risk of misclassification of tests done for screening versus those undertaken for diagnostic purposes, we strongly believe that such an accurate and scientifically sound study protocol has just been applied to the wrong test population, such as patients in the VA hospitals where co-morbidities worked against linkage to care. While a case-control study targeting general population is likely to offer more insights into screening effectiveness, it is worth reminding that in populations that for various reasons cannot access curative treatments of HCC, primary prevention is the only realistic option to abate cancer mortality therefore being likely more effective than secondary prevention with screening, as shown by the recent reports of massive reduction of all-cause mortality in veterans who successfully eradicated hepatitis C virus infection with direct acting antiviral agents (8).

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Footnote

Conflicts of Interest: Prof. Colombo has served in Advisory committees for Merck, Roche, Novartis, Bayer, BMS, Gilead Sciences, Tibotec, Vertex, Janssen Cilag, Achillion, Lundbeck, GSK, GenSpera, AbbVie, Alfa Wasserman, Intercept. Speaking and teaching: Tibotec, Roche, Novartis, Bayer, BMS, Gilead Sciences, Vertex, Merck, Janssen, AbbVie. Dr. Lleo has served as a speaker for Abbvie, BMS, Gilead, and Intercept.

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