

# Improving hepatocellular carcinoma surveillance in the United Kingdom: challenges and solutions

Maria Qurashi and Rohini Sharma\*

Department of Surgery & Cancer, Imperial College London, Hammersmith Hospital, Du Cane Road, London W12 0HS, UK



## Summary

Hepatocellular carcinoma (HCC) prognosis remains dismal due to late-stage diagnosis; surveillance has been demonstrated to increase early diagnosis rates and receipt of curative treatment. Acknowledging limitations in the evidence base for HCC surveillance, international professional bodies reiterate the recommendation for biannual HCC surveillance and NHS England supports measures aimed to increase surveillance uptake. The current ad hoc provision of HCC surveillance is prone to failures, evident by low surveillance uptake and high numbers of patients being diagnosed outside of surveillance. We discuss challenges related to HCC surveillance in the UK and potential solutions to addressing them. We highlight the requirements of a consistent and effective national surveillance process, and suggest pathways on how this can be achieved.

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## Introduction

Hepatocellular carcinoma (HCC) is the third leading cause of cancer-related death worldwide and unlike other cancer types, incidence and mortality rates continue to rise.<sup>1</sup> In the UK, mortality rates have tripled in the last 50 years and are projected to increase further in the next two decades.<sup>2</sup> The vast majority of HCC cases occur on a background of chronic liver disease (CLD) and its sequela, cirrhosis.<sup>3</sup> The annual risk of HCC in patients with cirrhosis ranges from 2 to 6%.<sup>3</sup>

The UK has the worst outcomes of hepatobiliary cancers amongst high-income countries.<sup>4</sup> Curative therapies for HCC, including resection or transplant, offer patients 5-year survival rates as high as 85%.<sup>3,5</sup> However, less than 20% of patients receive curative therapies, with the large majority presenting with late-stage malignancy or advanced liver disease precluding aggressive treatment. Late presentation of HCC is attributable to several factors, including a lack of regular cancer surveillance, and diagnostic and treatment delays.<sup>6,7</sup> Late-stage HCC carries a dismal prognosis, with 5-year survival <20%. Additionally, late presentation is associated with poor quality of life and more frequent hospital admissions, leading to significant economic impact on the NHS.<sup>8</sup>

The principle of targeted cancer surveillance is to repeatedly test asymptomatic individuals who are at risk of developing a disease, based on the premise that

detection of cancer at an early stage allows the receipt of curative therapy improving survival outcomes. Ninety per cent of HCC cases arise on a background of chronic liver disease, thus there is an “at risk” population suitable for surveillance. The ideal surveillance test should be minimally invasive, affordable, acceptable to patients and with a high sensitivity and specificity.<sup>9</sup>

The evidence base for HCC surveillance is drawn largely from a single randomised controlled trial in China,<sup>10</sup> assessing mortality in patients with hepatitis B. It demonstrated that 6-monthly ultrasound of the liver ± serum alpha-fetoprotein measurement reduced HCC-related mortality by 37%. Subsequent retrospective<sup>11</sup> and modelling studies<sup>12–14</sup> have concluded that HCC surveillance improves survival through early diagnosis and receipt of curative treatment. Consequently, biannual surveillance for HCC for patients with cirrhosis is recommended by all international professional bodies and NICE,<sup>3</sup> with compliance with biannual surveillance being associated with early diagnosis and improved survival outcomes.<sup>15</sup>

There are notable criticisms of the current evidence base for surveillance. Concerns have been raised about whether the effect size seen in a group of largely non-cirrhotic hepatitis B carriers can be generalised to populations with established cirrhosis, who may be less likely to tolerate and benefit from any HCC treatment offered.<sup>12</sup> A reduction in risk of HCC-related mortality may be of limited real-world benefit in patients with advanced liver disease facing multiple competing causes of death a particular issue in patients with NAFLD where cardiovascular disease is key cause of the death. Further randomised controlled trials have been

\*Corresponding author. Medical Oncology and Clinical Pharmacology, Imperial College London, Hammersmith Campus, Du Cane Road, London W12 0NN, UK.

E-mail address: [r.sharma@imperial.ac.uk](mailto:r.sharma@imperial.ac.uk) (R. Sharma).

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considered unfeasible or unethical, and novel data on surveillance benefits is largely drawn from modelling.

The modality of surveillance also draws criticism: ultrasound is operator-dependant and has poor sensitivity (47%, 95% CI: 33–61%) for early HCC, which is reduced further in patients with increased adiposity or advanced cirrhosis.<sup>13</sup> Twenty per cent of surveillance ultrasounds are considered inadequate to visualise the liver, a particular concern given the rising incidence of obesity related liver disease.<sup>14</sup> In cases with poor ultrasound visibility, European and American guidelines advise that CT or MRI could be utilised.<sup>3,5</sup>

However, it is recognised that the use of cross-sectional imaging is likely to be limited by expense, cumulative gadolinium and radiation risk. Additionally, there is a paucity of research on the harms of surveillance, including unnecessary radiation exposure and biopsies in false positives, and psychological distress in patients undergoing testing. Alternatives such as abbreviated MRI where limited sequences are used with or without contrast are being investigated in this population group and are gaining traction as possible alternate to ultrasound particularly in high risk groups.

Given the burgeoning numbers of patients with CLD, driven by high rates of obesity, risk models are being extensively investigated, whereby patients deemed at low risk of developing HCC may be discharged from a surveillance and high-risk patients may undergo more sensitive imaging with MRI. Modelling has illustrated that application of risk models would improve resource allocation and patient outcome.<sup>16</sup> There are a number of risk stratification tools under investigation, including aMAP and PAGE-B, and it is likely that the integration of these models for patient selection will be used in the future, ideally a single risk score across multiple aetiologies that utilises routinely collected patient data such as aMAP or GALAD but this remains to be determined.

Despite controversies, HCC surveillance continues to be recommended by all professional bodies, as the alternative (late-stage diagnosis) is universally fatal. However, there is under-utilisation of surveillance worldwide, especially in the UK and USA, where surveillance uptake is estimated to be less than 25%.<sup>17</sup> There is no formalised national HCC surveillance programme in the UK nor in most European countries, with surveillance currently provided on an ad hoc basis.<sup>18</sup> The lack of a formal surveillance programme means that patients are often not invited to regular appointments, contributing to late-stage diagnosis.<sup>6,19</sup> The NHS England Early Diagnosis Cancer Programme aims to diagnose 75% of cancers at a curative stage, with HCC being a priority area.<sup>20</sup> There is a clear need to develop and establish a robust, sustainable HCC surveillance programme for ready adoption by the Department of Health and Social Care, UK to improve cancer outcomes.

## Current challenges

HCC surveillance is recognised to be a complex, multistep process with several points of failure.<sup>21</sup> It relies on:

1. Recognition of individual risk and suitability for surveillance.
2. A suitable surveillance tool with high sensitivity for small HCCs.
3. Ability of healthcare professional to schedule and follow-up scan results.
4. Capacity of radiology departments.
5. Patient knowledge and engagement.

## Proposed solutions

### Identify the scale of the problem

The true numbers of patients with CLD and cirrhosis in the community are not known. It is estimated that 60,000 people in the UK have cirrhosis but it is possible the numbers are significantly larger, as most cases are diagnosed at a late stage.<sup>2</sup> A major step forward is NHSEs Liver Health Check program which utilises existing operational delivery networks to deliver community fibroscans to screen people identified by their GP as high risk of CLD. This is in addition to the launch of initiatives in primary care using FIB-4 and ELF testing to identify individuals at risk of cirrhosis.<sup>22</sup> The program will allow the identification of previously undiagnosed individuals with CLD within the community. “High-risk” patients, as defined by a Fibroscan score greater than 11.5kpa, are then referred to secondary care for ongoing specialist management and HCC surveillance. However, it is key that the additional patients with cirrhosis identified through community case finding are entered into a robust surveillance programme.

Most UK hospital trusts do not have a record of patients who are eligible for HCC surveillance. We propose the establishment of a national database of all patients with CLD at risk of HCC who have been identified both through community surveillance and through secondary care via International Classification of Diseases (ICD) coding. This will be a crucial first step in ensuring that surveillance is offered to all eligible patients, including those who may have been lost to follow-up. Additionally, the lack of robust call/recall system means that even those identified are at risk of being lost to follow-up. The development of a set of Standard Operating Procedures may ensure a standardised national programme. Dedicated staff and time are required to identify eligible patients and maintain a database: we propose that clinical nurse specialists could establish databases, and maintenance could be carried out by administrative staff. It is imperative that there is a single version of the database, not subject to local alterations.

### Automated recall systems for surveillance appointments

Current ad hoc surveillance provision relies on individual clinicians requesting imaging on time. Recall systems, aimed at mitigating human error from the surveillance process, generate automated reminders to health care professionals to book surveillance appointments. We instigated a liver cancer surveillance pilot across North West and South London and have demonstrated that the initiation of an automated recall system increased HCC surveillance uptake from 19% to 53% over a 12-month period.<sup>23</sup> Future automation of this process may involve automated booking of surveillance imaging following the identification of high-risk individuals using artificial intelligence algorithms in the future, further reducing the scope for human error in the bookings process. The management of a surveillance database and patient education will require funding which is likely to be tailored to each hospital's specific needs. We propose a national HCC surveillance working group to identify the needs of each region, provide oversight and ensure uptake and subsequent treatment are optimised.

Moving forward, national surveillance should ideally be organised in community health hubs: this will obviate the need for patients to attend hospital and will result in shared ownership of care, with community hubs organising routine surveillance and only those with abnormal results being referred for further investigation. Mobile imaging units, as used for lung cancer screening, should also be employed for HCC surveillance in an effort to try and engage the most marginalised in our community. In the near future, biomarkers for HCC may reduce the need for hospital attendance altogether, with patients expressing a clear preference for a convenient and accurate blood test over ultrasound.<sup>24</sup> However, suitable biomarkers will require further validation prior to implementation in clinical practice.

### Identifying barriers to surveillance uptake

There has been no research investigating the causes of low surveillance uptake in the UK. Studies in the USA have identified multifactorial factors—with patient, physician, and healthcare-system level barriers all contributing to low surveillance uptake. The UK Health Security Agency reports that many patients with liver disease are from “marginalised groups” living in “unstable accommodation” with limited English language skills.<sup>25</sup> In work done with community focus groups, patients emphasised the significance of psychological factors, with fear of a life-changing diagnosis and concern about stigma from healthcare professionals among the main barriers to surveillance attendance.<sup>26</sup> Additionally, patients consistently reported medical correspondence was difficult to understand due to overuse of medical jargon, patients' lower literacy skills or a limited understanding of English.

Correspondence with our patients should be designed to promote informed choice and encourage engagement with healthcare. Information about HCC surveillance should explain in clear, non-judgemental terms, the purpose and benefit of surveillance, as well as addressing concerns from patients about potential harms such as physical discomfort. This should be complemented by further identification of barriers to surveillance uptake in the UK, enabling implementation of interventions targeted at groups least likely to attend.

### Education and discussion with patients

In a questionnaire administered to 116 patients eligible for surveillance in London, 60% reported having never discussed cancer or surveillance with their healthcare professional (unpublished work from the authors). This is despite >80% of respondents wanting more information about HCC surveillance. A lack of understanding is one reason for a lack of engagement with health services and low attendance at appointments.<sup>27</sup>

Community focus groups with hepatology patients from diverse socio-economic, cultural, and linguistic groups highlighted high levels of trust in general practitioners, specialist hepatologists and in key charities including the British Liver Trust and Hepatitis C Trust.<sup>27,28</sup> We propose an education programme developed alongside charities and users, which focuses on the process of ultrasound and clearly articulates the rationale for screening i.e., early diagnosis of HCC to improve survival outcomes.

### Specialist engagement

Gastroenterologists, hepatologists and clinical nurse specialists form the backbone of HCC surveillance. For a successful screening programme to be implemented on a local or national scale, engagement with specialist colleagues is key. A recent UK-wide audit of surveillance practices revealed that centres estimate an 80% compliance rate of HCC surveillance.<sup>28</sup> There is a clear discrepancy between these estimated figures and the 20% surveillance attendance rate reported in larger studies, which is supported by our audit of surveillance attendance in London. A further study illustrated that 36% of specialists express doubt in the utility of surveillance<sup>18</sup> which will impact on clinician engagement. Engagement of individual clinicians will be critical to implementation of a successful surveillance programme: we propose local, respected champions and clear local governance arrangements to aid this process.

Concerningly, our community focus groups cited stigma from healthcare professionals as “one of the biggest setbacks” in attending surveillance<sup>29</sup>: this is supported by survey results from the British Liver Trust,<sup>25</sup> reporting that almost three-quarters of patients with liver disease have experienced stigma. This highlights the need for education of health care practitioners

and support workers involved in the care of patients with CLD, and more support for those with CLD such that they feel empowered to access healthcare. Areas of focus within clinician education might begin with medical school, where hepatology teaching is comparatively neglected, and in primary care, which is instrumental in community case finding, early diagnosis and addressing modifiable risk factors.

A further issue pertains to that of radiology capacity. The UK has the lowest number of radiologists per capita of any OECD nation.<sup>30</sup> Moreover, it has been clearly illustrated that the accuracy of detecting early cancer on ultrasound is directly related to the experience of the radiographer.<sup>31</sup> The NHSE minimum standards document for ultrasound surveillance calls for the regular training and accreditation of those involved in HCC surveillance to ensure that all sonographers and radiographers are working to a minimum standard. The document also clearly states the mandatory use of LI-RADS (Liver Imaging and Reporting Data System) in reporting surveillance ultrasounds to standardise terminology and classifications for liver imaging; its widespread adoption, not only in diagnostic but surveillance imaging. This will help improve interobserver agreements and performance across clinicians with different levels of experience.<sup>32</sup>

Central to the successful delivery of a national surveillance program will be adequate funding. Lung cancer screening, which is the only other large scale, targeted surveillance program in the UK, enrolling one million people a year, costs £270 million per year once fully instituted.<sup>33</sup> Cost-effectiveness analysis of HCC surveillance must be done focussing on QALYs gained with the current biannual ultrasound in order to create a viable surveillance model. Lung cancer screening also provides a framework on which to base the HCC surveillance pathway whereby an at-risk group of patients are identified in the community and undergo repeated testing. This model encompasses the key aspects proposed recall system, patient and clinician engagement and necessary infrastructure within the community.

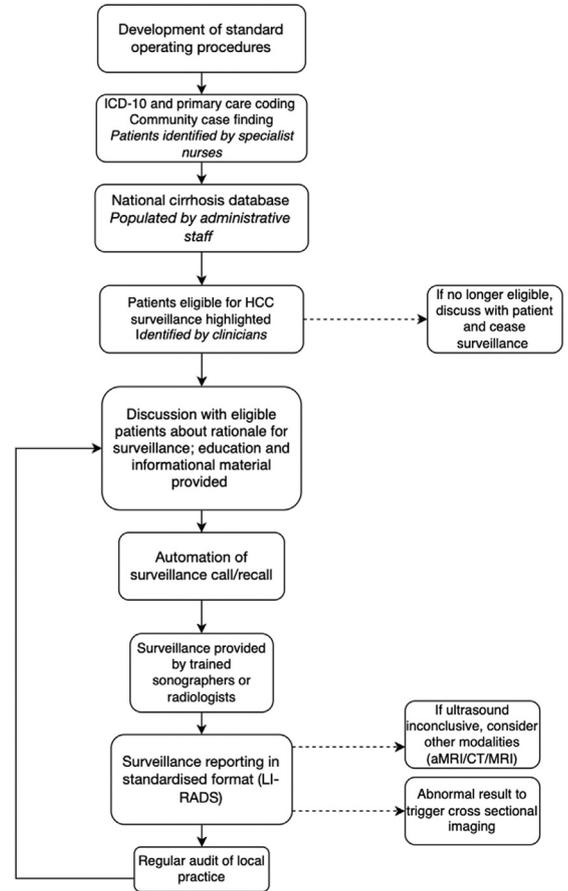


Fig. 1: A model of the “ideal” HCC surveillance pathway.

## Conclusions

HCC has poor outcomes due to late-stage diagnosis; HCC surveillance results in early diagnosis when disease is amenable to curative treatment. Acknowledging limitations in the evidence base for HCC surveillance, international professional bodies reiterate the recommendation for biannual HCC surveillance and NHS England support measures aimed to increase surveillance uptake. The current ad hoc provision of HCC surveillance is prone to failure, which is evident by low surveillance uptake and high numbers of patients being diagnosed outside of surveillance. We discuss some of the challenges related to HCC surveillance in the UK, and potential solutions to overcoming them (detailed in Table 1). In Fig. 1, we outline a proposal for the “ideal” surveillance pathway.

A consistent and effective surveillance process will require: a nationally agreed pathway; IT to ensure each patient is shepherded through this pathway, quality assurance to ensure adherence to protocol; public reports on performance against the standards and protocols; a central team to support, manage performance and drive consistency and quality. In our view, the

Problem	Proposed solution
Scale of problem unknown	Establishment of national cirrhosis database
Surveillance scheduling prone to human error	Automated recall system
Patient-related barriers	Identifying specific barriers; patient education; prioritising informed decision-making
Specialist engagement	Education of healthcare professionals; local champions of HCC surveillance; sonographer training and accreditation with adoption of LI-RADS
Variations in local practice	Establish national HCC surveillance programme with standard operating procedures and regular audit

Table 1: A summary of problems and proposed solutions regarding HCC surveillance.

establishment of a national programme with well-trodden routes to drive adherence to evidence-based care and ensure complete cohorts is key to the success of any public health or screening programme; this need is all the more urgent in liver disease, which disproportionately affects marginalised groups who are vulnerable to stigma. The obstacles and opportunities described are not unique to the UK and are of direct relevance to any European country, many of whom have a universal healthcare system with decision making bodies that share a similar conceptual framework with the UK. EASL is actively lobbying the European Commission to recommend liver cancer surveillance as part of Europe's Beating Cancer Plan. In establishing a national surveillance pathway the UK will act as a flagship for other nations that will be able to readily adopt the established model.

#### Contributors

MQ: writing—original draft; writing—review and editing. RS: conceptualisation; supervision; writing: review and editing.

#### Declaration of interests

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