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Surveillance for hepatocellular carcinoma - current status and advances

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Abstract

Aim: Hepatocellular carcinoma (HCC) is a common cancer worldwide, especially in Asia, with high mortality. Curative options are only available for early-stage HCC, which are usually asymptomatic and best diagnosed through surveillance. Risk factors associated with HCC include liver cirrhosis due to alcohol, chronic viral hepatitis infections and nonalcoholic steatohepatitis. We review the evidence supporting the benefits and drawbacks of HCC surveillance as well as new surveillance modalities.

Methods: A MEDLINE and Cochrane Database search with defined search phrases was performed. Studies published from Jan 2000 to Jul 2018 were reviewed and publications focusing on the benefits and harms of HCC surveillance were qualitatively synthesized. Modalities of HCC surveillance were also reviewed.

Results: A total of 5 randomized controlled trials (RCTs) and 24 cohort studies with sample size of more than 100 each were selected. Significant mortality reduction was demonstrated in 1 RCT. Cohort studies showed overall improved outcomes in the surveillance group with 61.3%-88% of HCC being detected in an early-stage and with up to 80% eligible for curative treatments. A quarter (27.5%) of the surveillance patients experienced additional scans or procedures due to false-positive results. Combination of ultrasound with alpha-fetoprotein increases HCC detection rate. Novel serum markers and liquid biopsy are attractive tools for surveillance as they are non-invasive and convenient.

Conclusion: The current evidence supports HCC surveillance as it detects earlier stage of tumor, allows more curative treatment and improves survival. Further research on hepatocarcinogenesis and novel surveillance modalities will continue to refine surveillance guidelines to reduce HCC-related mortality.

Keywords: Hepatocellular carcinoma, surveillance, surveillance modalities, screening, biomarkers

INTRODUCTION

Hepatocellular carcinoma (HCC) accounts for 80% of all primary liver malignancies. Worldwide, it is the fifth most common cancer in males, ninth in females, and over half a million of new cases are diagnosed annually. Asia-Pacific region, East Asia and Sub-Saharan Africa accounts for 82% of all liver cancer cases in the world[1]. HCC is the second most common cause of cancer-related deaths in 2012, 1% of all deaths in the world can be attributed to HCC every year. The overall survival of HCC was 3%-5%[2], and mortality to incidence ratio is 0.95[3], suggesting its poor prognosis attributable to the late stage of diagnosis in most of these cases. An early-stage HCC, on the contrary, is amenable to several curative therapeutic options, and a five-year survival of 70%-75% can be achieved[4]. Liver cirrhosis may be due to several risk factors including alcohol but chronic hepatitis B or C infections are the most common risk factors of HCC contributing to 70%-90% of the cases, and nonalcoholic steatohepatitis (NASH) is rapidly gaining prominence[5,6].

Several professional societies, including American Association for the Study of Liver Diseases (AASLD), European Association for the Study of the Liver (EASL), Japanese Society of Hepatology and Asian Pacific Association for the Study of the Liver, have recommended regular surveillance of HCC in at-risk populations[7-10]. The goal is to identify HCC at an early stage when it is amenable to curative treatment, therefore reducing mortality. Increasing usage of surveillance to detect early HCC is associated with improvement in outcomes[6]. The strongest evidence for surveillance is seen in patients with chronic hepatitis B infection[11]. However, whether surveillance for HCC is truly effective and beneficial is still a topic of debate, owing to the concern of the quality and paucity of existing evidence. We conducted a systematic review of the literature to better understand the benefits and disadvantages of HCC surveillance, and the current surveillance modalities.

METHODS

Data sources and searches

A search on the MEDLINE database and Cochrane Database of Systematic Reviews was performed on 19 Jul 2018. Search phrases used were "hepatocellular carcinoma" OR "HCC" OR "Carcinoma, Hepatocellular" OR "liver cancer" OR "Liver Neoplasms" AND "surveillance" OR "screening" OR "Early Detection of Cancer". We filtered the literature published from January 1 2000 to July 2018 and each literature was manually screened and selected based on our inclusion and exclusion criteria.

Study selection

All primary studies on HCC surveillance published in English, comprising randomized controlled trials, cohort studies, case studies and systematic reviews were included. We defined the term "surveillance" as "repeated use of a test at regular interval over time to detect a previously undiagnosed lesion". The analysis was focused on the effect of surveillance on survival and/or mortality of HCC patients, with or without adjustment for bias. Particular attention was paid to any lead-time bias analysis for survival reporting. Modalities of HCC surveillance and stages of disease on diagnosis are also included. Exclusion criteria include studies published in foreign languages, studies on patients with recurrent or metastatic HCC, studies irrelevant to primary liver cancer, animal or *in vitro* studies, studies with no mortality/survival data directly comparing surveillance and non-surveillance group, or cohort studies with a sample size of less than 100 in either group.

Data synthesis and analysis

The data were qualitatively synthesized and summarized on the survival and mortality benefit of HCC surveillance.

RESULTS

The literature search yield 4,557 results in PubMed and 273 in Cochrane Library. We manually screened the literature from the title and study aims, and full-text articles of all eligible studies were reviewed. All the

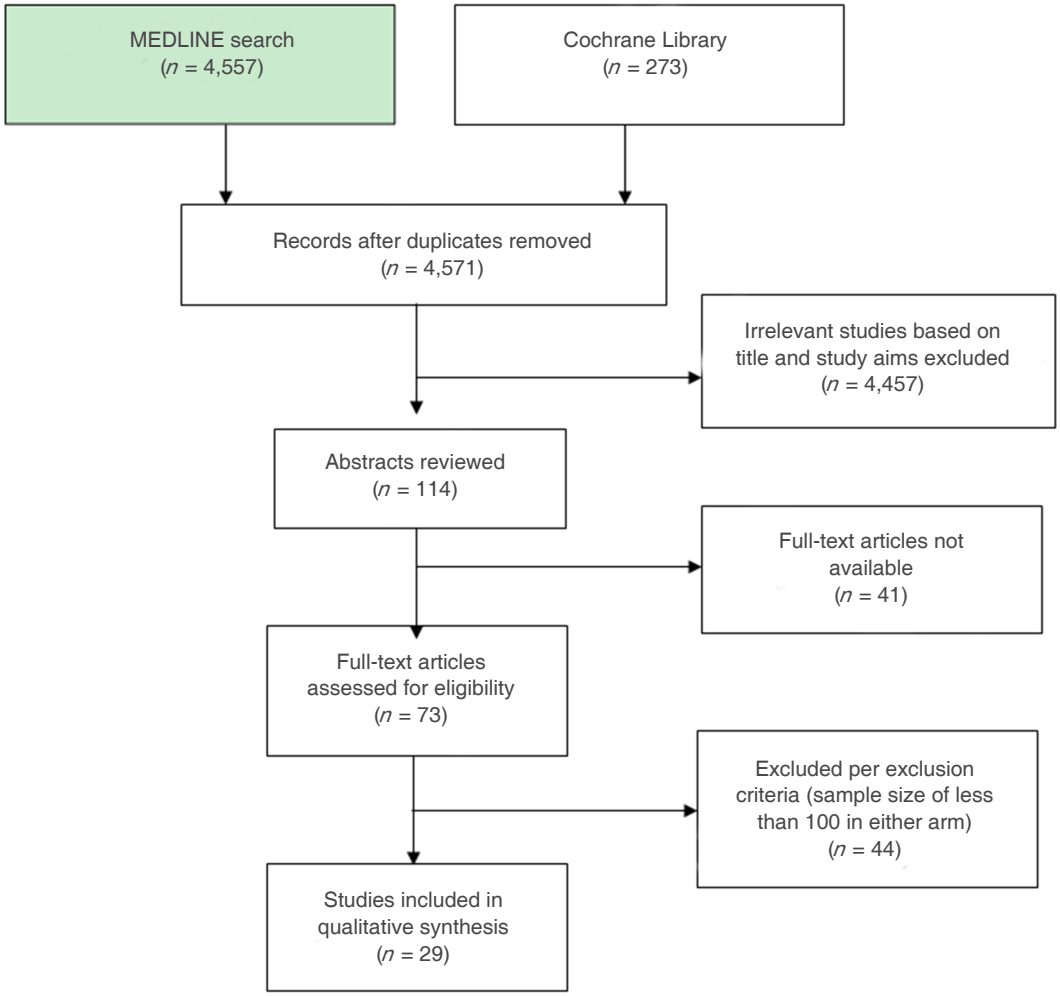

Figure 1. Study selection flowsheet[64]

randomized controlled trials and cohort studies with more than 100 subjects in the surveillance and non-surveillance groups were included for qualitative analysis [Figure 1][12].

Randomised trials

To date, there were only two randomised trials, both done in China, directly comparing patients with surveillance to no surveillance. In both trials, the study population was exclusively patients with chronic hepatitis B infection (positive serum hepatitis B surface antigen). The first study by Chen et al in 2003 conducted surveillance with six-monthly serum alpha-fetoprotein (AFP), followed by ultrasound for patients with high AFP levels[12]. No difference in mortality was found in the two groups. Zhang *et al.*[11] subsequently conducted surveillance with AFP with US 6-monthly in two randomized groups of hepatitis B patients, and a significant mortality difference was found with a mortality rate ratio of 0.63 (95% CI: 0.41-0.98). These two trials were heavily criticized due to the poor compliance rate in surveillance group, as well as the limited information on study design and a high risk of bias [Table 1].

Other randomized controlled trials (RCT) done in Europe and Taiwan addressed the impact of ultrasound surveillance intervals. Trinchet *et al.*[13] conducted a multicenter RCT comparing 3-monthly to 6-monthly ultrasound surveillance on HCC patients in France and Belgium. Study population was histology-proven cirrhosis and the main etiologies were alcohol and viral hepatitis. Three-monthly ultrasound detects more

Table 1. Randomised controlled trials on hepatocellular carcinoma surveillance

Author, year	Study period	Sample size (S *vs.* NS)	Continent	Surveillance modality	Etiology (%)	Stage at diagnosis (%)	Mortality	Survival (%)	Treatment (%)
Chen *et al.*[12], 2003	1989-1995	3712 *vs.* 1869	Asia (China)	AFP 6-mthly *vs.* none	HBV[#] Cirrhosis: NA	I[a,*]: 29.6 *vs.* 6 II: 50.6 *vs.* 53 III: 19.8 *vs.* 41	HCC mortality per 100,000: 1,138 *vs.* 1,114 (P = 0.86)	1-year: 23.7 *vs.* 9.7 3-year: 7 *vs.* 4 5-year: 4 *vs.* 4.1	NA
Zhang *et al.*[11], 2004	1993-1995	9373 *vs.* 9443	Asia (China)	US + AFP *vs*. none	HBV Cirrhosis: NA	I[a]: 60.5 *vs.* 0 II: 13.9 *vs.* 37.3 III: 25.6 *vs.* 62.7 (P < 0.010)	HCC mortality per 100,000: 83.2 *vs.* 131.5 RR 0.63 (95% CI: 0.41 to 0.98); (P < 0.010)	1-year: 65.9 *vs.* 31.2 3-year: 52.6 *vs.* 7.2 5-year: 46.4 *vs.* 0	Resection: 46.5 *vs.* 7.5 TACE or PEI: 32.6 *vs.* 41.8 Conservative treatment: 20.9 *vs.* 50.7
Trinchet *et al.*[13], 2011	2000-2006	640 (3 months) *vs.* 638 (6 months)	Europe (France, Belgium)	US 3 monthly *vs.* 6-monthly	Histo-proven cirrhosis: all Alcohol: 39.4 *vs.* 39 HCV: 44.7 *vs.* 43.6 HBV: 12.8 *vs.* 12.2 Hemochromatosis: 0.8 *vs.* 2.3 Others: 2.3 *vs.* 2.6	Within Milan criteria[b]: 79.2 *vs.* 71.4 (P = 0.4)	Overall mortality (%): 11.3 *vs.* 12.1 (P = 0.38)	2-year: 95.8 *vs.* 93.5 5-year: 84.9 *vs.* 85.8	LTx: 18.9 *vs.* 4.3 Resection: 5.7 *vs.* 9.7 Ablation: 37.7 *vs.* 44.3 Supportive care 9.4 *vs.* 17.1 (P = 0.1)
Wang *et al.*[14], 2013	2006-2010	387 (4 months) *vs.* 357 (12 months)	Asia (Taiwan, China)	US 4-monthly *vs.* 12-monthly	HepB: 30 *vs.* 25.2 HepC: 63 *vs.* 67.2 Cirrhosis: 87.5 *vs.* 100 (P = 0.27)	BCLC stage[c]: 0: 37.5 *vs.* 6.7 A: 54.2 *vs.* 66.6 Others: 8.3 *vs.* 26.7 (P = 0.017)	NA	1-year: 95.8 *vs.* 80 2-year: 78.8 *vs.* 64 5-year: 57.4 *vs.* 56 (P = 0.399)	Curative Rx: 13 *vs.* 3 Others: 45.8 *vs.* 80 (P = 0.049)
Taylor *et al.*[16], 2017	Markov model	1000 *vs.* 1000	NA	6-monthly US *vs.* none	Cirrhosis: all (simulated)	NA	HCC mortality 69 *vs.* 82 (NNS 77) Harm (additional imaging/biopsy) 150 (NNH 7)	NA	NA

[#]HBV: patients with positive serum Hepatitis B surface antigen; *including cases diagnosed with HCC within the first two months of enrolment; [a]clinical classification of the China Liver Cancer Study group; stage I (early stage, subclinical disease) included patients with no symptoms (and a tumour usually < 5 cm in diameter) at first diagnosis. Stage III (advanced stage), included patients with severe liver dysfunction. The remaining cases between stage I and III were classed as stage II (middle stage); [b]Milan criteria: one tumor ≤ 50 mm in diameter, or 2-3 tumors ≤ 30 mm in diameter without vascular extension or metastasis (based on computed tomography scan); [c]BCLC staging - stage 0: tumor < 2 cm, performance status (PS) 0 and the Child-Pugh A; stage A: single tumor < 5 cm, or up to 3 tumors all < 3 cm, PS 0 and Child-Pugh A or B; stage B: multinodular HCC, PS 0 and Child-Pugh A or B; stage C: portal, lymph node or organ invasion, or PS 1 or 2, Child-Pugh A or B; stage D: PS > 2 or Child-Pugh C. AFP: alpha-fetoprotein; BCLC: Barcelona Clinic Liver Cancer staging; HBV: hepatitis B virus; HCC: hepatocellular carcinoma; HCV: hepatitic C virus; TACE: transarterial chemoembolization; PEI: percutaneous ethanol injection; NA: not available; NNH: number needed to harm; NNS: number needed to screen; LTx: liver transplant; OR: odds ratio; S: surveillance group; NS: no surveillance group; Tx: treatment; US: ultrasound

small focal lesions, however no survival difference was observed between the 2 randomized groups. A community-based study in Taiwan compared 4-monthly to 12-monthly ultrasound surveillance for viral hepatitis B/C patients with platelet level more than 150,000/mL. More frequent surveillance detected smaller HCCs that were amenable for curative treatment modalities. However there was no significant difference in overall survival[14] [Table 1].

Poustchi *et al.*[15] attempted to conduct a RCT on HCC surveillance for cirrhotic patients. After risk and benefits of surveillance were discussed, 99.5% of the patients declined randomization, demonstrating the dif-

Table 2. Cohort studies on hepatocellular carcinoma surveillance

Author, year	Study design	Surveillance modality	Study period	Sample size (S *vs.* NS)	Continent	Etiology (%)	Stage at diagnosis (%)	Mortality	Survival (%)	Treatment received (%)
Chiang *et al*.[65], 2017	Retrospective	≥ 3 *vs.* < 3 US within 2 years of HCC dx	1997-2010	1,472 *vs.* 3,149	Asia (Taiwan, China)	Cirrhosis: 80.4 *vs.* 65 HBV: 42.1 *vs.* 35.5 HCV: 42.1 *vs.* 21	NA	NA	5-year: 14.4 *vs.* 7.7 (P < 0.001)	Resection: 15 *vs.* 10.9 RFA: 6.9 *vs.* 2.3 PEI: 6.4 *vs.* 16.6 LTx: 0.1 *vs.* 0.4 TACE: 18.5 *vs.* 30.8 Chemo 37.1 *vs.* 46 RT: 20.5 *vs.* 22.7
Chaiteerakij *et al*.[63], 2017	Retrospective	≥ 1 US within 1 year of HCC dx	2007-2013	103 *vs.* 343	Asia (Thailand)	Cirrhosis: 96.1 *vs.* 93.6 HBV: 61.2 *vs.* 52.2 HCV: 25.2 *vs.* 17.8 Alcohol 6.8 *vs.* 12.2 NASH: 3.9 *vs.* 11.1	BCLC: A: 80.6 *vs.* 33.8 B: 12.6 *vs.* 39.1 C 4.9 *vs.* 26.2 (P < 0.001)	Adju HR: 0.63 (0.45-0.87) (P = 0.005)	Median survival (months): 49.6 *vs.* 15.9 (P < 0.0001)	Curative Tx (resection, RFA, LTx, PEI): 73.8 *vs.* 44.9 (P < 0.001)
Singal *et al*.[21], 2017	Retrospective	Imaging (US, CEUS, CT, MRI), within 6 months of HCC dx	2012-2013	157 *vs.* 217	United States	Cirrhosis: all HCV: 67.5 *vs.* 49.8 HBV: 5.1 *vs.* 6.5 Alcohol: 12.7 *vs.* 16.1 NAFLD: 12.1 *vs.* 16.1 Others: 2.6 *vs.* 11.5	BCLC: A: 63.1 *vs.* 36.4 B: 15.3 *vs.* 12.4 C: 6.4 *vs.* 29 D: 15.3 *vs.* 22.1 (P < 0.001)	1-year mortality 22.3 *vs.* 39.6 (P < 0.001)	Median survival (months): 14.6 *vs.* 6; Survival: 1-year: 75.3 *vs.* 53.4 3-year: 68.7 *vs.* 35.5	Curative: 30.6 *vs.* 13
Mittal *et al*.[66], 2016	Retrospective	≥ 2 Imaging (US, CT, MRI) +/- AFP within 2 years of HCC dx	2005-2010	412 *vs*. 475	United States	Cirrhosis: all HBV: 4.6 *vs.* 4.6 HCV: 86.9 *vs.* 70.1 Alcohol: 90.3 *vs.* 86.7 NAFLD: 6 *vs.* 21	BCLC: 0/A: 27.2 *vs.* 11.6 B: 22.8 *vs.* 22.1 C: 26.5 *vs.* 35.4 D: 24.2 *vs.* 15	Adj HR 0.80 (0.69-0.94) Adj for: HCC stage, Tx	Median survival (months): 16.8 *vs.* 9.9	Curative: 20.9 *vs.* 11.6 Palliative: 59.2 *vs.* 45.5
Oeda *et al*.[20], 2016	Retrospective	US + AFP/DCP/AFP-L3 +/- imaging (CT/MRI)	2004-2012	226 *vs.* 107	Asia (Japan)	Cirrhosis: all HBV: 10.6 *vs.* 26.2 HCV: 89.4 *vs.* 73.8 (P < 0.001)	I[a]: 31.4 *vs.* 9.3 II: 37.6 *vs.* 23.4 III: 26.5 *vs.* 42.1 IV: 4.4 *vs.* 25.2 (P < 0.001)	NA	Median survival (months, corrected for lead-time bias): 56.5 *vs.* 31.4 (P = 0.011) 1-year: 81.8 *vs.* 48.9 3-year: 67.9 *vs.* 58.1 5-year 36.6 *vs.* 34.7 (P < 0.001)	Resection: 27.9 *vs.* 27.1 RFA 49.1 *vs.* 14 TACE 21.2 *vs.* 42.1 Others: 1.8 *vs.* 16.8 Curative: OR 3.213 (1.615-6.319, P = 0.001)

van Meer *et al.*[62], 2015	Retrospective	AFP +/- imaging +/-	2005-2012	295 *vs.* 779	Europe (Netherland)	Cirrhosis: 97 *vs.* 60 (*P* < 0.001) HBV: 20 *vs.* 14 HCV: 38 *vs.* 12 Alcohol: 24 *vs.* 30 NAFLD: 7 *vs.* 20	BCLC 0: 15 *vs.* 3 A: 46 *vs.* 18 B: 21 *vs.* 14 C: 12 *vs.* 30	> 9 months surveillance: unadjusted HR 0.55 (0.42-0.73) (*P* < 0.001)	1-year: 68 *vs.* 55 3-year: 47 *vs.* 29 5-year: 39 *vs.* 22	Surgical therapy: 34 *vs.* 25 RFA: 23 *vs.* 7
Thein *et al.*[22], 2015	Retrospective	US	2000-2010	943 *vs.* 540	Canada	Cirrhosis: 52.4 *vs.* 42 Viral hepatitis: all	NA	Lead-time corrected HR[b]: 0.76 (0.64-0.91) *vs.* 0.86 (0.75-0.98)	Median survival (days, lead-time corrected)[c]: 779 *vs.* 610 *vs.* 478 3-year: 42.6 *vs.* 35.7 *vs.* 29.9 5-year: 31.9 *vs.* 22.4 *vs.* 20.7	Curative (S *vs.* NS): 59.3 *vs.* 41.3 (*P* < 0.001)
Nusbaum *et al.*[19], 2015	Retrospective	AFP +/- imaging	2007-2012	126 *vs.* 162	US	Cirrhosis (majority HCV, HBV), no detailed data	Early-stage (I&II): 92% *vs.* 62% (*P* < 0.001)	Adj HR 0.62 (0.41-0.94)	Overall survival: 63 *vs.* 49 (*P* = 0.006)	LTx: 53 *vs.* 23 Surgical (LTx + resection): 61 *vs.* 33 (*P* < 0.01)
Wu *et al.*[23], 2015	Retrospective	US	2002-2007	31704 *vs.* 21119	Asia (Taiwan, China)	Cirrhosis: 62.5 *vs.* 38.6 HBV: 28 *vs.* 27 HCV: 30.8 *vs.* 12 Alcohol: 11.1 *vs.* 5	NA	5-year mortality[d]: 69.9 *vs.* 71.1 *vs.* 74.5 vs. 77.2 *vs.* 81	Median survival (lead-time corrected, year)[d]: 2 *vs.* 1.54 *vs.* 0.94 *vs.* 0.73 *vs.* 0.54	Curative therapy[d]: 24.3 *vs.* 26.9 *vs.* 22.9 *vs.* 21.3 *vs.* 18.3
Cucchetti *et al.*[67], 2014	Retrospective	US +/- AFP	1987- 2012	1084 *vs.* 296	Europe (Italy)	Cirrhosis: all HBV: 10.2 *vs.* 12.8 HCV: 61.6 *vs.* 34.5 Alcohol 8.9 *vs.* 23 Others 6.8 *vs.* 13.2	Milan criteria: 78.5 *vs.* 29.7	NA	3-year: 54.4 *vs.* 24.2 5-year: 31.1 *vs.* 12.2	LTx: 3 *vs.* 0.7 Resection: 14.8 *vs.* 13.9 RFA/PEI: 41.9 *vs.* 12.5
EL-Serag *et al.*[68], 2011	Retrospective	AFP + US	1998-2007	580 *vs.* 332	US	HCV: all Cirrhosis: NA	NA	HR: 0.71 (0.62-0.82)	3-year: 22 *vs.* 13	NA
Stroffolini *et al.*[69], 2011	Prospective	AFP + US	2008-2009	257 *vs.* 154	Europe (Italy)	Cirrhosis: 97.5 *vs.* 90.1 (*P* = 0.003) HBV: 14 *vs.* 15.1 HCV: 61.6 *vs.* 46 (*P* = 0.01) HBV + HCV: 1.3 *vs.* 2.2	Single tumor: 65.6 *vs.* 47.1 (*P* < 0.0001) Multinodular: 30.8 *vs.* 35.3 Diffuse: 3.6 *vs.* 17.6 Vascular invasion: 9.6 *vs.* 26.4 Metastasis: 2.2 *vs.* 5.6	NA	NA	NA
Yang *et al.*[70], 2011	Retrospective	Imaging (US/CT/MRI)	2007-2009	136 *vs.* 307	US	Cirrhosis: 98 *vs.* 77	Milan criteria: 63 *vs.* 20	NA	10 months: 52.9 *vs.* 33.9 20 months: 25% *vs.* 13.7 30 months: 9.6 *vs.* 5.2	Curative: 64 *vs.* 31

Kuo *et al*.[71], 2010	Retrospective	AFP + US, 1 year	2002-2004	318 *vs.* 1118	Asia (Taiwan, China)	Cirrhosis: all HBV: 48.7 *vs.* 47.1 HCV: 38.1 *vs.* 33.4	BCLC: 0: 8.2 *vs.* 3.7 A: 60.4 *vs.* 23.1 B: 21.7 *vs.* 35.2 C: 6.9 *vs.* 30.9 (*P* < 0.001)	NA	3-year: 59.1 *vs.* 29.3	Curative: 45.6 *vs.* 22.7 TACE: 47.2 *vs.* 38.2 Other: 7.2 *vs.* 39.1
Noda *et al*.[61], 2010	Retrospective	Imaging (US/CT/MRI)	2001-2007	124 *vs*. 116	Asia (Japan)	HCV: all Cirrhosis: 73 *vs*. 64.7	Milan criteria: 88 *vs.* 44 (*P* < 0.001)	NA	1-year: 90 *vs.* 50 3-year: 73 *vs.* 34 5-year: 54 *vs.* 9	Curative: 80 *vs.* 45
Pascual *et al*.[72], 2008	Retrospective	US + AFP every 6 months	1996-2005	117 *vs.* 173	Europe (Spain)	Cirrhosis: all Alcohol: 21 *vs.* 35 HCV: 61 *vs.* 35 HBV: 3 *vs.* 6 Others: 10 *vs.* 13	Tumor size: < 5 cm: 60 *vs.* 24 > 5 cm: 9 *vs.* 28 Multifocal: 14 *vs.* 32	NA	Mean survival (months): 27 *vs.* 6	LTx: 15 *vs.* 3 PEI/RF: 31.6 *vs.* 12.1 TACE: 39 *vs.* 20
Tanaka *et al*.[73], 2006	Retrospective	US + AFP, 6 months	1991-2003	182 *vs.* 202	Asia (Japan)	HCV: all Cirrhosis: 84 *vs.* 76	Milan: 86 *vs.* 50	NA	Median survival (year): 4.7 *vs.* 3.1 (*P* < 0.001) 3-year: 67 *vs.* 51 5-year: 46 *vs.* 32	Resection: 6 *vs.* 12 PEI/RFA: 60 *vs.* 34 TACE: 20 *vs.* 42 Chemo: 3 *vs.* 9 (*P* < 0.001)
Toyoda *et al*.[74], 2006	Retrospective	AFP/DCP +/- imaging	1968-2004	1050 *vs.* 591	Asia (Japan)	NA	Stage I: 24 *vs.* 3.6 Stage II: 33.6 *vs.* 16 Stage III: 24 *vs.* 15.7 Stage IV: 18.2 *vs.* 64.6	NA	3-year: 51.4 *vs.* 27.1 5-year: 35.9 *vs.* 18.6	LTx: 21.7 *vs*. 5.1 Resection: 22.6 *vs.* 9 TACE: 34.1 *vs.* 27.2 Others: 7 *vs.* 19.8
Ando *et al*.[75], 2006	Retrospective	AFP and imaging	1995-2000	392 *vs.* 182	Asia (Japan)	Cirrhosis: NA HCV: 87 *vs.* 74 HBV: 8.7 *vs.* 17	Early HCC: 73 *vs.* 26	NA	3-year: 62 *vs.* 38	Curative: 56.9 *vs.* 26 Supportive: 0 *vs.* 7
Trevisani *et al*.[24], 2004	Retrospective	US + AFP every 6-12 months	1998-2001	158 *vs.* 205	Europe (Italy)	Cirrhosis: all HBV: 9.5 *vs.* 8.3 HCV: 67.1 *vs.* 60.5 Alcohol: 5.7 *vs.* 11.7	Tumor ≤ 3 cm[e]: 68.7 *vs.* 49.3 *vs.* 6.7 Multifocal: 11.1 *vs.* 15.9 *vs.* 22.4 Advanced: 29.7 *vs.* 60.9 *vs.* 74.6	NA	Median survival (months, lead-time corrected)[e]: 24 *vs.* 21 *vs.* 7	Resection[e]: 8.4 *vs.* 2.9 *vs.* 0 TACE: 28.6 *vs.* 17.6 *vs.* 20 Others: 27.3 *vs.* 42.6 *vs.* 69.2
Yu *et al*.[18], 2004	Retrospective	US	1996-1997	164 *vs.* 516	Asia (Taiwan, China)	Cirrhosis: 91.9 *vs.* 68.2 HBV: 67.7 *vs.* 53.6 HCV: 43.9 *vs.* 31.3	TNM I: 66.2 *vs.* 19.3 II: 27.2 *vs.* 37.2 III: 3.7 *vs.* 28.0 IV: 2.9 *vs.* 14.6	NA	Unadj OR of survival at 1-year: 3.57 (5.26 - 2.38) 2-year: 3.7 (5.26 - 2.56) 3-year: 3.57 (5.26 - 2.44)	Resection: 53.5 *vs.* 34 (*P* < 0.0001) TACE: 35.1 *vs.* 29.9

Trevisani *et al.*[25], 2002	Retro-spec-tive	US + AFP every 6-12 months	1988-1998	370 *vs.* 451	Europe (Italy)	Cirrhosis: all 6 months *vs.* 12 months *vs.* NS HBV: 13.6 *vs.* 20.4 *vs.* 20.5 HCV: 66.6 *vs.* 62.5 *vs.* 55.9 Alcohol: 8.5 *vs.* 7.2 *vs.* 13.8	6 months *vs.* 12 months *vs.* NS: Non-advanced: 68.7 *vs.* 60.4 *vs.* 31 Advanced: 31.3 *vs.* 39.6 *vs.* 69	NA	Median survival (months, lead-time corrected): 30 *vs.* 14 3-year: 48 *vs*. 23	Curative 41 *vs.* 27 ($P < 0.001$)
Chen *et al.*[76], 2002	Retro-spec-tive	Clinical mar-kers[f] + US	1991- 1998	4385 *vs.* 458	Asia (Tai-wan)	Cirrhosis: 7 *vs.* un-known HBV: 65.9 *vs.* 67.0 HCV: 18.2 *vs.* 14.9	NA	HR: 0.76 (0.38-1.52)	NA	NA
Yuen *et al.*[60], 2000	Retro-spec-tive	AFP +/- US	1995-1997	142 *vs.* 164	Asia (HK)	Cirrhosis: 85.2 *vs.* 68.9 ($P = 0.0013$)	Tumor < 3 cm: 40.1 *vs.* 4.9 Tumor < 5 cm: 61.3 *vs.* 11.6 Multifocal: 32.4 *vs.* 50 PV invasion: 9.2 *vs.* 38.4 ($P < 0.001$)	NA	Median survival (months): 22 *vs.* 5	Curative resection: 26.8 *vs.* 7.9 ($P < 0.001$) TACE: 45.1 *vs.* 32.3 ($P = 0.03$)

[a]Tumor stages per Liver cancer study group of Japan guidelines, based on: (1) tumor diameter ≤ 20 mm; (2) single tumor; (3) no vascular invasion; tumors that met three, two, one or none of the conditions were classified as stage I, II, III, or IV respectively; [b]Hazard ratio in routine surveillance (≥ 1 US surveillance annually) *vs.* inconsistent surveillance compared to no surveillance; [c]comparison groups: routine surveillance *vs.* inconsistent surveillance *vs.* no surveillance; [d]comparison groups: surveillance 1-6 months *vs.* 7-12 months *vs.* 13-24 months *vs.* 25-36 months *vs.* never screened; [e]comparison groups: HCC diagnosed from surveillance 6-12 months *vs.* incidental diagnosis *vs.* symptomatic diagnosis; [f]6 markers: (1) positive hepatitis B surface antigen (HbsAg); (2) positive antibody for hepatitis C (anti-HCV); (3) alpha-fetoprotein (AFP) ≥ 20 ng/mL; (4) aspartate transaminase (AST) ≥ 40 IU/L; (5) alanine transaminase (ALT) ≥ 45 IU/L; and (6) family history of HCC. Adj HR: adjusted hazard ratio; BCLC: Barcelona Clinic Liver Cancer staging; CEUS: contrast-enhanced ultrasound; CT: computed tomography; DCP: des-gamma-carboxyprothrombin; dx: diagnosis; HBV: hepatitis B virus; HCC: hepatocellular carcinoma; HCV: hepatitic C virus; HK: Hong Kong; HR: hazard ratio; NA: not available; LTx: liver transplant; OR: odds ratio; RFA: radiofrequency ablation; PEI: percutaneous ethanol injection; S: surveillance group; NS: no surveillance group; TACE: transarterial chemoembolization; TNM: tumor, node, metastasis staging system of the American Joint Committee on Cancer; Tx: treatment; Unadj: unadjusted; US: ultrasound

ficulty of conducting RCTs on HCC surveillance among cirrhotic patients. Hence, Taylor *et al.*[16] used the Markov model to simulate a HCC surveillance program on cirrhotic patients, and to study the benefit and harm of surveillance. A small absolute mortality benefit was found in the HCC surveillance group, with a number needed to screen of 77. After a focal lesion was identified, further investigations were carried out based on EASL-EORTC (European Association for the Study of the Liver and the European Organization for Research and Treatment of Cancer) recall policy[17]. However, many more patients experienced additional unnecessary imaging or biopsy due to false positive results, with a number needed to harm of 7 only [Table 1].

Cohort studies

There are a large number of cohort studies on the efficacy of HCC surveillance in our literature search over the past 20 years. We included twenty-four retrospective cohort studies that compared survival and/or mortality of surveillance-detected HCC to incidentally diagnosed HCC [Table 2]. In general, the patients in the surveillance group have chronic viral hepatitis [hepatitis B virus (HBV) and hepatitis C virus (HCV)] infection or cirrhosis of any etiology [Table 2].

Patients in the surveillance group had earlier stages of HCC at diagnosis: 22.8%-80.3% of surveillance group patients had Barcelona Clinic Liver Cancer staging (BCLC) stage 0/A disease. Not surprisingly, more patients in the surveillance compared to non-surveillance group underwent curative HCC treatment [surgical resec-

tion, radiofrequency ablation (RFA)/percutaneous ethanol injection, liver transplant]. Among the reported studies, up to 53.5% of patients in the surveillance group underwent surgical resection[18], 53% received liver transplant[19], 49.1% received RFA[20]. The reported median survival in the surveillance group differs among the studies. Singal *et al.*[21] reported 14.6 months median survival in patients whose HCC was detected from surveillance imaging [computed tomography (CT)/magnetic resonance imaging (MRI)/contrast-enhanced ultrasound/ultrasound (US)] within 6 months of HCC diagnosis; while Oeda *et al.*[20] reported 56.5 months of median survival (corrected with lead-time) in the Japanese population, where high-risk cirrhosis patients were screened every 3-4 months with US and serum biomarkers [AFP/AFP-L3/des-gamma-carboxyprothrombin (DCP)] based on Japanese society of Hepatology practice guidelines. Most of these cohort studies carry selection bias (specialist centre referrals), lead-time and length-time bias inherent to the study design. Several studies attempted to correct for the lead-time bias in survival time reporting, based on HCC doubling time (90-120 days)[21,23-26]. Overall, the data from cohort studies demonstrated that HCC surveillance was associated with early-stage tumor detection and curative treatments. Improved overall survival was evidenced in the surveillance group as well. Thus, the benefits of surveillance included early diagnosis, more treatment options, and prolonged survival compared to no surveillance [Table 2].

Several prospective cohort studies were conducted to investigate the benefit of HCC surveillance in at-risk populations. Two studies examined surveillance in chronic hepatitis B patients. McMahon *et al.*[26] conducted a population-based prospective study for 16 years on Alaska natives with chronic hepatitis B patients. Surveillance modality was 6-monthly AFP. Surveillance detected more early resectable HCC and accorded significantly longer survival. A study in Thailand by Ungtrakul *et al.*[27] recruited 2,293 chronic hepatitis B patients and surveillance was carried out with 6-monthly AFP and ultrasound. A high 3-year survival of 90% was observed as most patients were able to receive curative treatments. A Taiwanese group evaluated a community-based HCC surveillance program with abdominal ultrasound. Subjects were selected from a risk score. Mortality in the surveillance group was reduced compared to the control group and the general population[28]. Overall, evidence supports HCC surveillance in at-risk populations because it detects smaller tumors that are amenable to curative treatment [Table 2].

Harm of surveillance

The study by Taylor *et al.*[16] simulated HCC surveillance in cirrhotic patients based on EASL-EORTC recall policy [Table 1]. It showed more patients experienced unnecessary biopsy or imaging due to false positive screening results, and the calculated number needed to harm was only 7 compared to a small mortality benefit. Few cohort studies mentioned the harm of HCC surveillance. One retrospective cohort study by Atiq *et al.*[29] aimed to characterize the correlation of harm and benefits in cirrhosis patients undergoing HCC surveillance. Surveillance-related harm was defined as additional scans, biopsies, or procedures performed for false-positive or indeterminate results. Around one quarter (27.5%) of the patients experienced harm, and it was more often related to ultrasound than AFP. This was associated with hepatology subspecialty care, elevated ALT, and portal hypertension with thrombocytopenia. However, psychological harm and financial harm were not evaluated in this study.

Surveillance modalities

Cancer surveillance tools should be accurate and cost-effective, and able to detect tumor at a stage that cure is possible. HCC usually develops in populations with defined risk factors. Cirrhosis is the major risk factor of HCC development, with an annual incidence of 1.5%, which makes HCC a good target for surveillance[30,31]. At present, ultrasound and serum AFP are widely accepted as the primary surveillance tools for HCC. Here we reviewed the current evidence of HCC surveillance tools.

Imaging

The recommended surveillance modality differs slightly in different parts of the world, but the majority recommends ultrasound imaging with or without serum AFP[32].

A shortcoming of ultrasound in HCC surveillance is its relatively low sensitivity and specificity[33]. A recent retrospective cohort study by Samoylova *et al.*[34] investigated the predictors for ultrasound failure of HCC detection. It was found that the sensitivity of ultrasound to detect HCC for subjects with BMI ≥ 30 was significantly lower (0.76) compared to those with BMI < 30 group (0.87). Patients with NASH had a ultrasound sensitivity of only 0.59 compared to 0.84 in other etiologies, suggesting 41% of HCC would be missed in this population. Thus we currently lack an ideal first-line imaging modality for surveillance of HCC in patients with NASH despite the latter becoming an increasingly prevalent liver disease worldwide.

A recent systemic review and meta-analysis studied the use of surveillance imaging, with or without AFP, for early detection of HCC in patients with cirrhosis. Thirty-two studies were reviewed and ultrasound was found to have a good sensitivity for detecting any stage HCC. However it performs poorly in detecting early-stage HCC with only 47% sensitivity. The combination of ultrasound with AFP increased the sensitivity (65%) but also lowered the specificity for HCC detection[33].

Pocha *et al.*[35] conducted a randomized trial comparing biannual ultrasound *vs.* annual CT in HCC surveillance of cirrhotic patients. CT has a comparable sensitivity (62.5%) to ultrasound-based surveillance. However, due to its high cost and repeated radiation exposure, no evidence so far supports the use of CT as surveillance modality. Studies comparing MRI and ultrasound showed that MRI has a significantly higher sensitivity than ultrasound (83.7% *vs.* 25.6%) for HCC detection in cirrhotic patients[36]. However, the high cost, limited availability of scanners and long scanning time make MRI not ideal as a surveillance tool.

Serum biomarkers

Serum biomarkers are cancer-related molecules or substances that are measurable in the peripheral blood, enabling early cancer detection. They are attractive tools in cancer surveillance and diagnosis as they are noninvasive with the convenience of repeated sample collections.

The most commonly used serum marker in HCC is AFP, which by itself has limited sensitivity and specificity, and serves as an adjunct to imaging in HCC diagnosis. AFP-L3 measures the AFP isoform that is reactive to lens culinaris agglutinin. It is widely used for HCC surveillance in Japan. A recent study on AFP-L3 by Kumada *et al.*[37] involving 2,830 patients in a HCC surveillance program found that 34.3% of the patients had elevated AFP-L3 1 year prior to the diagnosis of HCC, suggesting that it can be an earlier predictor of HCC development.

DCP, also known as prothrombin-induced by vitamin K absence-II, is an abnormal prothrombin formed in the presence of vitamin K antagonism. The performance of DCP varies among different studies[38,39]. One study by Ji *et al.*[40] studied DCP *vs.* AFP in HBV-related HCC, and concluded that DCP is complementary to AFP in detecting AFP-negative HCC, and excluding HCC in cirrhotic patients with false positive AFP, suggesting its complementary role in HCC surveillance. Similar conclusion was drawn in HCV cohorts by the Italian group[41].

Other biomarkers studied were GPC3 (plasma membrane bound protein), Golgi protein 73, interleukin-6, and squamous cell carcinoma antigen. These biomarkers have been studied for many years, but had inconsistent performance in different patient populations, precluding its wide use in HCC surveillance.

Liquid biopsy

Recent advances in genomics sequencing technologies allow identification and quantification of cancer genetic material in the circulating blood. This has enabled the discovery of novel biomarkers and increased our understanding of HCC cancer genomics.

Liquid biopsy refers to the sampling of bodily fluid instead of solid tissue for the genetic material of cancer. The most common sampling markers are cell-free DNA (cfDNA), circulating tumor DNA (ctDNA), circulating tumor cells (CTCs), and cell-free RNAs (e.g., miRNA), which are the byproducts of tumor cells. In contrast to solid tumor biopsy, liquid biopsy is less invasive and allows repeated sampling for dynamic evaluation of disease status and prediction of clinical outcomes. Solid tumour biopsy is infrequently done now as it is painful, carries risks of bleeding and iatrogenic tumor seeding. Liquid biopsy has been shown to have higher sensitivity in the early tumor detection and prognostication. The application of liquid biopsy in HCC is still under evaluation.

Liao *et al*.[42] conducted a meta-analysis to evaluate the use of cfDNA in HCC diagnosis. By quantitatively and qualitatively analysing the concentrations of circulating cfDNA, as well as single-gene methylation alterations, they found that the combination of AFP and cfDNA can attain an optimal sensitivity of 81% and specificity of 96% in the diagnosis of HCC in at-risk patients.

CTCs are mainly studied for its role in cancer recurrence, prognosis, and response to treatments. It has not been investigated in the context of HCC surveillance.

Data on the role of ctDNA in HCC are limited. Zhou *et al*.[43] studied the size profiles of plasma DNA in 90 HCC patients, and found aberrantly short DNA molecules in HCC patients as well as elevated amounts of mitochondrial DNA. Their presence raises the suspicion of early HCC during surveillance process. The detection of ctDNA can also predict metastasis in 86% of the HCC patients.

Several studies were done on quantification of circulating miRNA to facilitate the diagnosis of HCC in chronic hepatitis[44-46] and hepatitis C patients[47]. Li *et al*.[44] studied the serum miRNA levels of control, HBV and HBV-positive HCC patients. They found that miR-375 alone has a high diagnostic accuracy of HCC compared to control patients, and miRNA expression profiles can differentiate HBV patients from control, and HBV-positive HCC patients from HBV patients. The study suggested that serum miRNAs can be used as noninvasive biomarkers for the diagnosis of HBV infection and HBV-positive HCC. Hung *et al*.[45] demonstrated that serum circulating miRNAs, miR-122 and miR-let-7b, can differentiate dysplastic nodules from early HCC in chronic hepatitis B patients. A recently published paper by the Vietnamese group collected all the published data on miRNAs in HCC, and established a miRNA panel for HCC diagnosis. Three miRNAs, mir-21, 122, and 192, together with AFP can be combined to diagnose early HCC in hepatitis B patients[46].

In the current clinical setting, liquid biopsy has limited applications in HCC surveillance owing to the lack of standardized methodology and the high cost of genetic sequencing, which needs to be improved with more studies and standardization of assays. The high cost of genetic sequencing also precludes its use as a surveillance modality for HCC. However, liquid biopsy offers a noninvasive method of characterizing HCC tumor cells' genomic mutations and molecular pathways, hence offers opportunities for further studies on the therapeutic targets in HCC. It is promising as a non-invasive, accurate and convenient surveillance tool for HCC in the future.

DISCUSSION

This study reviewed the current status of the literature on the efficacy, benefit and harm of HCC surveillance, as well as new developments in surveillance modalities. The benefit of HCC surveillance was demonstrated in one RCT and supported by a significant number of cohort studies. Although significant bias may be present, it is not feasible to conduct further randomized trials due to ethical concerns[15]. Cohort studies demonstrated earlier tumor detection and longer survival in HCC patients diagnosed from surveillance. However, the proportion of patients diagnosed at early-stage and length of survival differs significantly in

different cohorts, suggesting that the benefit is not homogeneous in all HCC patients. Different ethnic origin and HCC etiologies likely contributed to this heterogeneity. Patients with NASH and alcoholic liver disease are more common in the United States than Asian and European population, and has lower risk of developing HCC[48].

Non-alcoholic fatty liver disease (NAFLD) and NASH are emerging causes of liver cirrhosis and HCC. It has been reported that the yearly HCC incidence among NASH-cirrhotic patients was 2.6%[49], and a significant number of patients with NAFLD-related HCC did not have cirrhosis[50,51]. NASH-related HCC patients received significantly less HCC surveillance compared to HCV or alcohol-related HCC patients, and received less HCC-related treatment. However, the one-year survival rate was similar[51]. At present, AASLD and EASL guidelines do not recommend routine HCC surveillance for non-cirrhotic NASH patients. More studies are needed to develop a cost-effective surveillance program in this population.

Chronic hepatitis C infection had been a major risk factor for liver cirrhosis and HCC in the world. The incidence of HCC in patients with chronic hepatitis C infection was reported to be 1%-4%, higher in patients with cirrhosis[52-54]. Treatment with direct-acting antivirals (DAAs) has impressive efficacy in Hepatitis C eradication. However, its effect on the long-term clinical outcome was lacking[55]. Conti *et al.*[56] found that unfortunately HCC occurrence was not reduced in successfully treated cirrhotic patients. Recently, a systemic review and meta-analysis was performed by Singh *et al.*[57] on oral DAAs use and risk of HCC development. A total of 8 controlled studies and 36 uncontrolled studies were reviewed, and the estimated incidence of HCC was 3.3% and 1.5% (1 in 67 DAA users) in controlled and uncontrolled studies respectively, not significantly different from the previously reported incidence in chronic hepatitis C patients. Moreover, the HCC recurrence rate was as high as 16.7%-20.1% with DAAs treatment. Hence, continuing HCC surveillance is still important in patients treated with DAA for hepatitis C, even after achievement of sustained virological response.

Two earlier reviews on HCC surveillance were published in 2014. A meta-analysis done by Singal *et al.*[58] aimed to determine the effect of surveillance on cirrhotic patients. Studies published from 1990 to 2014 were reviewed and pooled odds ratio was calculated on 47 selected studies with a total of 15,158 HCC patients. Surveillance was associated with early-stage cancer detection (OR 2.08 CI 1.8-2.37), curative treatment rates (OR 2.24 CI 1.99-2.52), and prolonged survival (OR 1.9 CI 1.67-2.17), supporting HCC surveillance in cirrhotic patients. On the other hand, Kansagara *et al.*[59] did a systemic review to study the strength of evidence supporting HCC surveillance. A total of 22 studies were selected and the overall strength of evidence on the effect of screening was very low owing to limited randomized trials and significant confounders in cohort studies. Screening identified early-stage HCC. However, its effect on mortality and survival in chronic liver disease patients is not clear. The conflicted evidence may have contributed to the underutilization of HCC surveillance in some regions.

The harm of HCC surveillance is an important issue but there were few studies published. One retrospective cohort study demonstrated that one fourth of the patients who underwent HCC surveillance required additional tests due to false positive or indeterminate results. This calls for development of new surveillance modalities that minimize false positive results without compromising the diagnostic accuracy for HCC. Although imaging modalities such as contrast-enhanced CT and MRI have high sensitivity and specificity, they are not recommended for surveillance due to the high cost and limited availability. Other than AFP, serum biomarkers are not widely accepted as surveillance tools except in a few countries, such as Japan. More studies are needed to evaluate the clinical utility of novel serum biomarkers and their role in HCC surveillance. Liquid biopsy is the latest tool in cancer diagnosis and prognosis. Emerging evidence indicates that liquid biopsy can be used in HCC surveillance as it is noninvasive and provides a dynamic profile of disease progression.

In conclusion, studies have shown that current surveillance strategies can detect significantly more early stage HCCs: 61.3%-88% were within Milan criteria and 61%-91.7% were BCLC stage 0/A compared to 11.6%-44% and 21%-73.3% respectively for subjects who were not on HCC surveillance[14,60-62]. Up to 73.8%-80% of the HCC patients in the surveillance group received curative management with a median survival as high as 4.7 years and a 3-year survival of up to 73% compared to only 45% of subjects not on surveillance being amenable to curative therapy with a median survival of only up to 2.6 years[20,61,63]. Hence, HCC surveillance in at-risk patients is beneficial and improves patient outcome.

Further research on hepatocarcinogenesis and novel surveillance tools will continue to help refine the surveillance guidelines. In particular, further understanding of the hepatocarcinogenesis pathway in non-alcoholic fatty liver disease-related HCC is needed to evolve a surveillance strategy for this huge group of patients. The aim is always to detect more curable HCC in patients with chronic liver disease and hence reduce HCC-related mortality in the near future.

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Author's contributions

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