Original Article

Detection of early-stage hepatocellular carcinoma: a retrospective evaluation of ultrasonography surveillance and surveillance adherence

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Background: Hepatocellular carcinoma (HCC) surveillance using 6-monthly ultrasonography (US) intervals is recommended. This study investigated the factors associated with early-stage HCC detection.

Methods: All patients with a new HCC diagnosis for the first time between 2019 and 2022 were included. All pre-treatment imaging was independently reviewed according to Liver Imaging Reporting and Data System (LI-RADS) criteria. Early-stage HCC was defined as a single tumour <50 mm or up to 3 tumours all <30 mm. Rate of adherence was expressed as the proportion of the number of 6-monthly surveillance US performed relative to the total number of surveillance US the patient should have undergone over the preceding 5 years or since the diagnosis of cirrhosis, if it was within the preceding 5 years.

Results: The study cohort included 175 patients with new HCC. The median age at diagnosis was 71 years; 78% were males; median body mass index (BMI) was 29.3 kg/m^2; 94% were of European ancestry and the most common aetiology was metabolic dysfunction-associated steatotic liver disease (MASLD) (58%). One third (37%) presented through primary surveillance (surveillance group) and the remainder were found to have HCC when investigated for other indications (incidental group). Only the age at presentation [P=0.003; odds ratio (OR) 0.937, 95% confidence interval (CI): 0.899–0.978] and being on HCC surveillance (P<0.001; OR 5.867, 95% CI: 2.533–13.586), but not surveillance adherence were independently associated with early-stage HCC detection.

Conclusions: Being part of primary surveillance, irrespective of adherence rate, is associated with early stage HCC detection. As many patients as possible should be enrolled into primary surveillance programme, even if adherence to recommended frequency is not followed rigorously.

Keywords: Hepatocellular carcinoma (HCC); primary surveillance; early stage detection; surveillance adherence

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Introduction

Hepatocellular carcinoma (HCC) is the most common primary liver cancer (1). It is a major global health problem with rising incidence worldwide (2). It is the fifth most common cancer and a leading cause of cancer-related deaths, accounting for more than 800,000 deaths worldwide annually (3) and it is expected to rise by more than 55% by 2040 (4). In 2020, HCC was in the top five causes of cancer-related deaths in nearly 100 countries worldwide (4).

The prognosis for HCC varies widely and largely depends on the disease stage at the time of diagnosis. HCC often presents late in its course, making curative treatment options difficult. Late diagnosis can be attributed to the asymptomatic nature of early-stage HCC. Thus, regular 6-monthly ultrasound (US) surveillance of at-risk individuals is recommended (i.e., primary HCC surveillance) for early-stage detection of HCC (5-7). Primary HCC surveillance has been shown to increase early-stage detection, increase curative treatment options, and improve survival (8).

Despite the proven benefits of HCC surveillance in treatment and survival, its implementation has been inconsistent and often inadequate, even within universal healthcare systems (9). Although the primary goal of HCC surveillance is to detect cancer at an early stage, there is limited literature on how compliance with surveillance impacts early-stage HCC detection. This study aims to evaluate whether adherence to surveillance—specifically, undergoing US scans every six months as recommended by guidelines—affects the likelihood of detecting HCC at an early stage. We present this article in accordance with the STROBE reporting checklist (available at https://tgh.amegroups.com/article/view/10.21037/tgh-24-119/rc).

Highlight box

Key findings

- Participation in surveillance, rather than adherence rate, plays a distinct role in early-stage hepatocellular carcinoma (HCC) detection.
- Age less than 64 years is a significant factor in detecting early-stage HCC.

What is known and what is new?

- Hepatocellular carcinoma surveillance leads to early stage HCC detection.
- Conventional wisdom holds that strict adherence to surveillance protocols is crucial for early detection.
- The study findings strongly support the role of surveillance in early-stage HCC detection.
- The findings suggest enrolling as many patients as possible in surveillance programs, even if adherence isn't perfect.

What is the implication, and what should change now?

- National policy should focus on enrolling at-risk populations into primary HCC surveillance, prioritising inclusion over strict protocol adherence.

Methods

Patient selection and data collection

A retrospective analysis was undertaken interrogating the prospectively collected data of patients presented to or referred to the regional hepatobiliary centre, Nottingham University Hospitals (NUH) NHS Trust, with HCC. All patients with a new diagnosis of HCC for the first time between 01 January 2019 and 31 December 2022 were eligible for inclusion. Those with previous history of HCC who presented with new recurrence of HCC were excluded.

Patients were divided into two groups depending on the mode of presentation. Those diagnosed to have HCC solely through primary HCC surveillance (surveillance group) and those diagnosed outside of the surveillance pathway (incidental group). Patients who were on primary surveillance but were diagnosed to have HCC outside of primary surveillance programme (e.g., imaging for haematuria) were included in the incidental group.

Demographic and clinical data were extracted entirely from the prospective database including details of pre-treatment imaging. The study was conducted in accordance with the Declaration of Helsinki and its subsequent amendments. The study was approved by the Nottingham University Hospital Clinical Effectiveness Board (approval ID 19-223C) and individual consent for this retrospective analysis was waived due to the retrospective nature. All pre-treatment imaging was independently reviewed by one of the three hepato-pancreato-biliary (HPB) radiologists to assess the tumour burden (M.S., A.G.B., C.C.).

Case definitions

Participants were said to have cirrhosis based on histological confirmation or radiological features such as irregular external contour of the liver, caudate lobe hypertrophy or elevated transient elastography reading or presence of clinically significant portal hypertension (CSPH). Presence of CSPH was defined as hepatic vein pressure gradient (HVPG)

>10 mmHg, presence of varices on upper gastrointestinal endoscopy or presence of intra-abdominal varices or recanalized umbilical vein or splenomegaly on imaging. Aetiology of liver disease was determined based on pre-existing clinical diagnosis, histological diagnosis, or both.

HCC surveillance was defined as a 6-monthly US scan in patients at risk of developing HCC, as per the national UK guidelines (10). A liver lesion was defined as HCC only if it fulfilled the Liver Imaging Reporting and Data System (LI-RADS) criteria to be deemed a LR-5 lesion on multiphasic contrast enhanced computed tomography (CT) and/or magnetic resonance imaging (MRI) or proved on histology (11).

Early-stage HCC was defined using the tumour burden criteria (size and number of HCC lesions) of Barcelona Clinic Liver Cancer (BCLC) staging system, as a single tumour less than 50 mm or up to 3 tumours all less than 30 mm in maximum diameter.

In this study, compliance with surveillance was measured as the rate of adherence to the recommended 6-monthly US surveillance. It was calculated as the proportion of surveillance US scans completed relative to the total number of US scans that should have been performed over the preceding five years, or since the diagnosis of cirrhosis if it occurred within that timeframe. Instead of categorising patients as merely compliant or non-compliant, compliance was evaluated as a continuous variable based on the rate of adherence.

Statistical analysis

Continuous and categorical variables were presented as median and interquartile range (IQR) or number and percentage, respectively. Statistical analyses were performed using GraphPad Prism 10 (San Diego, CA, USA) and IBM SPSS Statistics for Windows, Version 28.0.1.1 (Armonk, NY, USA). A P value of <0.05 was considered significant.

Predictors of early stage HCC detection were investigated using univariate and multivariate analysis. Univariate analysis was performed using Mann-Whitney test and Chi-square for continuous and categorical variables, respectively. Variables with a P value <0.10 and variables of interest were included in the multivariate stepwise forward regression model. Variables were considered to have independent association only if the P value reached Bonferroni-corrected level of significance. Continuous variables that were found to have an independent association were further interrogated using Youden's Index (J), to identify the optimal cutoffs for predicting the diagnosis of early stage HCC, where appropriate.

Results

Study cohort

Of the 224 HCC patients reviewed during the study period, 175 were diagnosed with HCC for the first time (study cohort). The median age at presentation was 71 years (IQR, 64–76 years); the majority were males (78%; n=136); and 94% (n=165) were of European ancestry. The median body mass index (BMI) was 29.3 kg/m^2 (IQR, 26.2–33.0 kg/m^2) and the most common aetiology of liver disease (58%, n=102) was metabolic dysfunction-associated steatotic liver disease (MASLD). Nearly two-thirds (65%, n=114) were current or previous smokers. About a fifth (21%, n=37) of the study cohort did not have underlying cirrhosis, and all of them were found to have HCC 'incidentally'. The median model for end-stage liver disease score (MELD$_{3.0}$) was 8 (IQR, 7–11) and the United Kingdom model for end-stage liver disease score (UKELD) was 48 (IQR, 46–50). Demographic and clinical parameters of the study cohort are summarised in *Table 1*.

Surveillance vs. incidental HCC groups

Of the study cohort, only about a third (n=64, 36.6%) presented through primary surveillance (surveillance cohort); the remainder (n=111, 63.4%) were found to have HCC 'incidentally' when investigated for other indications (incidental cohort). These two cohorts differed significantly from one another in ethnicity (P=0.02), aetiology of liver disease (P<0.001), presence of underlying cirrhosis (P<0.001), presence of CSPH (P<0.001) and liver disease severity MELD$_{3.0}$ (P=0.03). Demographic and clinical parameters of both, surveillance and incidental groups are summarised in *Table 1*.

In the surveillance cohort, the majority (n=34, 53.1%) were under surveillance for five or more years; 7.8% (n=5) were under surveillance for 4–5 years; 17.2% (n=11) for 2–3 years; and the remaining 21.9% for 1–2 years.

Within the incidental group, 37 patients (21% of the study cohort; 33% of the incidental group) did not have underlying cirrhosis. The most common aetiology of liver disease in this non-cirrhotic incidental group was MASLD (65%, n=24).

Table 1 Demographic and clinical characteristics of the entire study cohort and surveillance and incidental HCC groups

Demographic & clinical variables	Study cohort (n=175)	Surveillance group (n=64)	Incidental group (n=111)	Univariate P value
Age at diagnosis (years)	71 (64–76)	70 (65–74)	72 (65–77)	0.13
Male sex	136 [78]	47 [73]	89 [80]	0.30
BMI (kg/m^2)	29.3 (26.2–33.0)	29.8 (25.9–33.4)	29.1 (26.4–32.9)	0.82
Ethnicity (Caucasians)	165 [94]	57 [89]	108 [97]	0.02*
Indices of multiple deprivation decile	5 (2–8)	5 (2–8)	5 (2–8)	0.87
Aetiology				<0.001*
ArLD	32 [18]	16 [25]	16 [14]	
MASLD	102 [58]	31 [48]	71 [64]	
Hepatitis C/hepatitis B	19 [11]	16 [25]	3 [3]	
Others	22 [13]	1 [2]	21 [19]	
Smoking				0.35
Current	25 [14]	11 [17]	14 [13]	
Ex	89 [51]	28 [44]	61 [55]	
Never	61 [35]	25 [39]	36 [32]	
Cirrhosis	138 [79]	64 [100]	74 [67]	<0.001*
CSPH	81 [46]	43 [67]	38 [34]	<0.001*
$MELD_{3.0}$ score	8 (7–11)	9 (7–11)	7 (7–10)	0.03*
UKELD score	48 (46–50)	48 (47–50)	48 (46–50)	0.29

Data are presented as median (interquartile range) or number [percentage]. *, statistical significance of <0.05. ArLD, alcohol-related liver disease; BMI, body mass index; CSPH, clinically significant portal hypertension; HCC, hepatocellular carcinoma; MASLD, metabolic dysfunction-associated steatotic liver disease; MELD, model for end-stage liver disease score; UKELD, United Kingdom model for end-stage liver disease score.

Predictors of detection of early stage HCC

Of the study cohort (n=175), equal number of patients were diagnosed in the early stage (50%, n=88; early stage group) and in intermediate or advanced stages (50%, n=87; non-early stage group). Patients were younger on average (median 69 *vs.* 73 years, P=0.001) with a higher proportion of females (32% *vs.* 7%, P=0.05) in the early stage group compared to the non-early stage group, respectively. Further, viral hepatitis (18% *vs.* 3%) was more common while NAFLD was less common (53% *vs.* 63%) in the early stage group compared to the non-early stage group (P=0.01). Underlying cirrhosis (88% *vs.* 70%, P=0.004) was more prevalent in the early stage group and the majority were diagnosed through the primary HCC surveillance programme (57% *vs.* 16%, P<0.001). On multivariate analysis, only age [odds ratio (OR) 0.937, 95% confidence interval (CI): 0.899–0.978, P=0.003] and participating in the primary surveillance programme (OR 5.867, 95% CI: 2.533–13.586, P<0.001) were independent predictors of detection of early stage HCC. Demographic, clinical parameters and analysis are summarised in *Table 2*. Using Youden's Index (J), age less than 64 years at diagnosis (sensitivity 68%, specificity 67%) was found to be the optimal cutoff for predicting diagnosis of HCC at early stage.

Those who presented through the primary HCC surveillance (surveillance group, n=64) were analysed separately (*Table 3*) to identify potential independent predictive factors of early stage HCC. On univariate analysis, lower MELD score (P=0.03), longitudinal adherence rate (P=0.04) and female sex (P=0.06) were statistically significant or reached near significance. Sex, MELD score and longitudinal adherence rate were included in multivariate analysis but did

Table 2 Analysis of factors influencing early-stage HCC detection in the study cohort

Demographic & clinical variables	Early stage group (n=88)	Non-early stage group (n=87)	Univariate P value	Regression coefficient	OR (95% CI)	Multivariate P value
Age at diagnosis (years)	69 (62–74)	73 (66–77)	0.001*	–0.065	0.937 (0.899–0.978)	0.003**
Male sex	63 [72]	73 [84]	0.05*	–0.777	0.460 (0.187–1.131)	0.09
BMI (kg/m^2)	30.1 (27.0–34.8)	28.6 (26.0–32.6)	0.28			
Ethnicity (Caucasians)	81 [92]	84 [97]	0.20			
Indices of multiple deprivation decile	5.5 (3–8)	5 (2–8)	0.43			
Aetiology						
ArLD	17 [19]	15 [17]				
MASLD	47 [53]	55 [63]	0.01*	0.793	1.372 (0.535–3.520)	0.51
Hepatitis C/hepatitis B	16 [18]	3 [3]				
Others	8 [9]	14 [16]				
Smoking			0.42			
Current	15 [17]	10 [11]				
Ex	41 [47]	48 [55]				
Never	32 [36]	29 [33]				
Cirrhosis	77 [88]	61 [70]	0.004*	0.619	1.856 (0.668–5.159)	0.24
CSPH	47 [53]	34 [39]	0.06*	–0.319	0.727 (0.324–1.634)	0.78
Presentation (surveillance)	50 [57]	14 [16]	<0.001*	1.769	5.867 (2.533–13.586)	<0.001**
MELD score (2016)	8 (7–11)	8 (7–11)	0.31			
UKELD score	48 (46–50)	48 (46–50)	0.75			

Data are presented as median (interquartile range) or number [percentage], unless otherwise indicated. *, variables with P<0.10 in univariate analysis were included in multivariate analysis. **, Bonferroni-corrected level of significance was P<0.0083. ArLD, alcohol-related liver disease; BMI, body mass index; CI, confidence interval; CSPH, clinically significant portal hypertension; HCC, hepatocellular carcinoma; MASLD, metabolic dysfunction-associated steatotic liver disease; MELD, model for end-stage liver disease score; OR, odds ratio; UKELD, United Kingdom model for end-stage liver disease score.

not appear to impact early stage HCC detection.

Discussion

This study investigated the impact of primary HCC surveillance and adherence to surveillance on early-stage HCC detection. Participation in primary HCC surveillance significantly enhances the likelihood of early-stage detection, independent of adherence rates to surveillance schedules. This finding is pivotal, as it emphasizes the importance of surveillance itself, rather than the strict adherence to recommended surveillance intervals, in detecting early-stage HCC.

Interestingly, the study showed that strict adherence to a 6-monthly surveillance schedule did not significantly influence the detection of early-stage HCC. This is contrary to the common belief that more frequent surveillance would result in early stage detection. It is plausible that the underlying biological progression of HCC does not align precisely with the surveillance intervals, or that variations in HCC growth rates could account for this observation. Furthermore, the lower sensitivity and reduced quality of US imaging could also have contributed to adherence rate not influencing earlier HCC detection. The sensitivity of US imaging has been shown to be as low as 45% (12) and up to 20% of US examinations have been of inadequate quality for evaluation of liver lesions (13).

This study's findings corroborate previous studies that

Table 3 Analysis of early-stage HCC detection factors in surveillance group patients

Demographic & clinical variables	Early stage HCC (n=50)	Non-early stage HCC (n=14)	Univariate P value	Regression coefficient	OR (95% CI)	Multivariate P value
Age at diagnosis (years)	68 (63–73)	72 (67–76)	0.11			
Male sex	34 [68]	13 [93]	0.06*	–1.600	0.202 (0.022–1.857)	0.16
BMI (kg/m^2)	29.6 (25.9–35.3)	32.1 (25.9–32.8)	0.58			
Ethnicity (Caucasians)	45 [90]	12 [86]	0.65			
Indices of multiple deprivation decile	6 (3–8)	4 (2–7)	0.16			
Aetiology			0.17			
ArLD	13 [26]	3 [21]				
MASLD	21 [42]	10 [71]				
Hepatitis C/hepatitis B	15 [30]	1 [7]				
Others	1 [2]	0 [0]				
Smoking			0.53			
Current	10 [20]	1 [7]				
Ex	21 [42]	7 [50]				
Never	19 [38]	6 [43]				
CSPH	32 [64]	11 [79]	0.30			
Duration of primary surveillance (months)	50 (28–104)	34 (18–56)	0.13			
Adherence to surveillance (%)	80 (67–100)	67 (55–82)	0.04*	0.024	1.024 (0.991–1.057)	0.15
MELD score (2016)	9 (7–11)	11 (9–13)	0.03*	–0.161	0.851 (0.686–1.055)	0.14
UKELD score	48 (46–50)	48 (47–54)	0.18			

Data are presented as median (interquartile range) or number [percentage], unless otherwise indicated. *, variables with P<0.10 in univariate analysis were included in multivariate analysis. The Bonferroni-corrected level of significance was P<0.016. ArLD, alcohol-related liver disease; BMI, body mass index; CI, confidence interval; CSPH, clinically significant portal hypertension; HCC, hepatocellular carcinoma; MASLD, metabolic dysfunction-associated steatotic liver disease; MELD, model for end-stage liver disease score; OR, odds ratio; UKELD, United Kingdom model for end-stage liver disease score.

highlight the benefits of surveillance in enhancing early HCC detection, which is critical for enabling curative treatment and improving survival outcomes (8). In addition to early stage HCC detection, surveillance also plays a crucial role in providing regular opportunities to manage underlying liver conditions and associated risk factors, potentially slowing liver disease progression. Further, the cost-effectiveness of surveillance is underscored by the preference for treating early-stage HCC, which is generally less expensive and more effective than managing advanced HCC (14,15).

A significant observation in this study was that a considerable proportion of patients diagnosed with HCC incidentally had underlying cirrhosis and were not part of a surveillance programme. This underscores the importance of identifying patients with advanced liver fibrosis as early as possible and including them in surveillance programmes. Up to 7% of the adult population without documented liver disease has underlying liver fibrosis (16). Furthermore, an alarming 39% of individuals with advanced liver fibrosis remain undetected, highlighting significant shortcomings in the existing diagnostic strategies (17). Implementation of effective programmes such as commissioned community pathways, targeting individuals with risk factors for chronic liver disease, and providing general practitioners access to simple non-invasive investigations (e.g., transient elastography) to detect individuals with liver fibrosis, hold promise for early detection and enhanced patient outcomes.

Contrary to conventional wisdom, this study revealed a lack of association between adherence rates and detection

of early stage HCC. This finding challenges prevailing assumptions suggesting a direct link between heightened adherence and timely cancer detection. Previous research has largely failed to demonstrate a consistent association between adherence to surveillance and the identification of early-stage HCC. While the study by Haq *et al.* (18), which categorised adherence into adherent and non-adherent groups, reported a positive association, another study by Mohammed *et al.* (19) adopted an approach somewhat similar to ours by examining adherence as a continuous variable. This study, like ours, found no statistically significant association between adherence to surveillance and the detection of early-stage HCC. Further research is required to explore and understand the underlying reasons for these discrepancies.

Both this study and previous research (20) indicate that a significant portion, approximately one-fifth, of patients with HCC do not have underlying cirrhosis. Consequently, these individuals would not have been included in a surveillance program, even under optimal circumstances. This study highlights the increasing prevalence of HCC in patients with MASLD, even in the absence of cirrhosis, consistent with the growing body of evidence linking MASLD to HCC development. This highlights the urgent need for a comprehensive overhaul of the current risk stratification system to address this gap in HCC surveillance guidelines, particularly given the rising incidence of MASLD worldwide (20-22).

While this study adds to the expanding body of evidence concerning HCC surveillance, it is crucial to address its limitations. Although it is the largest study conducted in this area to date, the relatively small cohort size should be recognised as a potential limitation that may have influenced the results. As discussed above, the limited and conflicting data in the existing literature made a sample size calculation unfeasible. Further, the variability in the duration of surveillance among patients in the surveillance cohort may have influenced the study findings. However, as the surveillance practice at NUH remained consistent throughout the study period, this is less likely to have had a significant impact. Additionally, the study does not explore the underlying reasons why the adherence rate did not affect early-stage HCC detection, which should be acknowledged as another limitation.

Conclusions

This study reinforces the critical role of primary surveillance in the early detection of HCC. It challenges the traditional emphasis on strict adherence to surveillance intervals, suggesting that regular surveillance, regardless of frequency, is key to early detection. This has significant implications for clinical practice and policy, advocating for broader implementation and accessibility of HCC surveillance programs, even when perfect adherence to recommended intervals may not be feasible.

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Footnote

Reporting Checklist: The authors have completed the STROBE reporting checklist. Available at https://tgh.amegroups.com/article/view/10.21037/tgh-24-119/rc

Data Sharing Statement: Available at https://tgh.amegroups.com/article/view/10.21037/tgh-24-119/dss

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Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki and its subsequent amendments. The study was approved by the Nottingham University Hospital Clinical Effectiveness Board (No. 19-223C) and individual consent for this retrospective analysis was waived due to the retrospective nature.

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