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Original Article

Evaluation of Ultrasound-based Surveillance for Hepatocellular Carcinoma in Patients at Risk: Results From a German Multicenter Retrospective Cohort Study

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Abstract

Background and Aims: Hepatocellular carcinoma (HCC) surveillance in patients at risk is strongly recommended and usually performed by ultrasound (US) semiannually with or without alfa-fetoprotein (AFP) measurements. Quality parameters except for surveillance intervals have not been strictly defined. We aimed to evaluate surveillance success and risk factors for surveillance failure. ***Methods:*** Patients with ≥1 US prior to HCC diagnosis performed at four tertiary referral hospitals in Germany between 2008 and 2019 were retrospectively analyzed. Surveillance success was defined as HCC detection within Milan criteria. ***Results:*** Only 47% of 156 patients, median age 63 (interquartile range: 57–70) years, 56% male, and 96% with cirrhosis, received recommended surveillance modality and interval. Surveillance failure occurred in 29% and was significantly associated with lower median model for end-stage liver disease (MELD) score odds ratio (OR) 1.154, 95% confidence interval (CI): 1.027–1.297, p=0.025) and HCC localization within right liver lobe (OR: 6.083, 95% CI: 1.303–28.407, p=0.022), but not with AFP ≥200 µg/L. Patients with surveillance failure had significantly more intermediate/advanced tumor stages (93% vs. 6%, p<0.001), fewer curative treatment options (15% vs. 75%, p<0.001) and lower survival at 1 year (54% vs. 75%, p=0.041), 2 years (32% vs. 57%, p=0.019) and 5 years (0% vs. 16%, p=0.009). Alcoholic and non-alcoholic fatty liver disease (OR: 6.1, 95% CI: 1.7–21.3, p=0.005) and ascites (OR: 3.9, 95% CI: 1.2–12.6, p=0.021) were independently associated with severe visual limitations on US. ***Conclusions:*** US-based HCC surveillance in patients at risk frequently fails and its failure is associated with unfavorable patient-related outcomes. Lower MELD score and HCC localization within right liver lobe were significantly associated with surveillance failure.

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Introduction

Liver cancer, of which hepatocellular carcinoma (HCC) comprises 75–85% of cases, is the sixth most common cancer and the fourth leading cause of cancer death worldwide with 841,000 new cases and 782,000 deaths annually.[1] The main risk factors for HCC are chronic infection with hepatitis B or hepatitis C virus (HBV and HCV, respectively), aflatoxin-contamination, heavy alcohol intake, obesity, smoking, and type 2 diabetes, depending on the geographical region.[2] The incidence of HCC is projected to further increase mainly because of an increasing prevalence of nonalcoholic fatty liver disease (NAFLD).[3–6] An estimated 90% of HCCs occur in the context of cirrhosis irrespective of its etiology, but HCC also develops in non-cirrhotic chronic liver diseases such as chronic hepatitis B and NAFLD.[4,7] The prognosis of HCC depends on both tumor stage and liver function, ranging from potential cure at very early (0) and early stages (A) in patients with preserved

Keywords: Hepatocellular carcinoma; Surveillance success; Screening; Ultrasound.

Abbreviations: AASLD, American Association for the Study of Liver Diseases; AFP, alfa-fetoprotein; ALD, alcoholic liver disease; APASL, Asian Pacific Association for the Study of the Liver; BMI, body mass index; CI, confidence interval; CT, computed tomography; DEGUM, German Society for Ultrasound in Medicine; DGVS, German Society for digestive and metabolic diseases; EASL, European Association for the Study of the Liver; HBV, hepatitis B virus; HCC, Hepatocellular carcinoma; HCV, hepatitis C Virus; IQR, interquartile range; mBCLC, modified Barcelona Clinic Liver Cancer; MELD, model for end-stage liver disease; MRI, magnetic resonance imaging; NAFLD, nonalcoholic fatty liver disease; OR, odds ratio; SIRT, selective internal radiotherapy; TACE, transarterial chemoembolization; US, Ultrasound.

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liver function to only short-term survival at terminal stages (D) in patients with advanced HCC and impaired liver function according to the modified Barcelona Clinic Liver Cancer (mBCLC) staging system.[8,9] Because of these characteristics, HCC is suitable for surveillance which is recommended by national and international guidelines.[8,10–12] The target population for HCC surveillance differs slightly between guidelines including (1) cirrhotic patients Child-Pugh class A and B or Child-Pugh class C awaiting liver transplantation, non-cirrhotic HBV patients at intermediate or high risk of HCC, and non-cirrhotic F3 patients, regardless of etiology, based on individual risk assessment according to the European Association for the Study of the Liver (EASL), (2) adults with cirrhosis except patients with Child-Pugh class C-cirrhosis unsuitable for liver transplantation according to the American Association for the Study of Liver Diseases (AASLD), (3) patients with cirrhosis and chronic HBV carriers depending on ethnicity, age and family history according to the Asian Pacific Association for the Study of the Liver (APASL), and (4) patients with cirrhosis, chronic hepatitis B or steatohepatitis in whom HCC therapy can be offered according to the German Society for digestive and metabolic diseases (DGVS).[8,10,12,13] Ultrasound (US) is the recommended method of choice despite its limitations due to user dependency and a suboptimal sensitivity for the detection of HCC at any stage and early HCC.[8,10,12–15] In this regard, a semiannual surveillance interval is the most established and recommended mode.[16,17] Despite its general acceptance and wide application, recent studies highlighted barriers to successful surveillance on different levels.[18–21] Only 37% of HCC were diagnosed by surveillance according to a recent systematic review and meta-analysis, and 23–41% of HCC are detected at an advanced stage despite undergoing surveillance.[22–24] The ability to measure the efficacy of a certain procedure is a prerequisite of quality improvement initiatives. Although mortality reduction is the ultimate goal of surveillance and screening in general, this endpoint poses a challenge to studies evaluating particular aspects within the whole surveillance process.[25] In this context, del Poggio *et al*.[22] and Khalili *et al*.[23] proposed the Milan criteria to define the success of US-based HCC surveillance in their studies.

In our study, we aimed to evaluate the surveillance process in terms of surveillance success according to this definition, possible risk factors for surveillance failure, and the application of current guideline recommendations.

Methods

We retrospectively evaluated patients in whom HCC was diagnosed during surveillance at four tertiary referral centers in Germany (University Hospitals Cologne, Jena, Saarland and Frankfurt). Patients were included if they fulfilled all the following inclusion criteria: (1) diagnosis of HCC according to the current EASL guideline;[8] (2) at risk of HCC and with surveillance as recommended by the current EASL guidelines;[8] (3) ≥1 US at the study sites prior to HCC diagnosis. The HCC diagnosis dates ranged from 2008 to 2019. Exclusion criteria were diagnosis of HCC at first presentation or first US and patients who were referred with known HCC for further evaluation and treatment. The presence of cirrhosis was confirmed either by histology, by a typical result in the elastography or by the combination of typical clinical features, laboratory values and morphological results in US or cross-sectional imaging.

The following parameters were retrieved from medical records: sex, age, body mass index (BMI), etiology of chronic liver disease, presence of cirrhosis, Child-Pugh class, model of end-stage liver disease (MELD) score, laboratory values at HCC diagnosis and last US prior to HCC diagnosis, including aminotransferase (U/L), alfa-fetoprotein (AFP, µg/L), dates of HCC diagnosis and US prior to HCC diagnosis, number, size, and localization of HCC lesions, presence of extrahepatic HCC manifestation and portal vein invasion, diagnostic method of HCC diagnosis, presence of liver observations and visual limitations at US prior to HCC diagnosis, total number of US for all indications of each operator, US device, presence of ascites, fatty liver, and portal vein thrombosis on US at HCC diagnosis and prior to HCC diagnosis, primary HCC therapy, evaluation of liver transplantation, and mortality at 1, 2, and 5 years. For analysis of HCC localization, only HCC within the right or left liver lobe were considered, but not bilobar HCC. Ethnicity was not routinely documented in the patient records and information was not available for our analysis. We, however, estimated the vast majority of cases to be of Caucasian origin. Within each study center, US was performed according to a local standard operating procedure. Visual limitations and observations were retrospectively evaluated and categorized as no or minimal (score A), moderate (score B) and severe limitations (score C) and as negative (category 1), subthreshold (category 2) and positive (category 3), respectively, according to previously published recommendations.[26] Examples are shown in Figures 1 and 2. US devices were classified according to the recommendations of the German Society for Ultrasound in Medicine (DEGUM).[27]

The mBCLC staging system was retrospectively applied to all cases according to the current EASL guideline.[8] The Milan criteria were defined as tumor size ≤5 cm in diameter in patients with single HCC or ≤3 tumors with a tumor size ≤3 cm each in patients with multiple nodules in the absence of extrahepatic HCC manifestations and portal vein invasion as previously published.[28] In cases with more than one imaging study, we used the maximum diameter reported in all available studies to classify the HCC according to the Milan criteria, to ensure the best objectivity of our primary outcome. Elevated transaminases (alanine or aspartate aminotransferase) were defined as values greater than two times the upper limit of normal (i.e. >70 U/L in women and >100 U/L in men). We considered significant elevation (i.e. two times greater than the upper limit of normal) of transaminases for analysis to rule out its effect on US visibility.

Expertise was assessed by each operator's total US number for all indications which was then categorized into quartiles. Surveillance interval was defined as time between HCC diagnosis and last US prior to HCC diagnosis. In addition to the recommended surveillance interval of 6 months, we included 1 month more as range of tolerance, i.e. 7 months in total. Curative treatment included surgery and radiofrequency ablation (RFA) as well as transarterial chemoembolization (TACE), selective internal radiotherapy (SIRT) and systematic therapy in selective cases while evaluated for liver transplant in terms of a bridge to transplant strategy.

Surveillance policies of all four study sites contained US for all patients at risk for HCC at regular intervals, usually every 6 months. The accompanying measurement of AFP was optional. In cases of the detection of a nodule on primary imaging, multiphasic contrast-enhanced computed tomography (CT) or magnetic resonance imaging (MRI) and/or contrast-enhanced US was conducted. In cases, in which diagnosis remained inconclusive hereafter, histologic diagnosis was obtained.

The primary endpoint was surveillance success (1) in the overall cohort defined as the proportion of patients with HCC detected inside the Milan criteria and (2) in the subgroup of patients with available US at the time of HCC diagnosis and a surveillance interval ≤210 days (i.e. the recommended in-

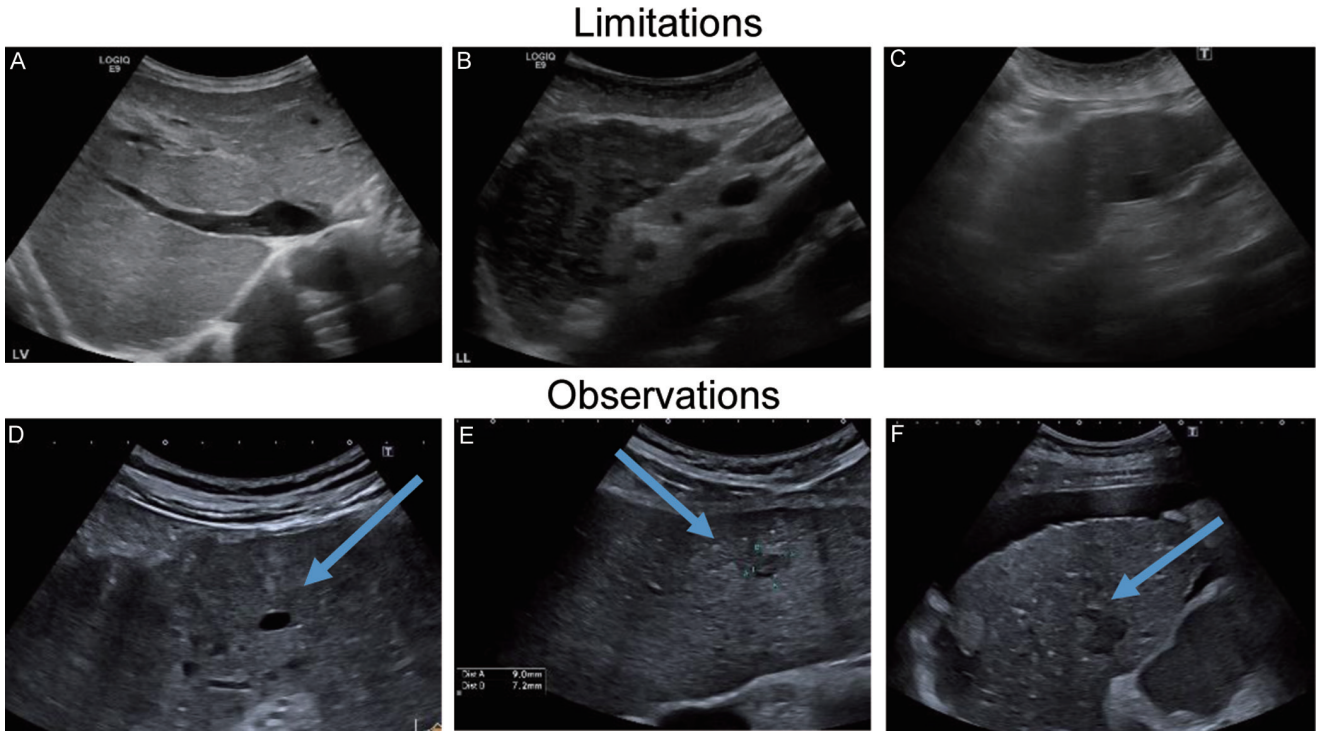

Fig. 1. Scoring of visual limitations (upper panel, A–C) and observations (lower panel, D–F) in ultrasound, adapted by Fetzer *et al*.[26] (A) Visualization score A (minimal limitations, i.e. limitations if any are unlikely to meaningfully affect sensitivity). (B) Visualization score B (moderate limitations, i.e. limitations may obscure small masses. (C) Visualization score C (severe limitations, i.e. limitations significantly lower sensitivity for focal liver lesions). (D) Category negative (i.e. no observation or only definitely benign lesion). (E) category subthreshold (i.e. observation <10 mm in diameter, not definitely benign). (F) category positive (observation ≥10 mm in diameter, not definitely benign or new thrombus in vein).

terval exceeded by 1 month or more) defined as the proportion of patients with HCC detected within the Milan criteria excluding patients in which HCC was not visible on US, but only on other imaging modalities. Secondary endpoints were (1) the evaluation of potential risk factors for surveillance failure, (2) the effect of surveillance success on tumor stage, curative treatment and survival, (3) the application of current guideline recommendations, and (4) the description of US performance.

Statistical analysis was performed with SPSS version 27 (IBM Corp., Armonk, NY, USA) and Excel (Microsoft, Richmond, CA, USA). Categorical variables were analyzed as absolute numbers and their relative frequencies, and continuous variables as median and interquartile range (IQR). Categorical variables were compared using χ^2-tests, continuous variables were compared using Mann-Whitney U-tests. Logistic regression analysis was performed for significant co-variables identified by univariate analysis using successful surveillance as dependent variable. *P*-values <0.05 were considered statistically significant.

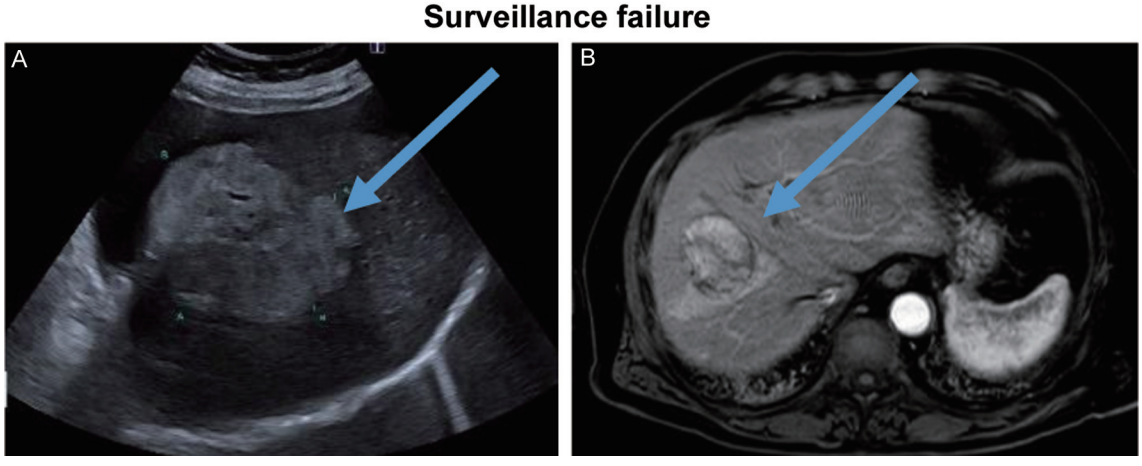

Fig. 2. Examples of surveillance failure. (A) Ultrasound (US) with HCC detected outside the Milan criteria after previous negative US. (B) Magnet resonance imaging (MRI) with HCC detected outside Milan criteria that was not seen on US.

Table 1. Baseline characteristics

Characteristic	Value
Patients, *n* (%)	156
Male/female, *n* (%)	88 (56) / 68 (44)
Age in years, median (IQR)	63 (57–70)
Etiology of liver disease, *n* (%)	
cHB	11 (7)
cHC	76 (49)
ALD	28 (18)
NAFLD	6 (4)
PSC	3 (2)
PBC	3 (2)
AIH	2 (1)
Hemochromatosis	4 (3)
Cryptogenic	2 (1)
Other	2 (1)
Combined etiology	19 (12)
cHB+cHC	2 (1)
cHB+ALD	4 (3)
cHB+NAFLD	2 (1)
cHB+AIH	1 (1)
cHC+ALD	8 (5)
cHC+NAFLD	1 (1)
PSC+AIH	1 (1)
Presence of liver cirrhosis, *n* (%)	150 (96)
Child Pugh class, *n* (%)[1]	
A	82 (55)
B	47 (31)
C	21 (14)
MELD score, median (IQR)[1]	9 (8–13)
Study site, *n* (%)	
A	74 (47)
B	40 (26)
C	11 (7)
D	31 (20)

[1]In patients with liver cirrhosis (*n*=151). AIH, autoimmune hepatitis; ALD, alcoholic liver disease; CHB, chronic hepatitis B; CHC, chronic hepatitis C; IQR, interquartile range; MELD, model for end-stage liver disease; NAFLD, non-alcoholic fatty liver disease; PBC, primary biliary cholangitis; PSC, primary sclerosing cholangitis.

This retrospective study was conducted in accordance with the Declaration of Helsinki and Good Clinical Practice guidelines. Approvals of responsible local ethic committees were obtained (Cologne: 20-1166; Jena: 2020-1900; Saarland: 271/11; Frankfurt SGI-3-2018, amendment 1 2019) and the need for informed consent was waived due to the strictly retrospective character of the study. STARD (Standards for Reporting Diagnostic accuracy studies) was applied as the recommended study-reporting guideline upon submission.

Table 2. Number of patients with HCC detected by US and/or cross sectional imaging during surveillance

	Milan criteria		Total
	Inside	Outside	
US+ (%)	78 (70)	34 (30)	112
US–, CT/MRI+ (%)	11 (69)	5 (31)	16
US n.a., CT/MRI+ (%)	21 (75)	7 (25)	28
Total	110 (71)	46 (29)	156

CT, computer tomography; MRI, magnetic resonance imaging; n.a., not available; US, ultrasound; +indicates detection of HCC; –indicates HCC not detectable.

Results

We identified 156 patients with HCC and ≥1 US prior to the diagnosis with a median of 63 (IQR: 57–70) years of age and a male-to-female-ratio of 1.29. The most frequent etiologies of underlying chronic liver disease were chronic hepatitis C (*n*=76, 49%), alcoholic liver disease (*n*=28, 18%), and chronic hepatitis B (*n*=17, 11%). Cirrhosis was present in the vast majority of patients (*n*=150, 96%). In cases with cirrhosis, the median MELD score was 9 (IQR: 8–13) and only 82 patients (55%) had preserved liver function corresponding to a Child-Pugh class A. In the absence of cirrhosis (*n*=6), chronic liver disease was attributed to chronic hepatitis B in two (33%) patients and chronic hepatitis C in four (67%) patients. At time of diagnosis, 95 (61%) patients had a single HCC, 37 (24%) patients had two or three HCC nodules, and 24 (15%) patients had four or more HCC nodules. Portal invasion and extrahepatic spread was present in 15 (10%) patients and seven (5%) patients, respectively. Median surveillance interval was 185 days (IQR: 120–361) with a surveillance interval ≤210 days in 92 (59%) patients and ≤365 days in 120 (77%) patients. The median surveillance interval did not differ significantly between patients with and without successful surveillance (176 days, IQR: 111–296 vs. 216.5 days, IQR: 167–369, *p*=0.114). Patients had a median of four US evaluations (IQR: 1–9) prior to HCC diagnosis. Baseline characteristics are shown in Table 1 and Supplementary Table 1.

According to our definition, surveillance success was 71% (*n*=110/156) in the overall cohort (Table 2) and 65% (*n*=49/75) in the subgroup. In the total cohort, surveillance failure was significantly associated with a lower median MELD score (8, IQR: 7–9 vs. 9, IQR: 8–14, *p*=0.015) and localization of HCC within the right liver lobe compared to the left liver lobe (77% vs. 97%, *p*=0.014) in univariate analysis, which translated into an OR of 1.154 (95% CI: 1.027–1.297, *p*=0.025) and 6.083 (95% CI: 1.303–28.407, *p*=0.022), respectively, in multivariate analysis. Sex, presence of cirrhosis, study center, and surveillance interval ≤210 days just missed statistical significance (Table 3). In the subgroup, a lower median MELD score (8.5, IQR: 7.3–11.6 vs. 10, IQR: 8.3–12.8, *p*=0.023), and no previous observations (88.5% vs. 53%, *p*=0.002) were significantly associated with unsuccessful surveillance, whereas the individual study center just failed statistical significance (77% vs. 65% vs. 33% vs. 38.5%, *p*=0.050). The corresponding ORs in the logistic regression analysis were 1.203 (95% CI: 1.008–1.203, *p*=0.040) for median MELD score and 7.128 (95% CI: 1.799–28.243, *p*=0.005) for no previous observations (Table 4).

According to our definition of surveillance success, HCCs in patients with unsuccessful surveillance were inevitably categorized into intermediate or later tumor stages, as defined

Table 3. Univariate and multivariate analysis of variables associated with surveillance success

	Univariate		*p* value	Multivariate		*p* value
	Successful	**Unsuccessful**		**OR**	**95% CI**	
Patients, *n* (%)	110 (71)	46 (29)				
Age in years						
Median (IQR)	62 (57–71)	63 (58–70)	0.842			
Sex, *n* (%)						
Male	57 (65)	31 (35)	0.074			
Female	53 (78)	15 (22)				
BMI >30 kg/m^2, *n* (%)*						
No	44 (64)	25 (36)	0.336			
Yes	20 (74)	7 (26)				
Etiology of chronic liver disease, *n* (%)						
Viral hepatitis	72 (73)	27 (27)	0.825			
NAFLD including cryptogenic	8 (73)	3 (27)				
ALD	20 (65)	11 (35)				
Others	10 (67)	5 (33)				
Presence of liver cirrhosis, *n* (%)						
No	6 (100)	0 (0)	0.106			
Yes	104 (69)	46 (31)				
Child-Pugh class, *n* (%)						
A	53 (65)	29 (35)	0.168			
B	34 (72)	13 (28)				
C	17 (81)	4 (19)				
MELD score						
Median (IQR)	9 (8–14)	8 (7–9)	0.015	1.154	1.027–1.297	0.025
Transaminases >2× ULN, *n* (%)**						
No	68 (71)	28 (29)	0.964			
Yes	31 (70)	13 (30)				
AFP, *n* (%)***						
<200 µg/L	69 (70)	30 (30)	0.923			
≥200 µg/L	5 (71)	2 (29)				
Study center, *n* (%)						
A	56 (76)	18 (24)	0.071			
B	29 (72.5)	11 (27.5)				
C	9 (82)	2 (18)				
D	16 (52)	15 (48)				
Surveillance interval, *n* (%)						
≤210 days	70 (76)	22 (24)	0.067			
>210 days	40 (62.5)	24 (37.5)				
Investigators' experience, *n* (%)						
Lowest quartile	23 (77)	7 (23)	0.815			
highest quartile	24 (75)	8 (25)				
Location of HCC						
Right liver lobe	68 (77)	20 (23)	0.014	6.083	1.303–28.407	0.022

(continued)

Table 3. *(continued)*

	Univariate		*p* value	Multivariate		*p* value
	Successful	**Unsuccessful**		**OR**	**95% CI**	
Left liver lobe	30 (97)	1 (3)				
Previous visual limitations, *n* (%)						
Score A	31 (84)	6 (16)	0.123			
Score B	61 (67)	30 (33)				
Score C	18 (64)	10 (36)				
Previous observations, *n* (%)						
No	77 (68)	37 (32)	0.180			
Yes	33 (79)	9 (21)				
Presence of ascites, *n* (%)						
No	78 (67)	38 (33)	0.127			
Yes	32 (80)	8 (20)				
Fatty liver, *n* (%)						
No	82 (68)	39 (32)	0.163			
Yes	28 (80)	7 (20)				
Portal vein thrombosis, *n* (%)						
No	107 (71)	43 (29)	0.261			
Yes	3 (50)	3 (50)				

*n=96; ** n=140; *** n=106. AFP, alfa-fetoprotein; ALD, alcoholic liver disease; BMI, body mass index; CI, confidence interval; IQR, interquartile range; MELD, Model for end-stage liver disease; NAFLD, non-alcoholic fatty liver disease; OR, odds ratio; ULN, upper limit of normal.

Table 4. Univariate and multivariate analysis of variables associated with surveillance success in patients with available US at time of HCC diagnosis and a surveillance interval ≤210 days

	Univariate		*p* value	Multivariate		*p* value
	Successful	**Unsuccessful**		**OR**	**95%-CI**	
Patients, *n* (%)	49 (65)	26 (35)				
Age in years						
Median (IQR)	61 (56, 67.5)	63.5 (57, 70)	0.728			
Sex, *n* (%)						
Male	23 (57.5)	17 (42.5)	0.128			
Female	26 (74)	9 (26)				
BMI >30 kg/m^2, *n* (%)*						
No	17 (47)	19 (52)	0.066			
Yes	8 (80)	2 (20)				
Etiology of chronic liver disease, *n* (%)						
Viral hepatitis	33 (66)	17 (34)	0.819			
NAFLD including cryptogenic	3 (60)	2 (40)				
ALD	10 (71)	4 (29)				
Others	3 (50)	3 (50)				
Presence of liver cirrhosis, *n* (%)						
No	3 (100)	0 (0)	0.198			
Yes	46 (64)	26 (36)				
Child-Pugh class, *n* (%)						
A	13 (93)	1 (7)	0.056			

(continued)

Table 4. *(continued)*

	Univariate		*p* value	Multivariate		*p* value
	Successful	**Unsuccessful**		**OR**	**95%-CI**	
B	27 (59)	19 (41)				
C	9 (60)	6 (40)				
MELD score						
Median (IQR)	10.0 (8.3, 12.8)	8.5 (7.3, 11.6)	0.023	1.203	1.008–1.203	0.040
Transaminases >2× ULN, *n* (%)**						
No	33 (66)	17 (34)	0.937			
Yes	13 (65)	7 (35)				
AFP, *n* (%)***						
<200 µg/L	27 (60)	18 (40)	0.819			
≥200 µg/L	2 (67)	1 (33)				
Study center, *n* (%)						
A	30 (77)	9 (23)	0.050			
B	13 (65)	7 (35)				
C	1 (33)	2 (67)				
D	5 (38.5)	8 (61.5)				
Investigator experience, *n* (%)						
Lowest quartile	12 (80)	2 (20)	0.761			
highest quartile	10 (71)	4 (29)				
Location of HCC						
Right liver lobe	13 (87)	2 (13)	0.271			
Left liver lobe	29 (72.5)	11 (27.5)				
Previous visual limitations, *n* (%)						
Score A	13 (93)	1 (7)	0.056			
Score B	27 (59)	19 (41)				
Score C	9 (60)	6 (40)				
Previous observations, *n* (%)						
No	26 (53)	23 (47)	0.002	7.128	1.799–28.243	0.005
Yes	23 (88.5)	3 (11.5)		1		
Presence of ascites, *n* (%)						
No	34 (64)	19 (36)	0.738			
Yes	15 (68)	7 (32)				
Fatty liver, *n* (%)						
No	40 (64.5)	22 (35.5)	0.745			
Yes	9 (69)	4 (31)				
Portal vein thrombosis, *n* (%)						
No	47 (65)	25 (35)	0.960			
Yes	2 (67)	1 (33)				

*n=46; **n=70; ***n=48. AFP, alfa-fetoprotein; ALD, alcoholic liver disease; BMI, body mass index; CI, confidence interval; IQR, interquartile range; MELD, Model for end-stage liver disease; NAFLD, non-alcoholic fatty liver disease; OR, odds ratio; ULN, upper limit of normal.

by the mBCLC staging system, more often compared with patients with successful surveillance (stage 0 or A: 7% vs. 94%, stage B–D: 93% vs. 6%, p<0.001). Correspondingly, surveillance failure was significantly associated with less frequent curative treatment options (15% vs. 75%, p<0.001) and shorter survival at 1 year (54% vs. 75%, p=0.041), 2 years (32% vs. 57%, p=0.019) and 5 years (0% vs. 16%, p=0.009). Detection outside the Milan criteria (n=46) was

attributed to a single HCC >5 cm in three patients (7%), 2–3 HCC nodules >3 cm in 10 patients (22%), ≥4 HCC nodules regardless of maximum size in 15 patients (33%), portal invasion in one patient (2%), extrahepatic spread in two patients (4%), and a combination of these reasons in 15 patients (33%).

US prior to HCC diagnosis was performed by 59 different operators, who performed a median of estimated 750 (IQR: 452–1,360) examinations for any indication. All examinations were conducted with US devices classified as DEGUM II or III. Visual limitations on US prior to HCC diagnosis were categorized as score A in 37 patients (24%), score B in 91 patients (58%), and score C in 28 patients (18%). Alcoholic liver disease (ALD) or NAFLD and ascites were independently associated with visual limitations score C (OR: 6.1, 95% CI: 1.7–21.3, p=0.005 and OR: 3.9, 95% CI: 1.2–12.6, p=0.021). No association was found for sex, age, obesity, steatosis on US, portal vein thrombosis, transaminases of two times the ULN or more, and Child-Pugh class (Table 5).

Discussion

In our retrospective multicenter cohort study of US-based HCC surveillance in dedicated liver clinics from Germany, success according to our predefined criteria was found in <75% of all patients and in less than two-thirds of the patients in the subgroup with the recommended surveillance modality and interval. Unsuccessful surveillance translated into the detection of HCCs at significantly later tumor stages according to the mBCLC staging system and significantly fewer curative treatment options which was associated with significantly lower survival rates at 1, 2, and 5 years compared with patients with successful surveillance. Among various variables, only lower median MELD score, HCC localization within the right liver lobe, and no previous observations on US were significantly associated with surveillance failure in univariate and multivariate analysis.

Surveillance of patients at increased risk for HCC development is recommended by national (i.e. DGVS) and international (i.e. EASL, AASLD, APASL) guidelines, aiming at a reduction of HCC-related and liver-related mortality overall.[8,10,12,13] A recent systematic review and meta-analysis found a prolonged survival associated with HCC surveillance even after adjusting for lead-time bias, which was attributed to improved early-stage detection and higher curative treatment rates.[14] The combination of US and AFP had a significantly higher sensitivity for HCC detection at any stage and early stage compared to US alone.[15] Accompanying measurement of AFP is recommended by APASL, and optional according to AASLD and DGVS.[10,12,13] Regarding the favorable surveillance interval, semi-annual surveillance was superior to annual surveillance in terms of less advanced HCCs, improved treatment applicability and survival, whereas a shorter surveillance interval of three months was not associated with any clinical benefit.[16,17,29,30]

US offers the advantage of noninvasiveness, the absence of risks, the ability to detect the onset of other complications of cirrhosis, good acceptance by patients, and relatively moderate cost.[8] On the other hand, the performance of US is highly dependent on the expertise of the operator and the quality of the equipment, especially in the context of cirrhosis, limits its efficacy.[8] According to a systematic review and meta-analysis, the pooled sensitivity of US to detect HCC was 94%, which dropped to 63% for the detection of early HCCs defined as one nodule of <5 cm or three nodules each <3 cm in diameter.[29] Interestingly, EASL strongly recommends that surveillance should be performed by experienced personnel, yet avoids defining the term "experienced," whereas AASLD and APASL do not comment on personal and technical requirements for US surveillance.[8,10,13] Only the German guideline suggests quality requirements for US operators and devices, although these recommendations are not evidence based.[12] We identified only two studies that focused on the evaluation of surveillance success rather than outcomes in patients with or without US surveillance.[22,23] In both studies, surveillance success was defined as HCC detection within the Milan criteria.[22,23] Additionally, del Poggio *et al*.[22] considered cases in which HCC was detected only by CT or MRI as surveillance failure. Results of surveillance success in the total cohort as well as in the subgroup were of similar magnitude in our study as reported by del Poggio *et al*.[22] and Khalili *et al*.[23] which demonstrated a surveillance success of 66% and 73%, respectively. In the study by del Poggio *et al*.,[22] the rate of HCCs detected by CT or MRI only was 8.3% of which 32% were beyond the Milan criteria at the time of detection, which conforms with our findings. Further indirect evidence for relevant rates of surveillance failure comes from studies investigating different surveillance intervals, in which HCCs were diagnosed outside the Milan criteria despite undergoing regular US surveillance: 20.8% at a 3 month interval,[16] 18.6%, 18.9%, 28.6%, and 30% at 6 months,[16,17,31,32] and 30.8% and 42.3% at 12 months.[17,31]

Del Poggio *et al*.[22] reported that annual surveillance, male sex, Child-Pugh class B and AFP level ≥200 ng/mL were independently associated with surveillance failure, whereas no association was found for age, etiology of cirrhosis, ALT level, comorbidities, type of center, period of diagnosis, alcohol intake, esophageal varices, platelet count, and albumin levels. In the study by Khalili *et al*.,[23] only a surveillance interval ≤12 months was significantly associated with the detection within the Milan criteria, with an adjusted OR of 2.76. On the other hand, they found no association with sex, ethnicity, etiology of underlying liver disease, age, detection year, Child-Pugh class, or residence area.[23] In our study, a significant association with MELD score was observed consistently in the overall cohort as well as in subgroup analysis, whereas severity of cirrhosis in terms of Child Pugh class had no impact. In addition to both studies, we also included further aspects into our analysis which may have impacted on quality of US examinations like operator expertise, HCC location, obesity, visual limitations, and previous observations on US, presence of ascites, fatty liver, and portal vein thrombosis. In this context, HCC localization within the right liver lobe in the total cohort and the absence of previous observations on prior US was independently associated with surveillance failure. There was also a trend for higher success rates in cases with visual limitations score A compared to score B or C. Taken together, this probably points to a combination that favors early HCC detection, namely increased operator alertness in a patient with assumed increased risk (i.e. higher MELD score) and with previous observation, and advantageous US conditions, (i.e. HCC localization within the left liver lobe) and less visual limitation. The numerical, albeit not significant, differences in success rates between study centers may point to the impact of local expertise, although there was no association with individual operator's experience.

According to a retrospective cohort study of patients who underwent US for cirrhosis-related indications, male sex, Child-Pugh class B or C, overweight and obesity versus normal weight, alcoholic liver disease and non-alcoholic steatohepatitis versus HCV and in-patient status were independently associated with inadequate US quality, whereas HBV and elevated ALT were not.[33] Using a different classification of visual limitations introduced by Fetzer *et al*.,[26] we also

Table 5. Univariate and linear regression analyses of visual limitations

	Visual limitations								
	Univariate				Multivariate				
	Score A	Score B	Score C	*p* value	Score A	OR (95% CI) for Score B	*p* value	OR (95%-CI) for Score C	*p* value
Sex, *n* (%)									
Male	20 (23)	48 (55)	20 (23)	0.207					
Female	17 (25)	43 (63)	8 (12)						
Age in years									
Median (IQR)	63 (58, 73)	63 (57, 70)	63 (58, 67)	0.990					
BMI >30 kg/m^2, *n* (%)*									
No	15 (22)	43 (62)	11 (16)	0.337					
Yes	3 (11)	21 (78)	3 (11)						
Steatosis, *n* (%)									
No	30 (25)	74 (61)	17 (14)	0.062					
Yes	7 (20)	17 (49)	11 (31)						
Portal vein thrombosis, *n* (%)									
No	37 (25)	87 (58)	26 (17)	0.305					
Yes	0 (0)	4 (67)	2 (33)						
Transaminases >2× ULN, *n* (%)**									
No	19 (20)	55 (57)	22 (23)	0.186					
Yes	13 (30)	26 (59)	5 (11)						
Child Pugh class, *n* (%)									
A	20 (24)	50 (61)	12 (15)	0.302					
B or C	12 (18)	40 (59)	16 (24)						
Ascites, *n* (%)									
No	29 (25)	74 (64)	13 (11)	0.010	1	0.844 (0.326–2.186)	0.727	3.939 (1.231–12.606)	0.021
Yes	8 (20)	17 (42.5)	15 (37.5)						
ALD/NAFLD, *n* (%)									
No	32 (28)	68 (60)	14 (12)	0.004	1	2.158 (0.751–6.197)	0.153	6.077 (1.733–21.311)	0.005
Yes	5 (12)	23 (55)	14 (33)						

*n=96, **n=140. ALD, alcoholic liver disease; BMI, body mass index; CI, confidence interval; IQR, interquartile range; NAFLD, non-alcoholic fatty liver disease; OR, odds ratio; ULN, upper limit of normal.

found ALD and NAFLD as well as the presence of ascites to be independently associated with severe, but not moderate visual limitations. Steatosis on US showed a trend towards more advanced visual limitations, whereas sex, BMI >30 kg/m^2, portal vein thrombosis, elevated transaminases and Child-Pugh class did not impact visual limitations.

Surveillance failure may be explained by missed HCC at early stage during a previous US or rapid development of HCC from undetectable to advanced stage between two US. Older studies on tumor growth reported median tumor doubling times of 117 and 172 days or a mean of 6.5 months, respectively.[34–36] However, a considerable variation in doubling time, ranging from 29–398 days and 27.2–605.6 days, has also been described.[34,35] Doubling time was significantly associated with albumin level and alcohol intake, but independent of severity and stage of cirrhosis, patient's age, sex, hepatitis B surface antigen status, tumor location, liver function tests, histologic type and grade of malignancy.[34,35] In the study by del Poggio *et al*.,[22] surveillance failure was attributed to biologically aggressive tumors defined as tumors with AFP >1,000 ng/mL, vascular thrombosis, distant metastasis or diffuse/infiltrative growth in 39.5% of patients undergoing semi-annual surveillance and 68.1% of patients undergoing annual surveillance.[22] Khalili *et al*.[23] reported successful surveillance in 84% of cases with an AFP <200 ng/mL compared with only 43% of cases with an AFP ≥200 ng/mL.[23] AFP was not associated with surveillance success in our study. However, information on AFP was available only in 106 cases (68%). On the other hand, 74% of cases detected outside the Milan criteria in our study may be attributed to a more aggressive tumor behavior (e.g., cases with ≥4 HCC nodules regardless of maximum size, portal invasion, or extrahepatic spread, among others. Missed lesions may be assumed especially in patients with a single lesion >5 cm and patients with 2–3 lesions >3 cm without accompanying vascular invasion and distant metastasis as these cases may represent a more benign nature of HCC with slower growth rates. Consequently, improvements in US quality would essentially focus on these cases. In our study, only 13 patients fell into this category, demonstrating the limited potential of US alone for improvement of surveillance success. Thus, other strategies to prevent surveillance failure such as biomarkers and biomarker-based models may be needed.[37]

DGVS recommends that HCC surveillance should be performed by physicians who are specialists in internal medicine, radiology or surgery, who have performed ≥6,000 US including ≥3,000 with pathologic findings, perform ≥800 US annually and participate in regular US training.[12] However, the requirements, have not been validated with respect to HCC surveillance. Operators in our study have performed between 49 and 18,000 US examinations, but only two of the 59 operators fulfilled the aforementioned criteria. However, in terms of surveillance success, performance was not different between operators from highest and lowest quartile of US examinations. Thus, we were unable to define a threshold of US numbers for quality assurance. All US devices in our study fulfilled the qualifications required by the DEGUM which is why this aspect was not amenable to further analysis.

Cirrhosis was present in 96% of our patients, and only 4% suffered from NAFLD (all with cirrhosis). Although cirrhosis is an important pathogenetic factor for HCC development, HCC also occurs in non-cirrhotic patients.[4,7,38,39] This especially applies to NAFLD, in which HCC developed in a non-cirrhotic livers in 23% of patients in a large population-based study in the UK and 42% in a large retrospective case control study in the USA.[4,39] Patients with NAFLD account for up to 21.5% of all patients with HCC.[4,39] Therefore, it may be assumed that such patients were underrepresented in our study, which may be attributed to an insufficient process of identification and inclusion. This assumption is supported by the above mentioned studies that reported a lower percentage of HCC detection during surveillance in patients with NAFLD.[4,39] Another study found a more than two-fold increased risk of not receiving surveillance in patients with NAFLD or alcoholic liver disease.[18]

A recently published review highlighted various barriers to surveillance at patient, physician and health system levels.[37] Several studies reported that the majority of HCCs was not detected during surveillance due to unrecognized liver disease or cirrhosis, missing surveillance orders, and incomplete or inconsistent surveillance despite orders.[4,18–21] In that regard, hepatology subspecialty care with an OR of 6.11 and active alcohol abuse with an OR of 0.14 were significant positive and negative predictors, respectively, of consistent HCC surveillance in a multivariate analysis.[19] However, even after initial HCC surveillance, retention within surveillance programs is as low as 48%[21] and 31% of patients with inconsistent surveillance contributed to 70% of HCCs beyond the Milan criteria.[20] Besides an insufficient consideration of patients with NAFLD, we also found low adherence to surveillance recommendations given by several guidelines in terms of surveillance modality and interval.

Our study has several limitations. Although this retrospective study is based on data from four tertiary referral hospitals, only a relatively small proportion of patients with HCC could be enrolled according to our inclusion and exclusion criteria. The majority of patients presented to each participating center with already diagnosed HCC for further evaluation. Also, only patients under surveillance at each participating center were included to get all data necessary for the analysis. Therefore, selection bias cannot be ruled out. However, the baseline characteristics of our study population were comparable to other published cohorts with respect to sex, age, and underlying chronic liver disease, except for NAFLD.[7,40] Furthermore, risk and protective factors that may impact HCC incidence (e.g., alcohol intake, treatment of underlying chronic liver disease, diabetes mellitus, coffee consumption, and concomitant use of statins or metformin) were not assessed, even though their effects on tumor doubling time and surveillance success are equivocal.[5,41–43] Unfortunately, we were not able to retrieve more information on the date of death of included patients for a detailed survival analysis.

Conclusions

In conclusion, we confirmed previously reported low success rates for US-based HCC surveillance in patients at risk, and identified lower median MELD score, HCC localization within the right liver lobe, and no previous US-observations to be independently associated with surveillance failure. We found a significant impact of surveillance success on tumor stage, curative treatment options and survival. US examinations of patients with ideal preconditions, using high quality equipment within the recommended intervals do not assure a high success rate for HCC screening. To prevent surveillance failure in a considerable number of patients by other strategies, such as biomarkers and biomarker-based models, should be tested.

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Conflict of interest

MB has obtained travel support from Pfizer. FF, PR, GA, HMS, JG, DN, MR, LL, FK, MN, PH, CS have no conflict of interests related to this publication.

Author contributions

Conception and design and administrative support (JG, CS), provision of study material or patients (JG, PR, PH, MR, LL, FF, MN, GA, FK, MB, DN, CS), carried out the statistical analysis (JG, HMS, CS), and drafted and revised the manuscript and approved of the finally submitted version (All authors).

Ethical statement

This retrospective study was conducted in accordance with the Declaration of Helsinki and Good Clinical Practice guidelines. Approvals of responsible local ethic committees were obtained (Cologne: 20-1166; Jena: 2020-1900; Saarland: 271/11; Frankfurt SGI-3-2018, amendment 1 2019) and the need for informed consent was waived due to the strictly retrospective character of the study.

Data sharing statement

All data generated or analyzed during this study are included in this article and its supplementary material files. Further enquiries can be directed to the corresponding author.

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