

References

Author names in bold designate shared co-first authorship

[1] **Serenari M, Han K-H**, Ravaoli F, Kim S-U, Cucchetti A, Han D-H, et al. A nomogram based on liver stiffness predicts postoperative complications in patients with hepatocellular carcinoma. *J Hepatol* 2020;73:855–862.

[2] Bureau C, Metivier S, Peron JM, Selves J, Robic MA, Gourraud PA, et al. Transient elastography accurately predicts presence of significant portal hypertension in patients with chronic liver disease. *Aliment Pharmacol Ther* 2008;27:1261–1268.

[3] Serenari M, Cescon M, Cucchetti A, Pinna AD. Liver function impairment in liver transplantation and after extended hepatectomy. *World J Gastroenterol* 2013;19:7922–7929.

[4] Serenari M, Pettinato C, Bonatti C, Zanoni L, Odaldi F, Cucchetti A, et al. Hepatobiliary scintigraphy in the preoperative evaluation of potential living liver donors. *Transplant Proc* 2018;51:167–170.

[5] Iimuro Y, Kashiwagi T, Yamanaka J, Hirano T, Saito S, Sugimoto T, et al. Preoperative estimation of asialoglycoprotein receptor expression in the remnant liver from CT/99mTc-GSA SPECT fusion images correlates well with postoperative liver function parameters. *J Hepatobiliary Pancreat Sci* 2010;17:673–681.

[6] de Graaf W, van Lienden KP, van Gulik TM, Bennink RJ. 99mTc-mebrofenin hepatobiliary scintigraphy with SPECT for the assessment of hepatic function and liver functional volume before partial hepatectomy. *J Nucl Med* 2010;51:229–236.

[7] Rassam F, Olthof PB, Takkenberg BR, Beuers U, Klumpen HJ, Bennink RJ, et al. Scintigraphic liver function and transient elastography in the

assessment of patients with resectable hepatocellular carcinoma. *HPB (Oxford)* 2019;21:626–635.

[8] Ravaoli F, Conti F, Brillanti S, Andreone P, Mazzella G, Buonfiglioli F, et al. Hepatocellular carcinoma risk assessment by the measurement of liver stiffness variations in HCV cirrhotics treated with direct acting antivirals. *Dig Liver Dis* 2018;50:573–579.

Matteo Serenari¹
 Federico Ravaoli²
 Alessandro Cucchetti¹
 Seung-Up Kim^{3,4}
 Matteo Cescon^{1,*}

¹Department of Medical and Surgical Sciences, General Surgery and Transplantation Unit, University of Bologna, Italy
²Department of Medical and Surgical Sciences, Gastroenterology Unit, University of Bologna, Italy
³Department of Internal Medicine, Yonsei University College of Medicine, Seoul, Korea
⁴Yonsei Liver Centre, Severance Hospital, Seoul, Korea
 *Corresponding author. Address: General Surgery and Transplant Unit, Department of Medical and Surgical Sciences, University of Bologna, Policlinico Sant’Orsola-Malpighi, Via Massarenti, 9, 40138 – Bologna, Italy. Tel.: +39 51 2143108 or + 39 51 2144785; fax: + 39 51 304902.
 E-mail address: matteo.cescon@unibo.it (M. Cescon)



Challenges associated with the roll-out of HCC surveillance in sub-Saharan Africa - the case of Uganda

To the Editor:

In their recent review article, Singal and coworkers describe the challenges associated with surveillance for hepatocellular carcinoma (HCC) and propose interventions to increase the effectiveness of surveillance.¹ We agree with the authors that improved uptake of screening and performance of HCC surveillance should be considered a high priority in Western countries.¹

In sub-Saharan Africa, where HBV infections are the main cause of HCC, surveillance programs are mostly not available.² Nonetheless, with an incidence rate of 8.9 cases per 100,000 inhabitants per year, which is likely to be an underestimate, HCC surveillance is a pressing medical need in this part of the world.^{2,3} The recent introduction of country-wide vaccination programs in these countries will likely result in a drop in HCC incidence a few decades from now, but this does not apply to patients that are currently infected.⁴ In a recent African cohort of 1,315 hepatocellular tumors, 84% of the tumors were diagnosed at a late, multifocal disease stage with a mean size of 8 ± 4 cm and a median survival of 2.5 months.² Given the strong association between early detection and improved survival, these findings highlight the need to set up surveillance

programs in sub-Saharan Africa, provided curative treatment options are available.¹

We have recently launched such a program in Uganda, where HCC is one of the most common malignancies. Age-standardized incidence rates of 6.5/100,000 in men and 6.0/100,000 in women have been reported. Unfortunately, its mortality rate almost mirrors its incidence.^{2,5–7}

Following a kick-off meeting in Kampala in August 2019 where representatives from the radiology and internal medicine departments of 5 Ugandan, tertiary care hospitals were present, a questionnaire was launched among the participants to identify gaps that needed bridging in order to set up an HCC surveillance program. Participants were asked about the number of patients with HBV and HCC in their centers, the availability of alpha-fetoprotein and ultrasound testing, as well as the available manpower to perform ultrasound. A summary of the findings is displayed in [Table 1](#).

None of the centers had an HCC surveillance program in place. However, outpatient HBV clinics are available in 3/5 centers and planned in the fourth. The estimated number of patients frequenting these HBV clinics varies between <100 and 500–1,000. Given a nationwide HBsAg seroprevalence of 10% in Uganda, these varying numbers might point to the regional differences in HBV-infected patients, but they may also point to variations in linkage to care.⁸ Ultrasound machines are widely available in all centers and except for 2, all were manufactured within the last

Received 8 May 2020; received in revised form 25 May 2020; accepted 28 May 2020; available online 14 August 2020
<https://doi.org/10.1016/j.jhep.2020.05.045>

Table 1. Overview of the results obtained from the questionnaires.

| | Center 1 | Center 2 | Center 3 | Center 4 | Center 5 |
|--|-------------------------------------|--|--|--|-------------------------------------|
| HBV clinic | Available | Not available | Available | Available | Foreseen for the future |
| HBV patients attending the HBV clinic | <100 (estimation) | Not available | 500-1,000 (estimation) | 100-500 (estimation) | 100-500 (estimation) |
| US equipment | Available | Available | Available | Available | Available |
| Number of machines | 3 | 5 | 3 | 3 | 1 |
| Year of production | All 2016 | 2010, 2012, 2014, 2014 and 2016 | All 2016 | 2012, 2015, 2007 | 2005 |
| Number of staff at the radiology department: | 1 | 31 | 39 | 12 | 3 |
| Staff trained to perform US | 1 | 22 | 39 | 10 | 3 |
| Training of US personnel | Theoretical + Hands-on: single time | Theoretical + Hands-on: with regular post-graduate updates | Theoretical + Hands-on: with regular post-graduate updates | Theoretical + Hands-on: with regular post-graduate updates | Theoretical + Hands-on: single time |
| AFP testing | Available | Available | Not always available (depending on reagent supply) | Not available | Not available |
| Number of HCC diagnoses | Not available | Not available | 1-3/week (estimation) | 1-3/month (estimation) | 120 cases in 2019 |
| Diagnosis of HCC based on | Clinical signs, AFP and ultrasound | Clinical signs, AFP and ultrasound | Clinical signs and ultrasound | Clinical signs and ultrasound | Clinical signs and ultrasound |
| Treatment for HCC | Not available | Not available | Hepatic resection available | Not available | Not available |

AFP, alpha-fetoprotein; HCC, hepatocellular carcinoma; US, ultrasound.

decade (Table 1). The number of staff trained to perform ultrasound largely varies between centers, ranging between 1 and 39, but corresponds to a coverage of 87% for the total number of medical staff at the radiology departments (radiologists/radiographers). Regular post-graduate training for ultrasound staff is provided in 3/5 centers. AFP testing is available in 2 centers; in a third center testing is offered based on reagent availability. A registry of the number of HCC cases is available in 1 center, though survival data are not systematically recorded.

Diagnosis of HCC is based on clinical signs, such as a palpable liver mass or liver lesions on ultrasound in patients with clinical deterioration and not identified during screening of patients at risk. Liver surgery for non-advanced HCC is available in 1 center.

Our survey highlights the feasibility of rolling out an HCC surveillance program in Uganda, as manpower, US equipment and treatment options are available. Further investment should aim at establishing HBV clinics with optimal linkage to care and broadening HCC treatment capacities. Our findings may guide other groups aiming to roll out surveillance programs in different countries.

Financial support

This study was funded by a Global Minds Initiative of the University of Antwerp.

Conflict of interest

The authors declare no conflict of interest.

Please refer to the accompanying ICMJE disclosure forms for further details.

Authors' contributions

SVH, TV and PO designed the study. WM, GE, AP, PO, ES and MO provided data. SVH, TVW and PM drafted the manuscript. All authors critically reviewed and approved the manuscript in its final form.

Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.jhep.2020.05.045>.

References

- [1] Singal AG, Lampertico P, Nahon P. Epidemiology and surveillance for hepatocellular carcinoma: new trends. *J Hepatol* 2020;72:250–261.
- [2] Yang JD, Mohamed EA, Aziz AO, Shousha HI, Hashem MB, Nabeel MM, et al. Characteristics, management, and outcomes of patients with hepatocellular carcinoma in Africa: a multicountry observational study from the Africa Liver Cancer Consortium. *Lancet Gastroenterol Hepatol* 2017;2: 103–111.
- [3] Sartorius K, Sartorius B, Aldous C, Govender PS, Madiba TE. Global and country underestimation of hepatocellular carcinoma (HCC) in 2012 and its implications. *Cancer Epidemiol* 2015;39:284–290.
- [4] Chang M-H, You S-L, Chen C-J, Liu C-J, Lee C-M, Lin S-M, et al. Decreased incidence of hepatocellular carcinoma in hepatitis B vaccinees: a 20-year follow-up study. *J Natl Cancer Inst* 2009;101:1348–1355.
- [5] Wabinga HR, Namboozee S, Amulen PM, Okello C, Mbus L, Parkin DM. Trends in the incidence of cancer in Kampala, Uganda 1991–2010. *Int J Cancer* 2014;135:432–439.
- [6] Wabinga HR, Parkin DM, Wabwire-Mangen F, Namboozee S. Trends in cancer incidence in Kyadondo county, Uganda, 1960–1997. *Br J Cancer* 2000;82:1585–1592.
- [7] Gondos A, Brenner H, Wabinga H, Parkin DM. Cancer survival in Kampala, Uganda. *Br J Cancer* 2005;92:1808–1812.
- [8] Bwogi J, Braka F, Makumbi I, Mishra V, Bakamutumaho B, Nanyunja M, et al. Hepatitis B infection is highly endemic in Uganda: findings from a national serosurvey. *Afr Health Sci* 2009;9:98–108.

Stijn Van Hees^{1,2}
 Winnie Muyindike³
 Geoffrey Erem^{4,5}
 Ponsianoo Ocama⁵
 Emmanuel Seremba⁵
 Apiyo Paska⁶
 Peter Michielsen^{1,2}
 Mark Okwir⁷
 Thomas Vanwolleghem^{1,2,*}

¹Department of Gastroenterology and Hepatology, Antwerp University Hospital, Antwerp, Belgium

²Laboratory of Experimental Medicine and Pediatrics, University of Antwerp, Belgium

³Department of Internal Medicine, Mbarara Regional Referral Hospital, Mbarara, Uganda

⁴Department of Radiology, Nsambya Hospital, Kampala, Uganda

⁵Makerere University School of Medicine, Kampala, Uganda

⁶Department of Internal Medicine, Gulu Regional Referral Hospital, Gulu, Uganda

⁷Department of Internal Medicine, Lira University Faculty of Health, Lira, Uganda

*Corresponding author. Address: Antwerp University Hospital, Department of Gastroenterology and Hepatology, Wilrijkstraat 10, 2650 Edegem, Belgium. Tel.: +32 3 281 38 53. E-mail address: thomas.vanwollegghem@uza.be (T. Vanwollegghem)



Reply to: “Challenges associated with the roll-out of HCC surveillance in sub-Saharan Africa – the case of Uganda”

To the Editor:

We read with great interest the letter from Dr. Van Hees and colleagues describing the current status and challenges of hepatocellular carcinoma (HCC) surveillance in resource-limited areas, including parts of sub-Saharan Africa.¹ We commend our colleagues for initiating these important efforts, particularly given the continued high burden of HCC in these areas.

In their survey of HCC surveillance capacity in Ugandan institutions, the authors found each had ultrasound availability, with most having multiple ultrasound machines and trained personnel. Although this availability provides a foundation for HCC surveillance programs, data from the Western world have highlighted that this is essential but not sufficient, with continued underuse of surveillance in clinical practice.² In addition to providers reporting competing clinical concerns, patient-reported barriers such as transportation and costs are associated with lower surveillance receipt.³ These patient- and provider-level barriers may be even more prevalent in resource-limited countries and would need to be aggressively addressed. Interventions such as reminder systems for providers and population health strategies for patients can significantly increase HCC surveillance receipt but have not been evaluated in routine clinical practice or resource-limited settings.² Although advances in surveillance biomarkers offer promise for improved effectiveness of early detection efforts, studies will be needed to assess their effectiveness in areas such as sub-Saharan Africa as only 2 of the 5 centers had consistent access to AFP testing.

Surveillance fits in a larger screening context and mortality reduction is dependent on timely follow-up of abnormal screening results and treatment of detected HCC lesions. A large study encompassing 1,315 patients from 8 African countries excluding Egypt demonstrated less than 3% of patients received any HCC specific treatment,⁴ regardless of their eligibility for curative procedures. This finding reflects that implementation of HCC surveillance programs in sub-Saharan Africa will not be successful if not conducted in parallel with improvement in access to HCC treatment. Challenges to HCC treatment in this region include a shortage of dedicated physicians as well as

training programs to develop specific skills such as liver surgery or interventional radiology.⁵ Weak healthcare infrastructure and inadequate supplies also strongly limit the implementation of sophisticated technological platforms, which are mandatory to achieve complex curative procedures such as surgical resection or percutaneous ablation.⁶ Nevertheless, the development of national cancer programs defining new frameworks of cancer care have been shown to be feasible and effective in some sub-Saharan African countries such as Rwanda.⁷ Hopefully, as reported by Van Hees *et al.*,¹ Uganda is following the same path by integrating both improvement of early HCC detection and increased access to care delivery: indeed, 1 out of 5 facilities specialized in HCC management is able to provide liver resection, which is key to translating recent surveillance efforts into a survival benefit. Moreover, the substantial number of personnel dedicated to ultrasound exploration in 3 out of 5 centers could also foretell the development of expertise in percutaneous approaches aimed at broadening the spectrum of curative options in the future.

Finally, continued emphasis should also be placed on HCC prevention efforts, as this is the most cost-effective means of reducing HCC-related mortality. Given chronic HBV accounts for most HCC cases in Africa, the role of HBV vaccination and anti-HBV treatment programs cannot be overstated. Data from Taiwan demonstrate the effectiveness of HBV vaccination programs to significantly reduce HCC incidence, but this simple measure continues to be underused in many African countries.⁸ Similarly, long-term administration of potent nucleos(t)ide analogues such as entecavir and tenofovir improves survival by preventing the progression to cirrhosis, improving portal hypertension and reducing by approximately 50% the risk of HCC, compared to untreated individuals.⁹ Traditional barriers such as costs are increasingly being addressed, as anti-HBV medicines are now available at affordable prices, as are standard diagnostics for treatment monitoring. These data highlight the need to implement anti-HBV therapy in countries where the toll of HBV-related deaths is very high. As the natural history of HBV in Africa differs from that reported in other areas including Europe, treatment eligibility criteria should be expanded and simplified. New treatment strategies aimed to deliver functional cure, *i.e.* HBsAg loss, by a finite treatment course might further scale up

Received 25 June 2020; accepted 1 July 2020; available online 13 August 2020
<https://doi.org/10.1016/j.jhep.2020.07.003>