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Is the American Association for the Study of Liver Diseases recommendation for hepatocellular carcinoma screening a cul-de-sac?

Braillon A. Hepatocellular carcinoma screening of AASLD

Alain Braillon

**Alain Braillon,** Public Health, Northern Hospital, 80000 Amiens, France

**Author contributions:** Braillon A solely contributed to this paper.

**Correspondence to: Alain Braillon, MD, PhD,** Public Health, Northern Hospital, 27 rue Voiture, 80000 Amiens, France.braillon.alain@gmail.com

**Telephone:** +33-3-22668883 **Fax:** +33-3-22668955

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**Abstract**

The American Association for the Study of Liver Diseases just confirmed a grade I recommendation for hepatocellular carcinoma (HCC) screening despite a growing controversy. Why should HCC be an exception from the long list of other cancers where the feasibility and the efficacy of screening were investigated by randomized trials? Only 12.0% of US patients are screened, a fact that preclude efficacy, as one has relevant figures to about the benefit risk ratio. Ethics of belief is treacherous reef. Screening is not performing a test, it is a public health issue: a national program is needed to ensure a minimal participation, quality controls and evaluation of the results for improving the process. Last, there are serious concerns with undisclosed potential conflicts of interest.

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**Key words:** Hepatocellular carcinoma; Screening; Public health

**Core tip:** Why should hepatocellular carcinoma be an exception from the long list of other cancers where the feasibility and the efficacy of screening were investigated by randomized trials? Ethics of belief is treacherous reef. Screening is not performing a test, it is a public health issue: a national program is needed to ensure a minimal participation, quality controls and evaluation of the results for improving the process.

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**TO THE EDITOR**

A recent editorial from the American Association for the Study of Liver Diseases (AASLD) Practice Guidelines Committee on hepatocellular carcinoma (HCC) screening deserves comments[1].

It is a recommendation for HCC screening, maintaining a grade I (best evidence from randomized trials) despite it should have been downgraded III (experts statement) considering rising controversies[2,3]. Indeed, only two randomized trials are available, both from China, one is negative, the other is positive but has several major flaws[2]. From developed countries, only observational studies are available, concluding that screening improve survival despite raw data consistently show that screened patients die younger than nonscreened patients (length time and lead time biases) [3,4]!

This is not a Byzantine comment on Evidence Medicine: this highest grade to a recommendation with flawed evidence blocks advances, is counterproductive and breaches patients’ rights.

The grade I level blocks further advances as randomized controlled trial (RCT) are no longer acceptable. Moreover, the recommendation tries to justify why a randomized controlled trial (RCT) is not feasible. Among others arguments it cites an Australian survey showing that 90% of patients would refuse participation in a RCT, preferring to undergo screening (see 29 in 1). This did not provide evidence that a trial is not possible, it only showed that the patients did not received balanced and unbiased information about screening. Randomized controlled trial are always difficult, however why should HCC be an exception from the long list of other cancers where the feasibility and the efficacy of screening were investigated by randomized trials? For example,French and US urologists, whose associations strongly promoted prostate cancer screening since long, did not hesistated to recruit patients for large multi-national trials. Everyone must support the trial recently submitted to the VA Cooperative Studies Program.

The maintenance of the grade I level cannot mask that the recommendation is not implemented. Only 12.0% of US patients are screened, a fact that preclude any efficacy[5]. Indeed, no one has relevant figures to trust screening and to inform patients about the benefit risk ratio, a pre-request for compliance. The benefit may be very limited, *e.g.*, 5-year HCC risk is 1.9% in patients with alcoholic cirrhosis[6]. Regarding harm, overdiagnosis is the inevitable trade-off involved with early cancer detection. Cancer overdiagnosis means that some cancers never progresses or progresses slowly enough that the patient dies of other causes before symptoms. Such patients, as patients with false-positive results, cannot benefit from diagnostic procedures and unnecessary treatments, they can only be harmed by them[7]. The magnitude of overdiagnosis can be estimated to about 25% of mamographically detected breast cancers and 60% of prostate-specific antigen–detected prostate cancers[7]. No data is available for HCC screening and stating that “the risk of this is felt to be small” is not the best way to reassure[1]. Moreover, both European Association for the Study of the Liver and AASLD noninvasive recall strategies for nodules of 10-30 mm in the cirrhotic liver, based on the vascular pattern, have a false-negative rate of approximately 20%[8]. Ultrasound screening is far from a simple a non invasive procedure because at the next step findings are frequently discordant on both computed tomography and magnetic resonance imaging, supporting the place of biopsy for the diagnosis of small HCCs[9,10].

Ethics of belief is treacherous reef when practicing at bedside, here it is also a dead end without hope for improvement and progress. Screening is not performing a blood test or a radiological exam, it is a complex issue which beyond the scope of any clinical disciplines. It is a public health issue: a national program is needed to ensure a minimal participation, quality controls (even more mandatory here as the algorithms are complex for recall strategies), and evaluation of the results for improving the process. Moreover, although on the rise, HCC is only the ninth leading cause of cancer deaths in the United States and has to compete with other priorities in a cost constrained economy[11].

# Last, the emptiness of the conflict of interest section is puzzling[1]. It contrasts with a previous one where both authors of the recommendation stated they served on the speaker's bureau of Bayer[12]. Bayer markets sorafenib, the $5000/month drug for advanced HCC, which is now investigated for the prevention of recurrence of early HCC after local ablation (NCT01126645). Early HCC could be a huge market for Bayer. Moreover AASLD which edits Hepatology receives grants from Bayer for its practice guidelines program and Bayer also held three different booth spaces during the last AASLD meeting.(see <http://www.aasld.org/practiceguidelines/Pages/ArchivePracticeGuidelines.aspx> and <http://www.aasld.org/lm2012/2012/exhibits/Pages/currentexhibitors.aspx>)

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