2014 The Korean Liver Cancer Study Group and the National Cancer Center 간세포암종 개정 가이드라인: 1 cm 미만 간세포암종의 비침습적 진단기준이 너무 엄격한가?

김남중 · 신동현 · 강원석 · 백용한 · 최문석 · 이준혁 · 고광철 · 백승운 · 곽금연

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Noninvasive Diagnostic Criteria of the Revised 2014 the Korean Liver Cancer Study Group and the National Cancer Center Guideline for Subcentimeter-sized Hepatocellular Carcinoma: Is It Too Strict?

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Background/Aims: Noninvasive diagnostic criteria for hepatocellular carcinoma (HCC) differ between guidelines, especially for subcentimeter-sized nodules. This study aimed to analyze clinical and radiological characteristics of subcentimeter-sized HCC, and assess the validity of noninvasive diagnostic criteria of the revised 2014 the Korean Liver Cancer Study Group and the National Cancer Center (KLCSG-NCC) guideline for subcentimeter-sized HCC.

Methods: A total of 33 consecutive patients (median age, 58.6 years; men, 60.6%; hepatitis B virus-infected, 87.9%) who were diagnosed with HCC between January 2009 and December 2013 and had a maximum tumor diameter less than 1 cm were retrospectively included.

Results: Among 33 subcentimeter-sized HCC cases, 6 cases were histologically proven and the remaining 27 patients were diagnosed by radiologically and/or serologically. Initial detection modality was dynamic contrast-enhanced computed tomography (CT) (66.7%, 22/33) or dynamic contrast-enhanced magnetic resonance imaging (MRI) (33.3% 11/33). No case was identified by surveillance ultrasonography. Typical radiological feature of HCC, which is arterial enhancement with delayed washout, was present in 51.7% (15/29 patients) in dynamic contrast-enhanced CT, and 90.9% (30/33 patients) in dynamic contrast-enhanced MRI. When these 33 cases were re-assessed by the revised 2014 KLCSG-NCC guideline, no one has fulfilled the noninvasive diagnostic criteria.

Conclusions: None of the cases that were diagnosed as subcentimeter-sized HCC including histologically confirmed cases did not fulfill the noninvasive diagnostic criteria of the revised 2014 KLCSG-NCC guideline. Refinement of the current noninvasive diagnostic criteria for subcentimeter-sized HCC may be required. (*J Liver Cancer* 2018;18:44-50)

Keywords: Diagnostic criteria; Hepatocellular carcinoma; KLCSG-NCC guideline; Subcentimeter

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INTRODUCTION

Liver cancer is the sixth most common cancer and the second leading cause of cancer mortality in Korea.¹ Hepatocellular carcinoma (HCC) represents more than 90% of primary liver cancers, and shows a clear geographical distribution, with the highest rates of incidence in East Asia.² Korea is an intermediate endemic area of hepatitis B virus (HBV) infection, which is a well-known etiology of HCC.^{1,3,4} To provide in-depth information and assistance to local physicians in decision-making based on scientific evidence, the Korean guideline for the management of HCC was first developed in 2003, which was revised in 2009 and 2014 by the Korean Liver Cancer Study Group and the National Cancer Center (KLCSG-NCC).⁵ The guideline covered epidemiology, risk factors, prevention, surveillance, diagnosis, staging, and treatment of HCC.

HCC diagnosis was based on biopsy until 2000 just like any other solid tumors. However, this approach was not entirely feasible due to the location and risk of complications, such as bleeding or needle-tract seeding.⁶ Hence, most of the international HCC guidelines including Korean guideline allow diagnosis of HCC based on noninvasive criteria.^{2,5,7}

Noninvasive diagnostic criteria for HCC slightly differ between the guidelines, especially for subcentimeter-sized nodules. According to the guidelines of the European Association for the Study of the Liver (EASL) and the American Association for the Study of Liver Disease (AASLD), the noninvasive criteria for HCC diagnosis is applied only for nodules >1 cm that are identified on surveillance ultrasonography (US) in patients with risk factors.^{2,7,8}

Meanwhile, the guidelines of Liver Imaging Reporting and Data System (LI-RADS), the Asian Pacific Association for the Study of the Liver (APASL), the KLCSG-NCC, and the Japan Society of Hepatology (JSH) recommend noninvasive diagnosis of HCC for subcentimeter-sized nodules (less than 1 cm) based on the hallmark imaging features of HCC in patients with chronic liver disease or cirrhosis.^{2,5,9-12} In the revised 2014 KLCSG-NCC guideline, nodules <1 cm in diameter that were identified on surveillance US in high-risk patients were diagnosed as HCC when all of the following conditions

are met: typical features of HCC in two or more modalities among dynamic contrast-enhanced computed tomography (CT), dynamic contrast-enhanced magnetic resonance imaging (MRI), and liver-specific contrast-enhanced MRI, and continuously rising serum alpha-fetoprotein (AFP) with hepatitis activity under control.⁵ However, the quality of evidence was low.⁵

In this study, we analyzed the clinical and radiological characteristics of subcentimeter-sized nodules, which were diagnosed and treated as HCC at our institution before the revised 2014 KLCSG-NCC guideline was released, and assessed the validity of noninvasive diagnostic criteria of subcentimeter-sized HCC of the revised 2014 KLCSG-NCC guideline.

METHODS

1. Study design, setting and participants

This is a retrospective cohort study using HCC registry performed at Samsung Medical Center, Seoul, Korea. The HCC registry of Samsung Medical Center is a prospective registry which records clinical characteristics, tumor characteristics, and treatment information of newly-diagnosed HCC patients since January 2005. HCC was diagnosed histologically, or radiologically and/or serologically by corresponding physicians. In this study, we screened HCC patients registered between January 2009 (when a liver-specific contrast-enhanced MRI was introduced at our institution) and December 2013 (when the revised 2014 KLCSG-NCC guideline was not yet released). Among a total of 4,089 HCC patients registered in this period, 33 patients who had a maximum tumor diameter less than 1 cm were enrolled. The study protocol was approved by the Ethics Committee of Samsung Medical Center and the study was conducted in accordance with the principles of the Declaration of Helsinki.

2. Variables and measurement

We used the following variables that were collected at the HCC registry: age at diagnosis, sex, body mass index, underlying liver disease, mode of detection, laboratory results such as serum AFP, alanine aminotransferase (ALT), aspartate ami-

notransferase, bilirubin, and albumin levels, Child-Turcotte-Pugh class, tumor characteristics including number, maximal size, presence of vascular or bile duct invasion, and extrahepatic spread, and initial treatment modality. The following information was additionally collected by retrospective review of electronic medical records of each patient: presence of cirrhosis, imaging modality which identified subcentimeter-sized nodules, use of antiviral therapy, imaging findings of dynamic contrast-enhanced CT and MRI, imaging findings of liver-specific contrast-enhanced MRI, histology, and AFP level prior to detection of subcentimeter-sized nodules. In cases with multiple tumors, the characteristics of the biggest tumor were collected.

Cirrhosis was defined either clinically or histologically. The clinical diagnosis of cirrhosis was based on documented evidence of ascites (by cross-sectional images, or the use of diuretics for control of ascites) or varices (by esophagogastroduodenoscopy, cross-sectional images, or history of variceal bleeding), or when imaging studies showed cirrhotic configuration of the liver in cross-sectional imaging studies (nodular liver surface or caudate lobe hypertrophy) with thrombocytopenia ($<150,000/\text{mm}^3$) and/or splenomegaly in cross-sectional images.¹³ In the absence of specific criteria defining 'hepatitis activity under control' in the revised 2014 KLCSC-NCC HCC guideline,⁵ 'hepatitis activity under control' was defined by an ALT level less than upper limit of normal (<40 U/L) for this study.

3. Statistical analyses

Variables were expressed as mean $\pm$ standard deviation, median (range), or number (percentage) as appropriate.

RESULTS

1. Patient and tumor characteristics

The characteristics of 33 cases diagnosed as subcentimeter-sized HCC are summarized in Table 1. All the patients had more than one risk factor for HCC. Cirrhosis was documented in 81.8% of patients. Twenty-nine patients were diagnosed

Table 1. Patient characteristics

Variables	N=33
Age, years	58.6 $\pm$ 9.5
Men, n (%)	20 (60.6)
Body mass index, kg/m ²	23.9 $\pm$ 3.1
Underlying liver disease, n (%)	
Hepatitis B	29 (87.9)
Hepatitis C	3 (9.1)
Alcohol	1 (3.0)
Antiviral therapy for hepatitis B virus, n/N (%)	23/29 (79.3)
Cirrhosis, n (%)	
Clinically diagnosed	23 (69.7)
Histologically diagnosed	4 (12.1)
No	6 (18.2)
High risk patients*, n (%)	33 (100)
Mode of detection, n (%)	
Under regular surveillance	29 (87.9)
Incidentally identified	3 (9.1)
Symptomatic	1 (3.0)
Initial detection modality, n (%)	
US	0 (0)
Dynamic contrast-enhanced CT	22 (66.7)
Dynamic contrast-enhanced MRI	11 (33.3)
Tumor characteristics	
Single, n (%)	27 (81.8)
Maximum diameter, cm	0.8 (0.5–0.9)
Vascular/bile duct invasion, n (%)	0 (0)
Extrahepatic spread, n (%)	0 (0)
AFP, ng/mL	23.9 (1.3–1,323.7)
ALT, U/L	26 (7–119)
AST, U/L	34 (18–148)
Bilirubin, mg/dL	1.0 (0.2–3.2)
Albumin, g/dL	4.0 $\pm$ 0.56
Child-Turcotte-Pugh Class A, n (%)	27 (81.8)
Initial treatment modality, n (%)	
Resection	3 (9.1)
RFA	11 (33.3)
TACE	17 (51.5)
TACE+RFA	1 (3.0)
Transplantation	1 (3.0)

Values are presented as mean $\pm$ standard deviation or median (range) unless otherwise indicated.

US, ultrasonography; CT, computed tomography; MRI, magnetic resonance imaging; AFP, alpha-fetoprotein; ALT, alanine aminotransferase; AST, aspartate aminotransferase; RFA, radiofrequency ablation; TACE, transarterial chemoembolization.

*High risk patients were defined as having hepatitis B, hepatitis C or liver cirrhosis.

under regular surveillance for HCC. Three patients were incidentally detected. One patient presented with symptom (dyspnea of exertion); however, it was considered to be unrelated to HCC. Initial detection modality was dynamic contrast-enhanced CT (66.7%, 22/33) or dynamic contrast-enhanced MRI (33.3% 11/33). No case was identified by surveillance US. Most of them (27/33, 81.8%) had single tumor and the median value of maximum diameter was 0.8 cm. No one had vascular or bile duct invasion, or extrahepatic spread. The most common initial treatment modality was transarterial chemoembolization, followed by radiofrequency ablation.

Radiological characteristics of subcentimeter-sized HCCs are summarized in Table 2. Dynamic contrast-enhanced CT revealed the typical feature of HCC (arterial enhancement with delayed washout) in 15 patients (51.7%). Dynamic contrast-enhanced MRI showed typical feature of HCC in 30 patients (90.9%).

Six out of 33 patients were diagnosed via histological evaluation (4 patients by surgical resection, and 2 patients by transplantation) (Table 3).

2. Assessment of noninvasive diagnostic criteria of HCC

When these 33 subcentimeter-sized HCC patients were re-assessed according to the revised 2014 KLCSSG-NCC guideline,⁵ no one fulfilled the noninvasive diagnostic criteria (Table 4). Radiological criteria of typical features observed in

two or more of the dynamic contrast-enhanced CT, dynamic contrast-enhanced MRI, and liver-specific contrast-enhanced MRI, were met in 15 patients (45.4%). When analysis was limited to histologically proven cases, radiological criteria were met in 2 patients.

DISCUSSION

In this study, we demonstrated that among 33 cases of subcentimeter-sized HCC, which were diagnosed and treated as HCC at our institution before the revised 2014 KLCSSG-NCC guideline was released, no one fulfilled the noninvasive diagnostic criteria of the revised 2014 KLCSSG-NCC guideline. Also, no patient was diagnosed under US surveillance.

According to several international guidelines, subcentimeter-sized nodules detected under US surveillance are recommended periodic follow-up rather than further diagnostic approach such as CT or MRI.^{2,7,8} However, most of the subcentimeter-sized nodules with typical features of HCC on imaging modalities that were detected in patients with a history of HCC (89.9%) progressed to overt HCC within 12 months.¹⁴ Furthermore, a risk of vascular invasion of subcentimeter-sized nodules existed in a relatively short follow-up period.¹⁴ Hence, noninvasive diagnosis criteria for subcentimeter-sized HCC are required to decrease the risk of tumor progression during the follow-up. Tumor size is a major determinant for the successful local control of HCC.¹⁵ Thus, identifying subcentimeter-sized HCC in high-risk patients and treating it early is a reasonable strategy. In the present study, we showed that none of the 33 cases (including the 6 histologically proven cases) fulfilled the noninvasive diagnostic criteria of the revised 2014 KLCSSG-NCC guideline. Thus, these criteria of the revised 2014 KLCSSG-NCC guideline might be re-considered. In addition, the diagnosis of HCC under the current guideline is based on the detection of a nodule under US surveillance. However, none of our cases was identified by US surveillance. The detection rate of nodule on conventional B-mode US is affected by nodule size. For nodules less than or equal to 1 cm, the detection rate was reported as low as 36.4% in one study, even if US was used for nodules diagnosed with CT or MRI.¹⁶ Although US sur-

Table 2. Radiological characteristics of subcentimeter-sized hepatocellular carcinomas

Variables	N (%)
Dynamic contrast-enhanced CT (n=29)	
Arterial enhancement and delayed washout	15 (51.7)
Arterial enhancement without delayed washout	8 (27.6)
No arterial enhancement	6 (20.7)
Dynamic contrast-enhanced MRI (n=33)	
Arterial enhancement and delayed washout	30 (90.9)
Arterial enhancement without delayed washout	3 (9.1)

In cases with multiple tumors, the characteristics of the biggest tumor were described.

CT, computed tomography; MRI, magnetic resonance imaging.

Table 3. Six cases of subcentimeter-sized hepatocellular carcinomas that were histologically diagnosed

	Case #1	Case #2	Case #3	Case #4	Case #5	Case #6
Age, years	48	42	53	53	68	70
Sex	Male	Male	Male	Female	Male	Female
Underlying liver disease	Hepatitis B	Hepatitis B	Hepatitis B	Hepatitis B	Hepatitis B	Hepatitis B
ALT at diagnosis, U/L	119	31	25	47	23	20
Initial detection modality	CT	CT	MRI	CT	CT	CT
Antiviral therapy for hepatitis B virus	Yes	Yes	Yes	Yes	Yes	Yes
AFP at diagnosis, ng/mL	40.9	13	19	7.7	2.7	1.3
AFP prior to diagnosis, ng/mL	4.7	22.3	5.2	7.1	2.7	1.8
Tumor characteristics						
Maximum diameter, cm	0.9	0.8	0.7	0.9	0.9	0.9
Number	2	1	1	4	1	1
Dynamic contrast-enhanced CT						
Arterial enhancement	Yes	Yes	Not done	Yes	Yes	Yes
Delayed washout	Equivocal	Yes	Not done	Yes	No	No
Dynamic contrast-enhanced MRI						
Arterial enhancement	Yes	Yes	Yes	Yes	Yes	Yes
Delayed washout	Yes	Yes	Yes	Yes	No	Yes
Moderately high SI on T2	Yes	Yes	Yes	Yes	Yes	Yes
High SI on diffusion weighted image	Yes	Yes	Yes	Yes	Yes	Yes
Low SI on hepatobiliary phase	Yes	Yes	Yes	Yes	Yes	Yes
Initial treatment	Segmentectomy	Transplantation	Hemihepatectomy	TACE, followed by transplantation	Tumorectomy	RFA, followed by segmentectomy

In cases with multiple tumors, the characteristics of the biggest tumor were described.

ALT, alanine aminotransferase; CT, computed tomography; MRI, magnetic resonance imaging; AFP, alpha-fetoprotein; SI, signal intensity; TACE, transarterial chemoembolization; RFA, radiofrequency ablation.

veillance of HCC is recommended in many guidelines,¹⁷ its performance is suboptimal, especially for the detection of small HCC.^{18,19} In real-life clinical practice, many physicians prefer CT or MRI for surveillance.²⁰ Hence, in order to facilitate noninvasive diagnosis of subcentimeter-sized HCC, the surveillance tools for HCC may be extended to CT or MRI.

In the present study, only 51.7% of patients showed typical features of HCC in dynamic contrast-enhanced CT whereas dynamic contrast-enhanced MRI revealed that 90.9% had typical features. Most of the guidelines suggest typical features of arterial enhancement and delayed washout in dynamic imaging to diagnose HCC. When using a liver-specific contrast media, there are several other ancillary features suggestive of HCC. The five diagnostic hallmarks of HCC on

gadoteric acid-enhanced MRI with diffusion-weighted imaging (DWI) are hypervascularity on the arterial phase, washout on the portal or delayed phase, moderately high signal intensity (SI) on T2-weighted images, high SI on DWI, and low SI on hepatobiliary phase images compared with the surrounding liver parenchyma.^{10,21,22} Before the revised 2014 KLCSSG-NCC guideline was released, most of our cases were diagnosed as HCC according to a combination of these hallmarks on liver-specific contrast-enhanced MRI with DWI and tumor markers. Among the 6 patients with histologically proven HCC, radiological criteria were met only in 2 patients, while five diagnostic hallmarks of HCC on gadoteric acid-enhanced MRI with DWI were met in 5 out of 6 patients (Table 3, 4). In the 2016 Consensus recommendations

Table 4. Reassessment according to the noninvasive diagnostic criteria of subcentimeter-sized hepatocellular carcinomas of the revised 2014 Korean Liver Cancer Study Group and the National Cancer Center guideline

Diagnostic criteria	N (%)
All cases (n=33)	
High-risk patients	33 (100)
Detected under US surveillance	0 (0)
Typical features in two or more imaging modalities	15 (45.4)
Continuous rising serum AFP with hepatitis activity under control	8 (24.2)
Fulfillment of all criteria	0 (0)
Histologically proven cases (n=6)	
High-risk patients	6 (100)
Detected under US surveillance	0 (0)
Typical features in two or more imaging modalities	2 (33.3)
Continuous rising serum AFP with hepatitis activity under control	1 (16.7)
Fulfillment of all criteria	0 (0)

In cases with multiple tumors, the characteristics of the biggest tumor were described.

US, ultrasonography; AFP, alpha-fetoprotein.

of the Korean Society of Abdominal Radiology, the diagnostic criteria were refined in addition to the typical vascular profile changes in subcentimeter-sized nodule.²³ Ancillary features on liver-specific contrast-enhanced MRI may improve the performance of enhancement pattern based-diagnosis of subcentimeter-sized HCC. This issue warrants further clarification.

Our study has several limitations. First of all, only six cases had histologically proven HCC in this study, which decreases the power of the study. Second, we included subcentimeter-sized nodules already registered as HCC based on decision of each physician. A prospective study involving all subcentimeter-sized nodules is needed to assess the performance of noninvasive diagnostic criteria of the revised 2014 KLCSC-NCC guideline. Finally, because of the long study duration, a lot of radiologists were involved in performing and interpreting imaging modalities. Hence, variability between radiologists might have led to measurement error. Also, since we used the radiologic reports on medical record, the imaging modalities were not interpreted in a blinded, independent

fashion.

In summary, we found that none of the 33 cases who were histologically or radiologically diagnosed as subcentimeter-sized HCC before the revised 2014 KLCSC-NCC guideline was released fulfilled the noninvasive diagnostic criteria of this guideline. In addition, none of our cases was identified by US which is a currently recommended surveillance tool for HCC. The current noninvasive diagnostic criteria for subcentimeter-sized HCC may require refinement.

AUTHOR CONTRIBUTIONS

Sinn DH and Gwak GY designed the study. Kim NJ collected the data. Kim NJ and Sinn DH performed the data analysis. Kim NJ, Sinn DH and Gwak GY wrote the final report. All authors contributed to critical revision of the final report.

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Conflicts of Interest

The authors have no conflicts to disclose.

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