Editorial Commentary

Surveillance of hepatocellular carcinoma by medical imaging

Christoph F. Dietrich[1,2], Andreas Teufel[3], Claude B. Sirlin[4], Yi Dong[5]

[1]Sino-German Tongji-Caritas Research Center of Ultrasound in Medicine, Department of Medical Ultrasound, Tongji Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan 430030, China; [2]Department of Internal Medicine II, Caritas-Krankenhaus Bad Mergentheim, Bad Mergentheim, Germany; [3]Division of Hepatology, Department of Medicine II, Medical Faculty Mannheim, Heidelberg University, Mannheim, Germany; [4]Liver Imaging Group, Department of Radiology, UC San Diego, San Diego, CA, USA; [5]Department of Ultrasound, Zhongshan Hospital, Fudan University, Shanghai 200433, China

Correspondence to: Christoph F. Dietrich, MD. Professor, Department of Internal Medicine II, Caritas-Krankenhaus Bad Mergentheim, Uhlandstraße 7, 97980 Bad Mergentheim, Germany. Email: christoph.dietrich@ckbm.de.

Comment on: Park JH, Park MS, Lee SJ, Jeong WK, Lee JY, Park MJ, Lee SS, Han K, Nam CM, Park SH, Lee KH. Contrast-enhanced US with perfluorobutane for hepatocellular carcinoma surveillance: a multicenter diagnostic trial (SCAN). Radiology 2019;292:638-46.

Submitted Aug 30, 2019. Accepted for publication Oct 05, 2019.
doi: 10.21037/qims.2019.10.04
View this article at: http://dx.doi.org/10.21037/qims.2019.10.04

Effective treatments for early-stage hepatocellular carcinoma (HCC) have provided the rationale for HCC surveillance since detection of the disease at an early stage is associated with more favorable outcome. In a prospective multi-institutional diagnostic study, Park *et al.* (1) evaluated the added value of (perfluorobutane) contrast-enhanced ultrasound (CEUS) when combined with conventional B-mode ultrasound (US) as an HCC surveillance tool in participants with liver cirrhosis using a single arm, intraindividual comparison study design. The primary end points were the detection rate of early-stage HCC (Barcelona clinic liver cancer staging system stage 0 or A) and false-positive rate. Of the initially included 524 participants, 493 (94.1%) had liver cirrhosis related to the hepatitis B virus (HBV). Ten HCCs were confirmed in eight participants. The detection rate for early-stage HCC was not significantly improved by adding perfluorobutane-enhanced US to conventional B-mode US. However, the false-positive rate was significantly reduced.

Some current clinical practice guidelines also recommend HCC surveillance in patients with chronic hepatitis C virus (HCV) infection and advanced liver fibrosis (stage F3) (2). Chronic HBV without cirrhosis is considered an indication for HCC surveillance if any of the following criteria is met (2-6):

- ❖ Active hepatitis [e.g., elevated serum alanine transaminase (ALT)] and/or high viral load (i.e., >100,000 copies/mL).
- ❖ Family history of HCC [first degree relative, adjusted rate ratio (ARR) 2.4] (7).
- ❖ Asian males over the age of 40 years, females over 50 years. The incidence of HCC in Asian patients with HBV is higher than in Caucasian patients (0.4 to 0.6 percent per year compared to less than 0.2 percent per year) (8,9). The incidence in male HBV carriers from Southeast Asia exceed 0.2% around the age of 40 years and is the basis for the recommendation that surveillance start in Asian men at age 40 years. The incidence in Asian women is lower, but it is not well defined.
- ❖ Africans and African Americans (10,11).
- ❖ Viral load >100,000 copies/mL (20,000 international units/mL) is a risk factor for disease progression and HCC in Asian patients (4-6).

Also, surveillance is recommended for patients who are on effective antiviral treatment for chronic HBV infection and are HBsAg seropositive, although the risk of HCC appears to be decreased among these patients (2,3). In contrast, the incidence of HCC is low for treatment-naïve patients with inactive hepatitis (long-term normal ALT and HBV DNA levels less than 2,000 international units/mL) (12,13). As a result, surveillance for such patients without cirrhosis and without an additional risk factor

is not generally recommended (3). Also, in patients with nonalcoholic steatohepatitis surveillance is generally not recommended until they progress to cirrhosis. Finally, surveillance is not generally recommended in patients with child-pugh score C, due to their limited life expectancy and low hepatic functional reserve to tolerate treatment for detected cancer.

Surveillance is defined as screening examinations at regular intervals. US with or without α-fetoprotein (AFP) is considered standard surveillance for HCC in patients at risk (2,3). The survival rate, size at time of diagnosis, and treatment options are meaningfully improved compared to populations without surveillance. This is due to an increased detection of early stage HCC by surveillance with an odds ratio of 2.11 compared to non-surveillance (14). A large, randomized Chinese surveillance study in 19,200 patients with chronic HBV (4) infection, with or without cirrhosis, confirmed a 37 % reduction in mortality under surveillance (6,15). A Japanese study confirmed that surveillance allows the detection of small, potentially curable HCCs, with the vast majority of detected cancers being ≤3 cm; only 2% of surveilled patients had HCCs exceeding 3 cm at diagnosis. In a meta-analysis, the pooled sensitivity of US in detecting early HCC was 63% (16,17). These convincing data on efficacy of HCC surveillance even hold true in large meta analyses comparing 38 pooled studies and demonstrating improved 3-year survival rates, increased detection of early-stage HCC and higher curative treatment rates compared with non-surveillance (18).

However, efficacy of surveillance and ultimately overall survival is clearly associated with compliance with HCC surveillance guidelines (fewer than 7 months between image evaluations) as recently demonstrated with the ANRS CO12 CirVir cohort (19).

Magnetic resonance imaging (MRI)

MRI is more accurate than US or computed tomography (CT) for detection of HCC (20) but the exams are long, complex, and expensive, and complete MRI is generally not recommended for routine HCC surveillance. To overcome some of the barriers of complete MRI, investigators in recent years have proposed abbreviated MRI exam protocols. These abbreviated protocols include only the sequences essential for HCC detection. Three abbreviated MRI approaches are reasonable:

- Non-contrast abbreviated MRI comprising unenhanced T1w dual-echo images, T2w images, and diffusion-weighted images. No intravenous catheter or contrast agent is required.
- Dynamic abbreviated MRI comprising T1w fat-suppressed images precontrast and in the arterial, portal venous, or delayed phases after administration of an extracellular agent. The agent is injected in the scanner using a power injector via an intravenous catheter.
- Hepatobiliary abbreviated MRI comprising T1w fat-suppressed images and T2w, with the possible addition of diffusion-weighted images, acquired about 20 minutes after administration of gadoxetate disodium, a hepatobiliary agent. The agent is injected outside the scanner room and the patient is brought into the scanner several minutes later.

Each of these abbreviated MRI exam protocols requires less than 15 minutes of scanner time, thereby improving throughput, decreasing patient burden, and reducing cost. Of the three approaches, hepatobiliary abbreviated MRI is the best studied. In three retrospective analyses, the performance of this method was simulated by extracting the relevant images from a complete gadoxetate-enhanced MRI: the sensitivity for HCC detection ranged from 81% to 85% (21-23). While this protocol is promising, it has not been validated prospectively. Moreover, while the exam has high sensitivity for HCC detection, it does not provide enough information for definitive HCC diagnosis. Hence, a positive hepatobiliary abbreviated MRI exam requires call-back for a complete, diagnostic exam.

Although both complete MRI and abbreviated MRI exams are more sensitive than US (20), there have been no prospective trials to assess whether they improve survival, and the cost-effectiveness of MRI for routine HCC surveillance has not been proven.

Currently, we suggest that MRI or abbreviated MRI be considered for HCC surveillance when US is compromised by severe patient obesity, hepatic steatosis, or parenchymal heterogeneity.

CT

Compared to MRI, CT is more widely available, easier to perform, faster, and provokes less claustrophobia. However, it exposes patients to radiation (24,25) and is generally not recommended for routine surveillance.

US

B-mode US as a screening procedure is generally accepted.

The current AASLD guidelines recommend surveillance using US, with or without AFP, every 6 months (14). Thus, US is the currently the method of choice and is often applied beyond HCC surveillance to monitor other conditions, such as the development of portal hypertension, including the onset of ascites or portal vein thrombosis (2). However, the results are operator-dependent, with sensitivities ranging widely from 47% to 84% depending on the experience of the examiner (17). For this reason, the most updated EASL guidelines suggested that surveillance should be performed only by experienced personnel (2).

At the time of diagnosis, the most commonly observed finding in HCC is a hypervascular appearance, independent of their sizes (26). A meta-analysis showed that US surveillance detected the majority of HCC tumors before they presented clinically, with a pooled sensitivity of 94%. However, US in this report was less effective for detecting early-stage HCC, with a sensitivity of only 63% (27). The sensitivity of US alone for detecting HCC at any stage is 78% and for early-stage HCC is 45% (17,20). This may be due to a decreasing sensitivity with decreasing lesion size. Also, decreasing sensitivity of 85%, 62%, and 21% were reported for lesions larger 4 cm, between 4 and 2 cm, and below 2 cm, respectively (28). Reported specificity is uniformly high at >90%. Thus, among the modalities for liver imaging, US is the least expensive and the most widely available but the least sensitive for detection of HCC (20,28).

Shear wave elastography (SWE)

SWE has been widely used for many years to non-invasively estimate liver stiffness as a biomarker of liver fibrosis and there has been increasing interest in using SWE to identify patients with advanced fibrosis who might benefit from HCC surveillance (29-34). The value of SWE to identify patients with chronic hepatitis at greater risk of HCC has been proven in replicating HCV, but has been insufficiently validated in patients who achieved sustained virologic response (SVR) after HCV eradication. In particular, the stiffness thresholds associated with sustained higher risk of HCC development, after achieving SVR with PegIFN-based therapies, ranged from 6.5 to 12.0 kPa (35,36).

CEUS

CEUS so far is not recommended for surveillance as its use in this context has not been validated. The entire liver cannot be imaged with US during the dynamic phase of contrast administration to characterize all detected nodules (37). Instead, CEUS permits characterization of one or a limited number of identified nodules. Therefore, pure blood pool US contrast agents have not been recommended for surveillance because they generally do not enable examination of the entire liver.

By comparison, perfluorobutane gas-containing microbubbles provide a prolonged postvascular phase during which the entire liver can be interrogated. The contrast agent Sonzaoid® is phagocytized by liver-specific macrophages including Kupffer cells, thereby amplifying US scattering to generate amplified sound waves (38). Since Kupffer cells may be less abundant or even completely absent in HCC, hypoenhancement in the postvascular phase is a relatively sensitive imaging feature liver cancer. Neoplastic focal liver infiltration with less liver-specific macrophages showed a contrast defect (39). Therefore, CEUS in the delayed phase may permit improved detection of HCC nodules. Sonzaoid® was approved in Japan, South Korea, Norway and recently in China; it can be also used in Denmark (40).

CEUS has improved characterization of HCC. Hyperenhancement during the arterial phase and mild washout are indicative for HCC in liver cirrhosis (41). The featured study hypothesizes that also the detection rate of early-stage HCC could be improved with fewer false referrals by adding perfluorobutane enhanced US to conventional B-mode US. The reference standards were based on the liver imaging reporting and data system (LI-RADS) (42-44), which currently include CEUS using SonoVue/Lumason but not Sonazoid. The operator dependency of US examination may be one reason why CEUS has not proven to increase the ability of US to detect small HCC tumors (45). The authors did neither observe an improvement in the detection rate of early stage HCC, nor improvement in the detection rate of any stage of HCC. However, perfluorobutane-enhanced US showed a lower false referral rate compared to conventional B-mode US. The previously reported benefit for additional HCCs detected with perfluorobutane-enhanced US not detected with B-mode US could not be reproduced (39). Possible explanations include an unexpectedly lower incidence of HCC far below the expected 5%, possibly due to antiviral treatment (46,47) and predominance of hepatitis B infection (94%) (48). In addition, small and well-differentiated HCCs may maintain the liver specific vessels and sinusoids and the number of phagocating cells, similar to the surrounding hepatic parenchyma (49,50). They conclude that CEUS in general (39,45) and perfluorobutane-enhanced US may be

used as a second-line tool at the same visit for surveillance if a lesion suspicious for HCC is detected with B-mode US.

Combination of US and biomarker analysis

The most commonly used tumor marker for HCC is AFP. As a screening test, AFP is generally associated with poor sensitivity and specificity for detection of HCC (27,44,51). When used as a diagnostic test, AFP levels at a value of 20 ng/mL showed good sensitivity but low specificity, whereas at higher cut-offs of 200 ng/mL the sensitivity drops to 22% with high specificity (52). Only a small proportion of HCC at an early stage (10–20%) present with abnormal AFP serum levels, a fact that has recently been correlated with a molecular subclass of aggressive HCCs (S2 class, EpCAM positive) (53,54). Thus, AFP is not used for HCC screening unless additional imaging is unavailable. Even in combination with US, AFP levels are only able to provide additional detection of 6–8% of HCC cases not previously identified by US (55). Since the combined use of AFP and abdomen US increases detection rates compared with US alone (17,56), AFP may be added to US for surveillance, although this increases false-positive rates (27).

Harm

Besides detection rate and benefit for the patient, the possible harm of HCC surveillance merits discussion (17,27,48). A significant proportion of patients with liver cirrhosis undergo possibly harmful imaging with potential radiation exposure or interventional procedures (CT, MRI, liver biopsy, or angiography) (56). Psychological and financial harms are additional considerations. Therefore, false-positive or indeterminate surveillance tests should be avoided. CEUS in general and perfluorobutane-enhanced US specifically may reduce the number of false positive findings in surveillance (57).

Costs

Cost effectiveness is among the keys to acceptance of surveillance strategies and potentially even reimbursement by health insurance companies (57,58). Decision analysis and cost-effectiveness models suggest that an intervention is considered cost-effective if it provides life expectancy increase of at least three months with a cost below an established threshold (59). Besides imaging surveillance, risk evaluation needs biochemical and serological test results (e.g., AFP, HBV, aminotransferases, and others) all of which increase the cost of surveillance.

Costs of surveillance for HCC vary significantly among diverse countries. An Italian surveillance programme showed the overall cost of the surveillance programme was US $753,226, the cost per treatable HCC was US $17,934, and the cost for year of life saved was US $112,993 (60). Generally, the decision whether to adopt a surveillance policy towards HCC also relies on the prevalence of the disease in the population and on the resources of a particular country. From a patient's standpoint and with currently increasing incidence of HCC, surveillance must be recommended.

Acknowledgments

The authors acknowledge Bad Mergentheimer Leberzentrum e.V.

Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

References

1. Park JH, Park MS, Lee SJ, Jeong WK, Lee JY, Park MJ, Lee SS, Han K, Nam CM, Park SH, Lee KH. Contrast-enhanced US with perfluorobutane for hepatocellular carcinoma surveillance: a multicenter diagnostic trial (SCAN). Radiology 2019;292:638-46.
2. European Association for the Study of the Liver. EASL clinical practice guidelines: management of hepatocellular carcinoma. J Hepatol 2018;69:182-236.
3. Marrero JA, Kulik LM, Sirlin CB, Zhu AX, Finn RS, Abecassis MM, Roberts LR, Heimbach JK. Diagnosis, staging, and management of hepatocellular carcinoma: 2018 practice guidance by the American association for the study of liver diseases. Hepatology 2018;68:723-50.
4. Chen CJ, Yang HI, Su J, Jen CL, You SL, Lu SN, Huang GT, Iloeje UH, REVEAL-HBV Study Group. Risk of hepatocellular carcinoma across a biological gradient of serum hepatitis B virus DNA level. JAMA 2006;295:65-73.
5. Iloeje UH, Yang HI, Su J, Jen CL, You SL, Chen CJ, Risk Evaluation of Viral Load Elevation and Associated Liver Disease/Cancer-In HBV (the REVEAL-HBV) Study Group. Predicting cirrhosis risk based on the level of circulating hepatitis B viral load. Gastroenterology

2006;130:678-86.
6. Lok AS, Heathcote EJ, Hoofnagle JH. Management of hepatitis B: 2000--summary of a workshop. Gastroenterology 2001;120:1828-53.
7. Yu MW, Chang HC, Liaw YF, Lin SM, Lee SD, Liu CJ, Chen PJ, Hsiao TJ, Lee PH, Chen CJ. Familial risk of hepatocellular carcinoma among chronic hepatitis B carriers and their relatives. J Natl Cancer Inst 2000;92:1159-64.
8. Kew MC. Epidemiology of chronic hepatitis B virus infection, hepatocellular carcinoma, and hepatitis B virus-induced hepatocellular carcinoma. Pathol Biol (Paris) 2010;58:273-7.
9. Sakuma K, Saitoh N, Kasai M, Jitsukawa H, Yoshino I, Yamaguchi M, Nobutomo K, Yamumi M, Tsuda F, Komazawa T, Nakamura T, Yoshida Y, Okuda K. Relative risks of death due to liver disease among Japanese male adults having various statuses for hepatitis B s and e antigen/antibody in serum: a prospective study. Hepatology 1988;8:1642-6.
10. Kew MC, Macerollo P. Effect of age on the etiologic role of the hepatitis B virus in hepatocellular carcinoma in blacks. Gastroenterology 1988;94:439-42.
11. Kew MC, Marcus R, Geddes EW. Some characteristics of Mozambican Shangaans with primary hepatocellular cancer. S Afr Med J 1977;51:306-9.
12. Manno M, Camma C, Schepis F, Bassi F, Gelmini R, Giannini F, Miselli F, Grottola A, Ferretti I, Vecchi C, De Palma M, Villa E. Natural history of chronic HBV carriers in northern Italy: morbidity and mortality after 30 years. Gastroenterology 2004;127:756-63.
13. Bellentani S, Dal Molin G, Miglioli L, Crocè LS, Masutti F, Castiglione A, Campello C, Tiribelli C. Natural history of HBV infection: a nine years follow-up of the dionysius cohort. J Hepatol 2002;36:228.
14. Heimbach JK, Kulik LM, Finn RS, Sirlin CB, Abecassis MM, Roberts LR, Zhu AX, Murad MH, Marrero JA. AASLD guidelines for the treatment of hepatocellular carcinoma. Hepatology 2018;67:358-80.
15. Zhang BH, Yang BH, Tang ZY. Randomized controlled trial of screening for hepatocellular carcinoma. J Cancer Res Clin Oncol 2004;130:417-22.
16. Kokudo N, Hasegawa K, Akahane M. Evidence-based clinical practice guidelines for hepatocellular carcinoma: the Japan Society of Hepatology 2013 update (3rd JSH-HCC guidelines). Hepatol Res 2015;45:123-7.
17. Tzartzeva K, Obi J, Rich NE, Parikh ND, Marrero JA, Yopp A, Waljee AK, Singal AG. Surveillance imaging and alpha fetoprotein for early detection of hepatocellular carcinoma in patients with cirrhosis: a meta-analysis. Gastroenterology 2018;154:1706-18.e1.
18. Singal AG, Pillai A, Tiro J. Early detection, curative treatment, and survival rates for hepatocellular carcinoma surveillance in patients with cirrhosis: a meta-analysis. PLoS Med 2014;11:e1001624.
19. Costentin CE, Layese R, Bourcier V, Cagnot C, Marcellin P, Guyader D, Pol S, Larrey D, De Lédinghen V, Ouzan D, Zoulim F, Roulot D, Tran A, Bronowicki JP, Zarski JP, Riachi G, Calès P, Péron JM, Alric L, Bourlière M, Mathurin P, Blanc JF, Abergel A, Serfaty L, Mallat A, Grangé JD, Attali P, Bacq Y, Wartelle C, Dao T, Thabut D, Pilette C, Silvain C, Christidis C, Nguyen-Khac E, Bernard-Chabert B, Zucman D, Di Martino V, Sutton A, Letouzé E, Imbeaud S, Zucman-Rossi J, Audureau E, Roudot-Thoraval F, Nahon P, ANRS CO12 CirVir Group. Compliance with hepatocellular carcinoma surveillance guidelines associated with increased lead-time adjusted survival of patients with compensated viral cirrhosis: a multi-center cohort study. Gastroenterology 2018;155:431-42.e10.
20. Colli A, Fraquelli M, Casazza G, Massironi S, Colucci A, Conte D, Duca P. Accuracy of ultrasonography, spiral CT, magnetic resonance, and alpha-fetoprotein in diagnosing hepatocellular carcinoma: a systematic review. Am J Gastroenterol 2006;101:513-23.
21. Marks RM, Ryan A, Heba ER, Tang A, Wolfson TJ, Gamst AC, Sirlin CB, Bashir MR. Diagnostic per-patient accuracy of an abbreviated hepatobiliary phase gadoxetic acid-enhanced MRI for hepatocellular carcinoma surveillance. AJR Am J Roentgenol 2015;204:527-35.
22. Besa C, Lewis S, Pandharipande PV, Chhatwal J, Kamath A, Cooper N, Knight-Greenfield A, Babb JS, Boffetta P, Padron N, Sirlin CB, Taouli B. Hepatocellular carcinoma detection: diagnostic performance of a simulated abbreviated MRI protocol combining diffusion-weighted and T1-weighted imaging at the delayed phase post gadoxetic acid. Abdom Radiol (NY) 2017;42:179-90.
23. Tillman BG, Gorman JD, Hru JM, Lee MH, King MC, Sirlin CB, Marks RM. Diagnostic per-lesion performance of a simulated gadoxetate disodium-enhanced abbreviated MRI protocol for hepatocellular carcinoma screening. Clin Radiol 2018;73:485-93.
24. Thomsen HS. Nephrogenic systemic fibrosis: history and epidemiology. Radiol Clin North Am 2009;47:827-31, vi.
25. Tao SM, Wichmann JL, Schoepf UJ, Fuller SR, Lu GM, Zhang LJ. Contrast-induced nephropathy in CT:

incidence, risk factors and strategies for prevention. Eur Radiol 2016;26:3310-8.
26. Ignee A, Weiper D, Schuessler G, Teuber G, Faust D, Dietrich CF. Sonographic characterisation of hepatocellular carcinoma at time of diagnosis. Z Gastroenterol 2005;43:289-94.
27. Singal A, Volk ML, Waljee A, Salgia R, Higgins P, Rogers MA, Marrero JA. Meta-analysis: surveillance with ultrasound for early-stage hepatocellular carcinoma in patients with cirrhosis. Aliment Pharmacol Ther 2009;30:37-47.
28. Yu NC, Chaudhari V, Raman SS, Lassman C, Tong MJ, Busuttil RW, Lu DS. CT and MRI improve detection of hepatocellular carcinoma, compared with ultrasound alone, in patients with cirrhosis. Clin Gastroenterol Hepatol 2011;9:161-7.
29. Dietrich CF, Ferraioli G, Sirli R, Popescu A, Sporea I, Pienar C, Kunze C, Taut H, Schrading S, Bota S, Schreiber-Dietrich D, Fang C, Yi D. General advice in ultrasound based elastography of pediatric patients. Med Ultrason 2019;21:315-26.
30. S ftoiu A, Gilja OH, Sidhu PS, Dietrich CF, Cantisani V, Amy D, Bachmann-Nielsen M, Bob F, Bojunga J, Brock M, Calliada F, Clevert DA, Correas JM, D'Onofrio M, Ewertsen C, Farrokh A, Fodor D, Fusaroli P, Havre RF, Hocke M, Ignee A, Jenssen C, Klauser AS, Kollmann C, Radzina M, Ramnarine KV, Sconfienza LM, Solomon C, Sporea I, tef nescu H, Tanter M, Vilmann P. The EFSUMB guidelines and recommendations for the clinical practice of elastography in non-hepatic applications: update 2018. Ultraschall Med 2019;40:425-53.
31. Berzigotti A, Ferraioli G, Bota S, Gilja OH, Dietrich CF. Novel ultrasound-based methods to assess liver disease: the game has just begun. Dig Liver Dis 2018;50:107-12.
32. Ferraioli G, Wong VW, Castera L, Berzigotti A, Sporea I, Dietrich CF, Choi BI, Wilson SR, Kudo M, Barr RG. Liver ultrasound elastography: an update to the World Federation for ultrasound in medicine and biology guidelines and recommendations. Ultrasound Med Biol 2018;44:2419-40.
33. Dietrich C, Sirli R, Ferraioli G, Popescu A, Sporea I, Pienar C, Kunze C, Taut H, Schrading S, Bota S. Current knowledge in ultrasound-based liver elastography of pediatric patients. Appl Sci 2018;8:944.
34. Dong Y, Sirli R, Ferraioli G, Sporea I, Chiorean L, Cui X, Fan M, Wang WP, Gilja OH, Sidhu PS, Dietrich CF. Shear wave elastography of the liver - review on normal values. Z Gastroenterol 2017;55:153-66.
35. Wang HM, Hung CH, Lu SN, Chen CH, Lee CM, Hu TH, Wang JH. Liver stiffness measurement as an alternative to fibrotic stage in risk assessment of hepatocellular carcinoma incidence for chronic hepatitis C patients. Liver Int 2013;33:756-61.
36. Wang JH, Yen YH, Yao CC, Hung CH, Chen CH, Hu TH, Lee CM, Lu SN. Liver stiffness-based score in hepatoma risk assessment for chronic hepatitis C patients after successful antiviral therapy. Liver Int 2016;36:1793-9.
37. Choi BI, Lee JM, Kim TK, Dioguardi Burgio M, Vilgrain V. Diagnosing borderline hepatic nodules in hepatocarcinogenesis: imaging performance. AJR Am J Roentgenol 2015;205:10-21.
38. Yanagisawa K, Moriyasu F, Miyahara T, Yuki M, Iijima H. Phagocytosis of ultrasound contrast agent microbubbles by Kupffer cells. Ultrasound Med Biol 2007;33:318-25.
39. Kudo M, Hatanaka K, Kumada T, Toyoda H, Tada T. Double-contrast ultrasound: a novel surveillance tool for hepatocellular carcinoma. Am J Gastroenterol 2011;106:368-70.
40. Numata K, Fukuda H, Nihonmatsu H, Kondo M, Nozaki A, Chuma M, Morimoto M, Oshima T, Okada M, Murakami T, Takebayashi S, Maeda S, Inayama Y, Nakano M, Tanaka K. Use of vessel patterns on contrast-enhanced ultrasonography using a perflubutane-based contrast agent for the differential diagnosis of regenerative nodules from early hepatocellular carcinoma or high-grade dysplastic nodules in patients with chronic liver disease. Abdom Imaging 2015;40:2372-83.
41. Dong Y, Wang WP, Mao F, Dietrich C. Contrast-enhanced ultrasound features of hepatocellular carcinoma not detected during the screening procedure. Z Gastroenterol 2017;55:748-53.
42. Darnell A, Forner A, Rimola J, Reig M, Garcia-Criado A, Ayuso C, Bruix J. Liver imaging reporting and data system with mr imaging: evaluation in nodules 20 mm or smaller detected in cirrhosis at screening US. Radiology 2015;275:698-707.
43. Elsayes KM, Hooker JC, Agrons MM, Kielar AZ, Tang A, Fowler KJ, Chernyak V, Bashir MR, Kono Y, Do RK, Mitchell DG, Kamaya A, Hecht EM, Sirlin CB. 2017 version of LI-RADS for CT and MR imaging: an update. Radiographics 2017;37:1994-2017.
44. Llovet JM, Fuster J, Bruix J, Barcelona-Clinic Liver Cancer G. The Barcelona approach: diagnosis, staging, and treatment of hepatocellular carcinoma. Liver Transpl 2004;10:S115-20.
45. Lencioni R, Piscaglia F, Bolondi L. Contrast-enhanced

ultrasound in the diagnosis of hepatocellular carcinoma. J Hepatol 2008;48:848-57.
46. Lin D, Yang HI, Nguyen N, Hoang J, Kim Y, Vu V, Le A, Chaung K, Nguyen V, Trinh H, Li J, Zhang J, Hsing A, Chen CJ, Nguyen MH. Reduction of chronic hepatitis B-related hepatocellular carcinoma with anti-viral therapy, including low risk patients. Aliment Pharmacol Ther 2016;44:846-55.
47. Ahn J, Lim JK, Lee HM, Lok AS, Nguyen M, Pan CQ, Mannalithara A, Te H, Reddy KR, Trinh H, Chu D, Tran T, Lau D, Leduc TS, Min A, Trong Le L, Bae H, Van Tran S, Do S, Hann HW, Wong C, Han S, Pillai A, Park JS, Tong M, Scaglione S, Woog J, Kim WR. Lower observed hepatocellular carcinoma incidence in chronic hepatitis b patients treated with entecavir: results of the ENUMERATE study. Am J Gastroenterol 2016;111:1297-304.
48. Yeh YP, Hu TH, Cho PY, Chen HH, Yen AM, Chen SL, Chiu SY, Fann JC, Su WW, Fang YJ, Chen ST, San HC, Chen HP, Liao CS, Changhua Community-Based Abdominal Ultrasonography Screening G. Evaluation of abdominal ultrasonography mass screening for hepatocellular carcinoma in Taiwan. Hepatology 2014;59:1840-9.
49. Korenaga K, Korenaga M, Furukawa M, Yamasaki T, Sakaida I. Usefulness of Sonazoid contrast-enhanced ultrasonography for hepatocellular carcinoma: comparison with pathological diagnosis and superparamagnetic iron oxide magnetic resonance images. J Gastroenterol 2009;44:733-41.
50. Rich NE, Parikh ND, Singal AG. Overdiagnosis: An understudied issue in hepatocellular carcinoma surveillance. Semin Liver Dis 2017;37:296-304.
51. Caraiani C, Dong Y, Rudd AG, Dietrich CF. Reasons for inadequate or incomplete imaging techniques. Med Ultrason 2018;20:498-507.
52. Trevisani F, D'Intino PE, Morselli-Labate AM, Mazzella G, Accogli E, Caraceni P, Domenicali M, De Notariis S, Roda E, Bernardi M. Serum alpha-fetoprotein for diagnosis of hepatocellular carcinoma in patients with chronic liver disease: influence of HBsAg and anti-HCV status. J Hepatol 2001;34:570-5.
53. Villanueva A, Minguez B, Forner A, Reig M, Llovet JM. Hepatocellular carcinoma: novel molecular approaches for diagnosis, prognosis, and therapy. Annu Rev Med 2010;61:317-28.
54. Yamashita T, Forgues M, Wang W, Kim JW, Ye Q, Jia H, Budhu A, Zanetti KA, Chen Y, Qin LX, Tang ZY, Wang XW. EpCAM and alpha-fetoprotein expression defines novel prognostic subtypes of hepatocellular carcinoma. Cancer Res 2008;68:1451-61.
55. Biselli M, Conti F, Gramenzi A, Frigerio M, Cucchetti A, Fatti G, D'Angelo M, Dall'Agata M, Giannini EG, Farinati F, Ciccarese F, Andreone P, Bernardi M, Trevisani F. A new approach to the use of alpha-fetoprotein as surveillance test for hepatocellular carcinoma in patients with cirrhosis. Br J Cancer 2015;112:69-76.
56. Chang TS, Wu YC, Tung SY, Wei KL, Hsieh YY, Huang HC, Chen WM, Shen CH, Lu CH, Wu CS, Tsai YH, Huang YH. Alpha-fetoprotein measurement benefits hepatocellular carcinoma surveillance in patients with cirrhosis. Am J Gastroenterol 2015;110:836-44; quiz 45.
57. Cui XW, Chang JM, Dietrich CF. Should hepatocellular carcinoma screening with ultrasound be recommended in hepatocellular carcinoma high-incidence areas? Hepatology 2015;61:1091-2.
58. Forner A, Reig M, Bruix J. Hepatocellular carcinoma. Lancet 2018;391:1301-14.
59. Neumann PJ, Cohen JT, Weinstein MC. Updating cost-effectiveness--the curious resilience of the $50,000-per-QALY threshold. N Engl J Med 2014;371:796-7.
60. Bolondi L, Sofia S, Siringo S, Gaiani S, Casali A, Zironi G, Piscaglia F, Gramantieri L, Zanetti M, Sherman M. Surveillance programme of cirrhotic patients for early diagnosis and treatment of hepatocellular carcinoma: a cost effectiveness analysis. Gut 2001;48:251-9.

Cite this article as: Dietrich CF, Teufel A, Sirlin CB, Dong Y. Surveillance of hepatocellular carcinoma by medical imaging. Quant Imaging Med Surg 2019;9(11):1904-1910. doi: 10.21037/qims.2019.10.04

