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Review

Surveillance of Hepatocellular Carcinoma in Nonalcoholic Fatty Liver Disease

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Abstract

Nonalcoholic fatty liver disease (NAFLD) is becoming the leading cause of hepatocellular carcinoma (HCC), liver-related mortality, and liver transplantation. There is reasonable epidemiological cohort data to recommend surveillance of patients with NAFLD based upon the incidence of HCC. The American Gastroenterology Association (AGA) expert review published in 2020 recommend that NAFLD patients with cirrhosis or advanced fibrosis estimated by non-invasive tests (NITs) should consider HCC surveillance. NITs include fibrosis-4 (FIB-4) index, the enhanced liver fibrosis (ELF) test, FibroScan, and MR elastography. The recommended surveillance modality is abdominal ultrasound (US) given that it is cost effective and noninvasive with good sensitivity. However, US is limited in obese patients and those with NAFLD. In NAFLD patients with a high likelihood of having an inadequate US or if US is attempted but inadequate, CT or MRI may be utilized. The GALAD score, consisting of age, gender, AFP, lens culinaris-agglutinin-reactive fraction of AFP (AFP-L3), and protein induced by vitamin K absence or antagonist-II (PIVKA-II), can help to identify high risk of incident HCC in NAFLD patients. Innovative parameters including Mac-2 binding protein glycated isomer , type IV collagen 7S, free apoptosis inhibitor of macrophage, combination of single nucleoside polymorphisms are expected to be established. Considering a large number of NAFLD population, optimal screening tests must meet several criteria including high sensitivity, cost effectiveness and availability.

Key words: hepatic fibrosis; Mac-2 binding protein glycated isomer; apoptosis inhibitor of macrophage; patatin-like phospholipase domain-containing protein 3; α-fetoprotein; PIVKA-II protein induced by vitamin K absence or antagonist-II

1. Introduction

Control of viral hepatitis (hepatitis B virus [HBV] and hepatitis C virus [HCV]) has become possible, and so-called “non-HBV non-HCV hepatocellular carcinoma (NBNC-HCC)” has become 1/3 of the total HCC in Japan [1]. The main background of NBNC-HCC is fatty liver disease (FLD), which is caused by alcohol consumption and/or lifestyle-related diseases [1]. In the past, low-drinking FLD has been called nonalcoholic fatty liver disease (NAFLD). The nomenclature “NAFLD” has proposed to change the name to metabolic dysfunction associated fatty liver disease (MAFLD) [2]. A part of NAFLD patients with progression of fibrosis is leading to liver disease-related mortality (HCC, liver failure, or esophageal varices hemorrhage) and liver transplantation [3]. NAFLD affects about 25% of adults [4,5] , but about 25% (6.7%-59%) of the transition to nonalcoholic steatohepatitis (NASH) [6], and 25% of that change to

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cirrhosis. Since 25% of cancers occur in 10 years [7] (Fig. 1, **25% rule**), it is estimated that only 1 or 2 of 100 NAFLD cases develop HCC (Fig 1). [8,9] Although it is clear that NAFLD portends a lower risk for HCC than HBV or HCV, the high prevalence of NAFLD in the population underlies the importance of NAFLD in the development of HCC [10]. However, poor surveillance is a constant problem for patients with NAFLD. According to cohort studies from Italy and US cohort, a lot of patients with NAFLD-related HCC were not diagnosed on regular surveillance compared to patients with HCV-related HCC, resulting in more advanced HCC burden at diagnosis [11,12]. This review outlines the efficient surveillance of HCC in NAFLD.

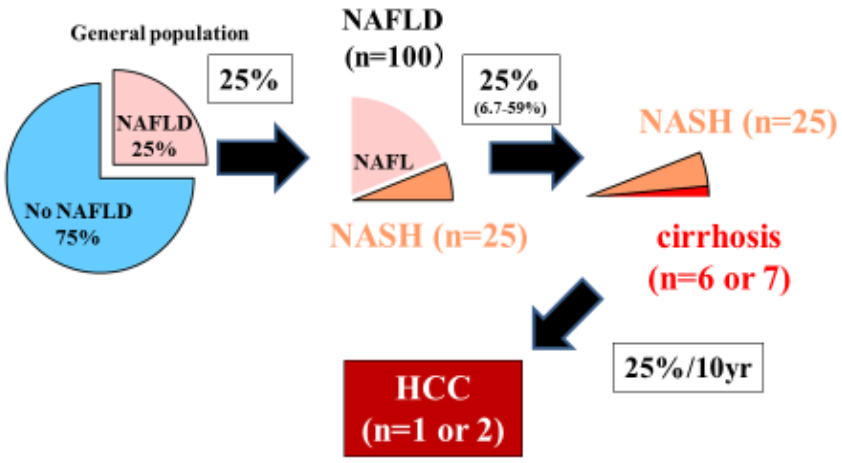

Figure 1 "25% rule" in NAFLD [8]

Although 25% of adults have NAFLD, about 25% will progress to NASH in their lifetime, 25% will progress from NASH to liver cirrhosis, and the incident HCC rate for 10 years after liver cirrhosis will be about 25%. Among 100 NAFLD patients, it is rare for 1-2 people with NAFLD to develop HCC. J-SMARC has copyright of this figure.

2. Carcinogenic risk in nonalcoholi8c fatty liver disease

The risk of hepatocarcinogenesis from NAFLD varies depending on the background of the population. Comparing 296,707 NAFLD patients with 296,707 matched controls without known liver disease, the incident HCC rate was 0.02 per 1,000 person-years in normal subjects, while 0.21 per 1,000 person-years in NAFLD. NAFLD has higher risk compared to healthy people (hazard ratio [HR] 7.62, 95% confidence interval [CI] 5.76-10.09) [2]. In Japan, the annual rate is 0.04% in cases of NAFLD diagnosed by ultrasonography (US) [13], 0.4-0.8% in cases of NAFLD diagnosed by liver biopsy [14], and 2 to 3% with NASH associated cirrhosis [7]. In a study comparing the incidence of HCC among patients with HCV infection and NAFLD [15], 315 patients with HCV-cirrhosis and 195 with cirrhosis due to NAFLD were followed for a median of 3.2 years. Cumulative incidence of HCC is slightly lower in NAFLD related cirrhosis compared to HCV cirrhosis (2.6% vs. 4% , p=0.09)[15]. The best available evidence suggests that NAFLD-related cirrhosis is a risk factor for HCC, but at a lower rate compared to HCV-related cirrhosis though the annual incidence rate in NASH-cirrhosis remains higher than 1%. HCC has also been observed in NAFLD patients without cirrhosis, but incidence rates at lower than 1% a year [16, 17]. Surveillance of HCC in every patient with NAFLD is unrealistic, while screening for HCC in cirrhotic patients is justifiable, based on cost-effectiveness considerations. An important issue is how to enclose high-risk cases from a large number of NAFLD patients and to lead to early diagnosis and treatment of HCC. Advanced fibrosis (F3/4), old age, male, low platelets (less than 150,000/μL), high AST, existence of diabetes, patatin-like phospholipase domain-containing protein 3 (PNPLA3) single nucleotide polymorphism (SNP) GG homozygote [4.13.14] have been established as carcinogenic risk factors in Japan, and these results are consistent with the data form Asian and western countries [15, 18-20].

3. Non-invasive diagnostic method for liver fibrosis

The degree of liver fibrosis also contributes to the prognosis of NAFLD [20, 21]. In the United States, HCC surveillance targets highly fibrotic cases (particularly liver cirrhosis) [22]. The American Association for the study of Liver Disease (AASLD) Practice Guide 2018 recommends four noninvasive test (NITs) to evaluate hepatic fibrosis such as Fibrosis-4 (FIB-4) index, NAFLD fibrosis score (NFS), vibration-controlled transient elastography (VCTE), and magnetic resonance elastography (MRE) [23]. Kanwal et al.[18] showed that FIB-4 index >2.67 is associated with increased risk of HCC not only in those with known cirrhosis but also in those without prior diagnosis of cirrhosis. When utilizing NITs to risk stratify patients for HCC screening, a higher cut-point threshold is desirable to maximize specificity (90%). The following cut points for VCTE and MRE may be considered for noninvasive detection of cirrhosis for purposes of HCC screening: VCTE 16.1 kPa and MRE of 5 kPa [23]. In recent years, a two-step diagnostic algorithm that combines these has become widespread [24-26] for stratify patients with advanced fibrosis. The simplest FIB-4 index has become the first step, and the use of VCTE (FibroScan) is recommended mainly in the United States as the second step [25,26]. Since FIB-4 index has a high negative predictive value, it is useful for excluding highly fibrotic cases. There is no problem regarding FIB-4 index as the 1st step premised on the use at the primary care physician or health checkup facility. However, among hepatologists, the low cutoff value should be 1.45 [27,28]), or 1.3 [29], or the low cutoff value should be 2.0 because Fib-4 index can overpredict in the elderly [30-31], the possibility that the FIB-4 index may show a false low value in diabetic patients [32] is not controversial, but it is sufficient to use it for the 1st step targeting 2 billion NAFLD patients

[24]. On the other hand, VCTE (FibroScan) is not widely used in all institutions, and there are great expectations for serum markers. In Europe, the ELF (enhanced liver fibrosis) test, consisting of hyaluronic acid and tissue inhibitor of matrix metalloproteinase type 1 (TIMP-1), and P3NP (aminoterminal propeptide of type 3 procollagen), established a position as the 2nd step [33]. A validation study for efficacy of ELF test was conducted in Japan [34]. In Japan, liver fibrosis markers such as type IV collagen 7S and Mac-2 binding protein glycosylation isomer (M2BPGi) are generally used by hepatologists. Elevated type IV collagens 7s reflecting severe fibrosis [35,36] are at increased risk for extrahepatic cancer and overall mortality in Japanese patients with biopsy-proven NAFLD [37]. Type IV collagen 7S was previously measured by the radioimmunoassay (RIA) method, but since August 2020 it has become possible to measure by the high-sensitivity ELISA method, we hope that it will spread internationally in the future. We would like to expect future discussion on which parameter is best to use, but it is necessary to discuss not only the diagnostic accuracy but also the cost-benefit balance including medical economic efficiency [24,37].

Table 1 NIT for stratifying high risk of HCC in NAFLD

NIT	Formula	HCC high risk
FIB-4 index	(age [years] × AST [U/L]/(platelet count [10^9/L] × √ALT [U/L]) https://www.eapharma.co.jp/medicalexpert/product/livact/fib-4/calculator.html	>2.67
NAFLD fibrosis score	–1.675 + 0.037 × age (years) + 0.094 × BMI (kg/m^2) + 1.13 × impaired fasting glucose/diabetes (yes=1, no=0) + 0.99 × AST/ALT ratio – 0.013 × platelet count (×10^9/L) - 0.66 × albumin (g/dL) http://nafldscore.com/	>0.676
ELF test	–7.412 + (In [HA] × 0.681) + (In [P3NP] × 0.775) + (In [TIMP1] × 0.494)	>11.3
GALAD score	10.08+1.67 × gender (male: 1, female :0) + 0.09 x age (years) + 2.34 x log10 (AFP [ng/mL]) + 0.04 x AFP-L3 (%) + 1.33 x log10 (DCP [ng/mL]) https://www.mdcalc.com/galad-model-hepatocellular-carcinoma-hcc	>-0.63

FIB-4: fibrosis-4, AST: aspartate aminotransferase, ALT: alanine aminotransferase, BMI: body mass index, HA: hyaluronic acid, P3NP: aminoterminal propeptide of type 3 procollagen. TIMP-1: tissue inhibitor of matrix metalloproteinase type 1, ELF: enhanced liver fibrosis, AFP: αfetoprotein, DCP: des-γ-carboxy pro-thrombin

4. HCC Surveillance in NAFLD Advocated by the American Gastroenterology Association

This year, eight recommendations (best practices) were published by the American Gastroenterology Association (AGA) for HCC surveillance in NAFLD patients [22] (Table 2). It is recommended that HCC surveillance be performed in cases of cirrhosis or in cases where NIT suspects severe liver fibrosis (Recommendations 1 and 2). According to the data of NASH-associated HCC from Ministry of Health, Labor and Welfare NASH research group (Director: Dr. Takeshi Okanoue , Saiseikai Suita Hospital, Osaka, Japan), most women (%) developed HCC from severe fibrosis (F3/4), while men (%) developed HCC even from mild fibrosis [17]. It has also been reported that NASH has a high risk of carcinogenesis from non-cirrhotic liver

compared with other liver diseases in the United States [39]. However, the incidence of HCC in those with NAFLD and earlier stages of fibrosis (F0–F2) is extremely low and not precisely defined. Threshold incidence for efficacy of surveillance (> 0.25 Life-years gained) is 1.5% per year [40], but NAFLD without cirrhosis is annual incidence of HCC < 1.5% per year. Therefore, systematic HCC screening may not be prudent at this time [18,40]. Although there is a higher risk of developing HCC in those with earlier stages of NAFLD than people without NAFLD, the incidence rates and determinants of risk have not been well-quantified and are probably too low to justify routine screening at this point. The American Association for the Study of Liver Diseases (AASLD) practice guide 2018 [41] recommends that the risk of HCC is significantly lower in those with NAFLD and no cirrhosis compared to those with cirrhosis, and surveillance is not recommended for these patients. The risk factors of carcinogenesis from non-cirrhotic NAFLD includes men, low alcohol consumption, and high FIB-4 index [42]. Given the large number of cases with mild liver fibrosis, routine surveillance is irrational, and it may be efficient to focus on males, light alcohol consumption, and high FIB-4 index. Although AFP measurement is taken up as a tumor marker in the recommendations (Proposal 5), PIVKA-II has a higher positive rate than AFP in the data of the NASH research group of the Ministry of Health, Labor and Welfare [38], or Japan Study Group of NAFLD (JSG-NAFLD) data from Japanese multi-center study [43]. PIVKA-II may be superior to AFP for detecting NASH-HCC, although this point needs to be validated in an international study. In HCV infected patients, HCC screening using either biannual AFP and annual abdominal US or triple phase computed tomography (CT) were cost effective compared to no surveillance, with cost effectiveness ratio less than $50000 quality-adjusted life year (QALY) [44,45]. The AASLD guidance 2018 for HCC surveillance recommends HCC surveillance using US with or without AFP every 6 mo [44]. US is an inexpensive and noninvasive surveillance method without any risk or radiation exposure for the patient [41]. The AGA expert review recommends to consistently record the adequacy of liver US, including parenchyma heterogeneity, visualization of entire liver, and beam attenuation, because Surveillance on abdominal US are often difficult to visualize in many cases of severe obesity. The visualization US score for HCC screening is graded into the following categories: A as no or minimal limitation; B as moderate limitation defined, as the examination may obscure small masses; and C as severe limitation, defined as the examination may miss focal liver lesions [22]. Consequently, if US quality is inadequate (especially if category C or in some cases with category B), we recommend considering other imaging modalities (eg, CT scan or magnetic resonance imaging [MRI]) for HCC screening (Proposal 5). Compared with multidetector CT (MDCT) and extracellular contrast media-enhanced MRI (ECCM-MRI), Gd-EOB-DTPA-MRI could be the first-choice imaging modality for medical care of HCC among patients with hepatitis or liver cirrhosis in Japan [46], China [47], Thailand and Korea [48].

Optimal interval of imaging studies are obscure. In the aforementioned meta-analysis by Singal et al. [49], surveillance US every 6 mo significantly improve the sensitivity for detection of early stage HCC when compared to annual exams. More frequent imaging (every 3 mo) did not improve survival or increase detection of small HCC lesions and is therefore not recommended at this time [50]. It is also necessary to discuss domestic best practices for this recommendation in NAFLD.

Table 2 Summary of recommendations for HCC surveillance in Nonalcoholic Fatty Liver Disease [22]

Best Practice Advice 1	Screening for HCC Should Be Considered in All Patients With Cirrhosis Due to NAFLD
Best Practice Advice 2	Patients With NAFLD With Noninvasive Markers Showing Evidence of Advanced Liver Fibrosis or Cirrhosis Should Be Considered for HCC Screening
Best Practice Advice 3	Patients With NAFLD in the Absence of Advanced Liver Fibrosis Should Not Be Routinely Considered for HCC Screening
Best Practice Advice 4	Adequacy of Ultrasound in Assessing the Liver Parenchyma for Mass Lesions Should Be Documented When Used for HCC Screening in Patients With Cirrhosis Due to NAFLD
Best Practice Advice 5	When the Quality of Ultrasonography Is Suboptimal for Screening of HCC (eg, Due to Obesity) Future Screening Should Be Performed by Either Computed Tomography or Magnetic Resonance Imaging Scan, With or Without α-Fetoprotein, Every 6 Months
Best Practice Advice 6	Patients With Cirrhosis Due to NAFLD Should Be Counseled on Abstaining From Alcohol Drinking and Tobacco Smoking
Best Practice Advice 7	Optimal Management of Diabetes and Dyslipidemia Through Lifestyle Modification and Pharmacotherapy Is Encouraged in Patients With NAFLD and Advanced Liver Fibrosis Who Are at Risk for HCC
Best Practice Advice 8	Optimal Management of Obesity Through Lifestyle Modification, Pharmacotherapy or Endoscopic or Surgical Bariatric Procedures Is Encouraged in Patients With NAFLD and Advanced Liver Fibrosis Who Are at Risk for HCC

HCC: hepatocellular carcinoma, NAFLD: nonalcoholic fatty liver disease

5. Novel indicators for predicting incident HCC risk

A method of assessing the risk of hepatocarcinogenesis itself, rather than the assessment of advanced fibrosis, has also been studied. It has been reported that FIB-4 index and NFS are also useful for predicting cancer risk [51]. In a national multicenter study led by JSG-NAFLD, Kawaguchi and colleagues reported that a favorable prognostic factor in NASH-HCC includes serum albumin was 4.0 g/dl or more, and early detection of HCC that is an indication for curative treatment such as surgery and radiofrequency ablation therapy [52]. This suggests the importance of diagnosing HCC at an early stage when hepatic reserve is maintained. Most of NASH-HCC patients did not undergo regular surveillance, and the tumor size is large at the time of diagnosis, resulting in a poor prognosis [53,54].

5.1. Mac2 protein glycosylated isomer

M2BPGi was developed in Japan and its usefulness as a liver fibrosis marker in various liver diseases including NAFLD has been reported [55,56]. According to a report by Kawanaka et al.[57], the carcinogenic rate was as high as 6.8% for 5 years and 21.1% for 10 years in NAFLD cases where M2BPGi was 1.26 or higher, while the rate was as low as 1.7% for 5 years and 1.7% for 10 years in patients where M2BPGi was below 1.26 [57]. It has been suggested that it may be a predictor of hepatocarcinogenesis as well as fibrosis, but its mechanism has not been clarified.

5.2. GALAD Score

In Japan, AFP, AFP-L3 fraction, and PIVKA-II (des-γ-carboxy pro-thrombin [DCP] in foreign countries) have been used for many years as a tumor marker. According to Toyoda et al. , the sensitivity was 60% and the specificity was 85% in HCC stage 1 (n=235) when these three types of tumor markers were combined [58]. In Japan, the combination of these tumor markers has been followed up with combination of imaging tests as surveillance for HCC. The GALAD score calculated from age, sex, AFP, AFP-L3 fraction and DCP has been reported to be useful in the early diagnosis of HCC from all over the world [59]. PIVKA-II 1 mAU/mL = DCP 0.012 ng/mL can be calculated. Even in a study comparing NASH with HCC and without HCC at 8 facilities in Germany, the GALAD score was highly diagnostic for HCC (AUROC 0.93) compared to AFP (AUROC 0.88), AFP-L3 fractionation (AUROC 0.86), PIVKA2 alone (AUROC 0.87) [22]. The GALAD score was useful independent of the existence of liver cirrhosis, and a cutoff value of -0.63 was appropriate even if only 25 patients within the Milan criteria were examined. The sensitivity was good at 68%, specificity 95%, and AUROC 0.91. In a prospective

study of 392 NAFLD patients (of which 17 had HCC incidence during the course) at Ogaki Municipal Hospital, the GALAD score was characterized by an upward trend from one and a half years before the diagnosis of HCC. GALAD score was effective for surveillance of NASH patients [60]. This is data from a single facility, and a multi-center validation study is desired in the future.

5.3. Apoptosis inhibitor of macrophage

Apoptosis inhibitor of macrophage (AIM) is a protein with a molecular weight of about 40 kD that was discovered by Professor Miyazaki of the University of Tokyo in 1999 [61] and is produced by Kupffer cells in the liver and macrophages in the abdominal cavity [62]. IgM behaves as a carrier of the AIM protein, storing a large amount of the inactivated form of AIM in the blood. Under certain disease conditions, AIM can dissociate from IgM locally or systemically to exert its function, inducing the removal of various biological debris such as excess fat, bacteria, cancer cells or dead cell debris.[63]. In patients with NASH-HCC, AIM is dissociated from the IgM pentamer as compared with non-tumor-bearing patients, and IgM-unbound AIM (free AIM) in blood increases in NASH-HCC [64]. Since free AIM (cutoff value: 1.6 μg/mL) can detect HCC with higher sensitivity (88.5%) than PIVKA-II (53.8%) or AFP (26.9%) , it is expected as a diagnostic marker for detecting NASH-HCC. Since it may be used as a predictor of carcinogenesis in the future, we would like to pay attention to future data collection. Since AIM has an inhibitory effect on HCC carcinogenesis in animal models [65,66] , clinical application of AIM to HCC treatment is also expected. Increased blood free AIM in NASH-HCC may be a biodefense response.

5.4. SNP “combo”

Various SNPs can related to hepatocarcinogenesis in NAFLD. PNPLA3 SNP, which has the most abundant evidence, contributes not only to the development of hepatic fibrosis but also to hepatocarcinogenesis [14, 67, 68]. According to the report from the United Kingdom, 100 Caucasian NAFLD associated HCC cases were reported. In a study of 275 NAFLD non-carcinoma cases diagnosed by liver biopsy, it was revealed that CG hetero carriers had a 2.52-fold higher risk and GG homo carriers had a 12.19-fold higher risk of liver carcinogenesis than PNPLA3 CC homo carriers [67]. Since PNPLA3 GG homozygotes were a risk factor even when examined only in patients with liver cirrhosis, PNPLA3 SNP GG homozygotes were at high risk of hepatocarcinogenesis independently of liver fibrosis. The cumulative hepatocarcinogenesis

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rate of 238 Japanese NAFLD patients diagnosed by biopsy was examined by PNPLA3 SNP [14], and GG homozygotes had significantly higher hepatocarcinogenesis rates than C allele carriers. 4,047 in Sweden A study on the risk of hepatocarcinogenesis from obese individuals using an example obesity cohort revealed that the G allele carriers were 5.9 times higher (95% CI: 1.5-23.8 times) [19]. An analysis of the risk of hepatocarcinogenesis in Japanese diabetic patients whose denial was confirmed revealed that JAZF1 G allele in addition to PNPLA3 SNP GG homozygotes was a risk factor [69]. It has been reported that the T allele of membrane bound O-acyl-transferase domain circulating 7 (MBOAT7) is involved in hepatocarcinogenesis in patients without cirrhosis [70]. We previously reported that the combination of PNPLA3 and dysferlin in patients with NAFLD in Japan had a high risk of developing HCC in the case of both risk alleles [71], but further cases need to be accumulated for validation. PNPLA3 G alleles is prevalent in Japan, South Korea, Taiwan, and Mexico [5], and there is concern that NASH-HCC will increase in these countries. A report from Europe indicates that risk alleles of PNPLA3, transmembrane 6 superfamily member 2 (TM6SF2), hydroxysteroid 17- beta dehydrogenase 13 (HSD17B13) were 29 times as high as the risk of hepatocarcinogenesis compared to the general population [72]. NAFLD patients with TM6SF2 risk allele accumulate hepatic steatosis, but atherosclerosis is low in NAFLD risk alleles due to excretion as VLDL. HSD17B13 modulates the action of the PNPLA3 gene, and when PNPLA3G allele is a TA variant of HSD17B13, inflammation and fibrosis are suppressed [73]. In this way, it is important to incorporate the SNP “combo” into the risk assessment, but the issue is its versatility in daily clinical practice, such as cost and protection of personal information. It is important to take a family history of HCC and cirrhosis as a simple alternative method [74].

5.5. Noninvasive 'liquid biopsy'

The concept of liquid biopsy was developed to address the need for reliable, minimally invasive methods of diagnosis, prognosis and overall disease monitoring. It is a modality where body fluids samples, instead of solid tissue, are used for pathophysiological or molecular analyses. It has been introduced for many clinically relevant fields, including cancer research and, in general, any body fluids can be used as potential samples for liquid biopsy. The term liquid biopsy can apply to cancer by-products including circulating tumor cells (CTC), cell-free DNA (cfDNA), cell-free RNA (cfRNA), microRNA (miRNA), extracellular vesicles (EVs), and tumor-derived metabolites [75]. The most widely used markers are CTCs and ctDNA. ctDNA carrying cancer-specific genetic and epigenetic aberrations may enable a noninvasive 'liquid biopsy' for diagnosis and monitoring of cancer [76, 77].

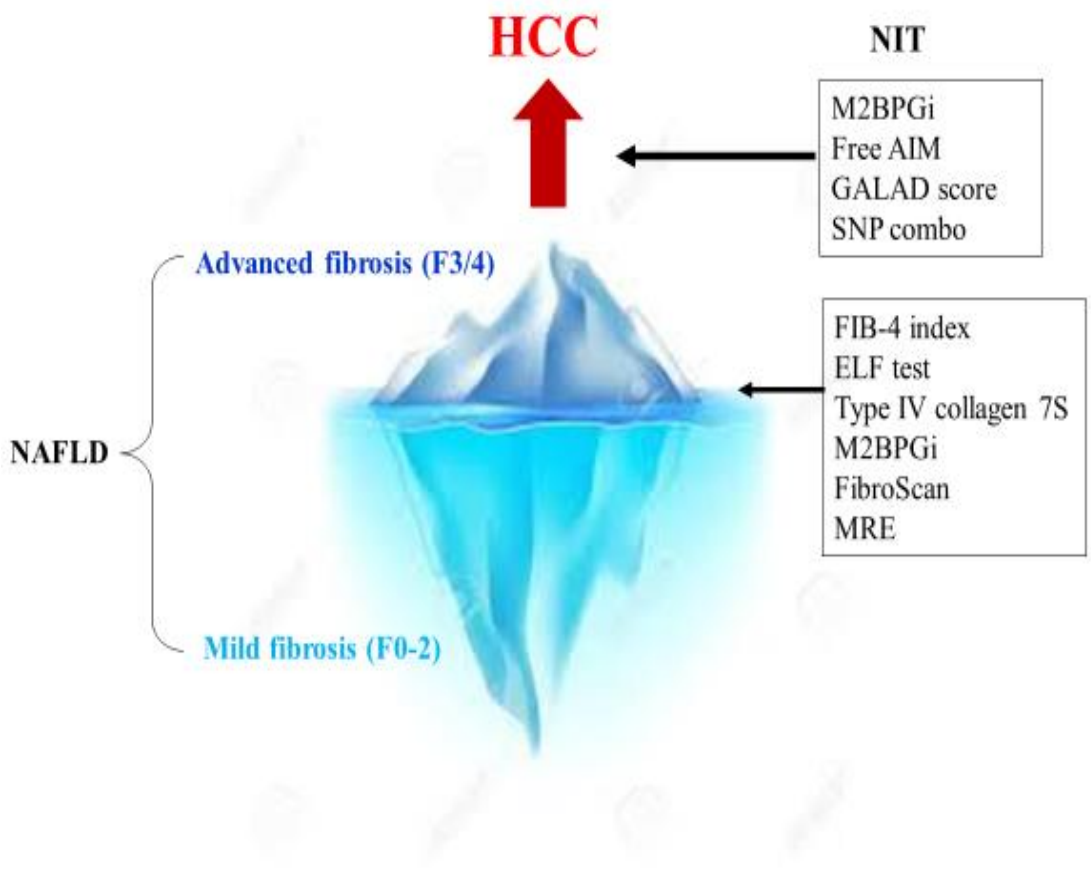

Figure 2. NITs for surveillance of severe fibrosis and HCC in NAFLD

First of all, NIT is used to pick up advanced fibrosis (F3/4) from NAFLD. In cases of advanced fibrosis, regular image examination is performed to detect HCC early. Then we conduct strict surveillance in patients with high GALAD score (> -0.63), high M2bpGi cases (> 1.26), and PNPLA3 GG homozygous cases.

6. Algorithm for HCC surveillance in Nonalcoholic Fatty Liver Disease

We construct algorithm for HCC surveillance in NAFLD in reference to the AGA expert review (Figure 3). NAFLD patients with cirrhosis should underdo HCC surveillance. NAFLD patients who are likely to have advanced fibrosis evaluated by NITs (FIB-4 index, ELF test, VCTE, and MRE) should consider HCC surveillance. US is the first method for surveillance of HCC, but adequacy of US should be documented because of is difficulty in obese patients. In NAFLD patients with a high likelihood of having an inadequate US or if US is attempted but

inadequate, CT or MRI may be utilized. Tumor markers such as PIVKA-II, AFP, AFP-L3 may help us to identify high risk of incident HCC in NAFLD. NAFLD patients who are unlikely to have advanced fibrosis evaluated by NITs should not undergo routine surveillance.

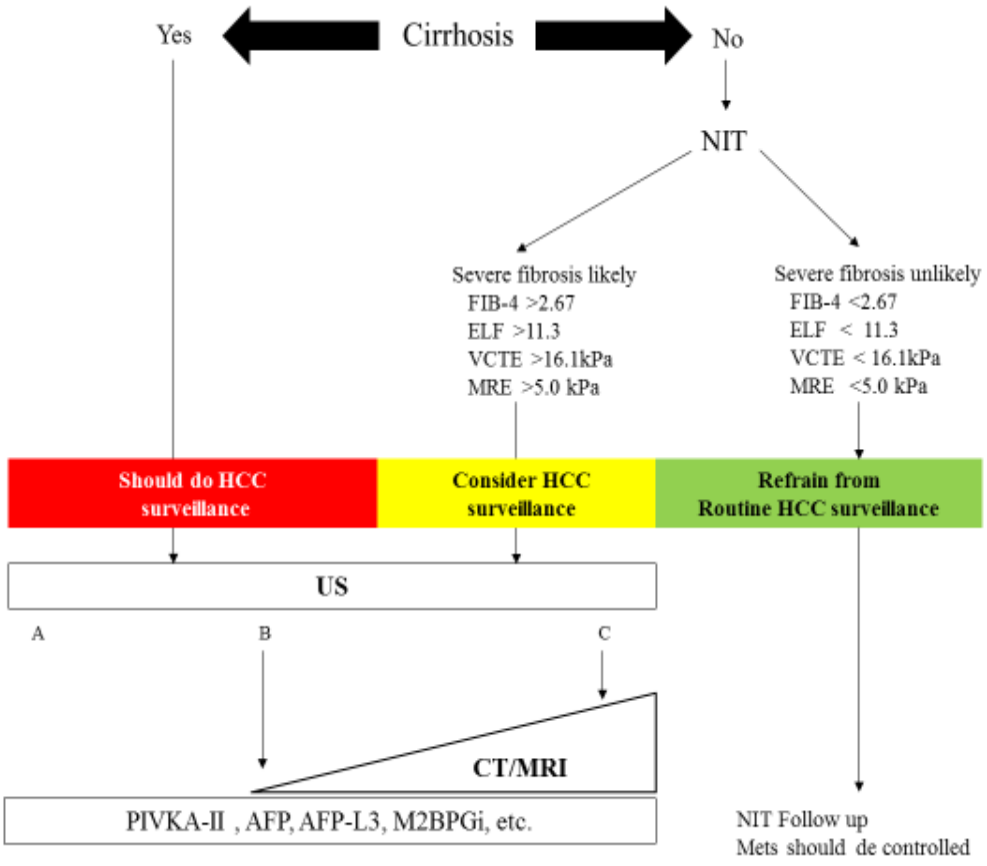

Figure 3. Algorithm for HCC surveillance in Nonalcoholic Fatty Liver Disease

NIT: noninvasive test, FIB-4: fibrosis-4, ELF: enhanced liver fibrosis, VCTE: vibration-controlled transient elastography, MRE: magnetic resonance elastography, HCC: hepatocellular carcinoma, US: ultrasonography, CT: computed tomography, MRI: magnetic resonance imaging, PIVKA-II: protein induced by vitamin K, AFP: α-fetoprotein, M2BPGi: Mac-2 binding protein glycosylated isomer. MetS: metabolic syndrome. The visualization score for ultrasound for HCC screening is graded into the following categories: A as no or minimal limitation; B as moderate limitation defined, as the examination may obscure small masses; and C as severe limitation, defined as the examination may miss focal liver lesions [22].

Conclusion

Surveillance of HCC is unreasonable for every patient with NAFLD estimated to be more than 2 billion worldwide. For cases of cirrhosis, suspected advanced fibrosis by NITs, and cases of diabetes mellitus, HCC should be surveyed by semi-annual US and tumor marker measurements such as AFP, AFP-L3, or PIVKA-II (Fig. 3). Because it is difficult to visualize the HCC in NAFLD patients by abdominal US due to obesity, we will consider alternative imaging such as CT or MRI. Early identification through surveillance provides more curative treatment options. If SNP measurement can be performed in general clinical settings, more efficient surveillance can be expected, but evidence construction considering cost benefit balances will be necessary in the future [78,79]. We also hope to establish innovative parameters for HCC surveillance such as M2bpGi, GALAD score, and free AIM. Precision tools that better predict the development of HCC in individual patients with NAFLD are needed.

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Abbreviation

AASLD American Association for the study of Liver Diseases

AFP: α-Fetoprotein

AFP-L3: Lens culinaris-agglutinin-reactive fraction of AFP

AGA: American Gastroenterology Association

AIM Apoptosis inhibitor of macrophage

AST: aspartate aminotransferase

ALT: alanine aminotransferase

BMI: body mass index

HA: hyaluronic acid

P3NP: aminoterminal propeptide of type 3 procollagen

TIMP-1: tissue inhibitor of matrix metalloproteinase type 1

CTC circulating tumor cells

CfDNA cell-free DNA

cfRNA cell-free RNA

EV extracellular vesicle

DCP: des-γ-carboxy pro-thrombin

CI confidence interval

CT: computed tomography

ELF: enhanced liver fibrosis

ELISA:

FIB-4: Fibrosis-4

NFS: NAFLD fibrosis score

HBV: hepatitis B virus

HCV: hepatitis C virus

HCC: hepatocellular carcinoma

HR: hazard ratio

HSD17B13 hydroxysteroid 17- beta dehydrogenase 13

FLD: fatty liver disease

M2BPGi Mac-2 binding protein glycosylation isomer

MBOAT7 membrane bound O-acyl-transferase domain circulating 7

MDCT multidetector CT

miRNA microRNA

MRE: magnetic resonance elastography

MRI: magnetic resonance imaging

ECCM-MRI: extracellular contrast media-enhanced MRI

NAFLD: nonalcoholic fatty liver disease

NASH: nonalcoholic steatohepatitis

NIT: noninvasive test

TIMP-1: tissue inhibitor of matrix metalloproteinase type 1,

PIVKA-II: protein induced by vitamin K

P3NP: aminoterminal propeptide of type 3 procollagen

PNPLA3: patatin-like phospholipase domain-containing protein 3

QALY: quality-adjusted life year (QALY)

RIA: radioimmunoassay

SNP: single nucleotide polymorphism

TIMP-1: tissue inhibitor of matrix metalloproteinase type 1

TM6SF: transmembrane 6 superfamily member 2

US: ultrasonography

VCTE: vibration-controlled transient elastography