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Hepatocellular carcinoma detected by regular surveillance: Does timely confirmation of diagnosis matter?

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ABSTRACT

Background: Although current guidelines recommended surveillance of hepatocellular carcinoma, prognosis in patients undergoing enhanced follow-up has yet to be evaluated.
Aims: Examine outcomes of hepatocellular carcinoma diagnosed during enhanced follow-up.
Methods: During 2010–2012, 194 patients underwent ultrasonography surveillance were diagnosed with hepatocellular carcinoma and divided into: (A) immediate diagnosis ($N = 105$, 54.1%) after positive ultrasonography, (B) enhanced follow-up: ($N = 38$, 19.6%) for initial negative recall procedures, (C) late call back: ($N = 28$, 14.4%) recall procedures were deferred after positive ultrasonography, and (D) beyond ultrasonography: ($N = 23$, 11.9%) surveillance ultrasonography had been negative.
Results: Median time from positive ultrasonography to confirmation of hepatocellular carcinoma were 9.5 months (2–67) in the Group B and 6.5 months (3–44) in the Group C. Stage distribution and 3-year survival rates were similar amongst all Groups. Surveillance intervals longer than 6 months were associated with the non-curative stage (3.7% vs. 12.5%, $p = 0.04$). Nine (4.6%) patients underwent surveillance were diagnosed as Barcelona-Clinic Liver Cancer stage C.
Conclusion: Enhanced follow-up by current guidelines is appropriate that treatment can be deferred until a definite diagnosis. Despite optimal surveillance interval and recall policies, few non-curative stage diagnoses seemed inevitable under current standard of care.

1. Introduction

Regular ultrasonography surveillance in patients with liver cirrhosis or chronic viral hepatitis has improved the outcome of hepatocellular carcinoma (HCC) [1] owing to early diagnosis and appropriate curative treatment [2,3]. Current international guidelines advocate recall procedures, including: dynamic computer tomography (CT), magnetic resonance image (MRI), or biopsy in any suspicious liver nodule ≥1 cm for definite diagnosis [4–6]; based on previous observation that nodules <1 cm were unlikely to be HCC [7]. In addition, when two consecutive recall procedures have been negative, the "enhanced follow-up" or similar strategies, by close ultrasonography follow-up and repeated workup, are recommended by the American Association for the Study of Liver Diseases as well as other guidelines [4–6]. However, in real world practice, not all patients receive immediate CT or MRI whenever a seemingly benign 1–2 cm nodule is detected; in addition, some suspicious nodules during enhanced follow-up are ultimately proved to be HCC after months or even years; yet whether this represents a diagnostic delay was not known. On the contrary, regular ultrasonography might well fail to show tumors when a dynamic CT or MRI confirmed their presence due to coarse liver parenchyma. These situations are not uncommon, however, it is not known whether they are associated with different outcomes or patient characteristics compared to other patients whose HCC were immediately confirmed by recall procedures after a positive surveillance ultrasonography. In this study, we aimed to examine if different patterns of diagnosis affected the outcome of patients receiving ultrasonography surveillance for HCC.

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2. Material and methods

2.1. Patient selection and definition of surveillance ultrasonography

This is a single center, retrospective cohort study. From 2010 through 2012, a total of 194 patients with Child-Pugh class A or B liver function status who's HCC were detected during ultrasonography surveillance (the surveillance Group) in the tertiary referral center. In the same period, another 1098 patients who also had Child-Pugh A or B status and HCC registration without regular surveillance in the hospital, either by active referral from other facilities or having symptomatic disease upon presentation, were served as the non-surveillance Group.

All the patients in the surveillance Group had to receive more than one liver ultrasonography, performed by a hepatologist, one who is considered an expert in the diagnosis and treatment of HCC, within the preceding year before definite diagnosis was made. Dynamic images or liver biopsy might be arranged upon detection of suspicious nodule(s) or as clinically indicated, and all the diagnostic images were reviewed by two hepatologists (YJH and LSN). In Taiwan, the common practice regarding ultrasonography surveillance intervals were every 3–6 month in cirrhotic patients and 6–12 month in other chronic liver disease patients. Accordingly, in this study, the intervals were established by the referring physicians (3 [ranged 1–4] month in 135 [69.6%], 6 [ranged 5–8] month in 49 [25.2%], and 12 [ranged 9–12] month in 10 [5.2%] patients, respectively).

The "positive ultrasonography" must fulfill the following criteria: (1) any new nodules more than 1 cm were detected, (2) the location and characteristics were consistent with the HCC biopsied or noted in the final confirmation image under critical review; and the duration from first positive ultrasonography to final confirmation of a tumor was documented. According to the patterns of diagnosis, the surveillance Group was subdivided into four: (A) Immediate diagnosis Group (n = 105, 54.1%): the diagnosis of HCC was made by an immediate recall procedure after suspicious ultrasonography, (B) Enhanced follow-up Group (n = 38, 19.6%): the initial recall procedures were negative or indecisive, and the diagnosis was made later through repeated workup during follow-up (Fig. 1), (C) Late call back Group (n = 28, 14.4%): ultrasonography had revealed new ≥1 cm nodule(s) but the recall procedures were performed at least three months later, (D) Beyond ultrasonography Group (n = 23, 11.9%): the diagnosis of HCC were made purely by dynamic CT or MRI surveillance or any recall procedure triggered by elevation of alpha-fetoprotein (AFP), and if the tumor had never been detected by prior ultrasonography despite regular surveillance (Fig. 2). In Group C, the indications to receive recall procedures altered the ultrasonography pattern of the suspicious nodule (n = 20, 74.1%) and progressive AFP elevation (n = 7, 25.9%); whereas in Group D, regular annual exam for cirrhotic patients with overt coarse parenchyma [8] (n = 7, 30.3%) and elevated AFP (n = 16, 66.7%) accounted for these cases.

2.2. Diagnosis and staging of HCC

In this study, the diagnostic criteria adhered to current international guidelines [4–6] that either a typical dynamic image or histologic proof was required. For the purpose of this study, Barcelona-Clinic Liver Cancer (BCLC) staging system [9] was used in all the patient Groups. The BCLC stage 0 and A are referred as "curative stage", as curative treatments are mostly recommended in this Group of patients; on the other hand, the BCLC stage B and C were referred to as being in a non-curative stage.

2.3. Analysis of AFP level at and before diagnosis

Measurement of AFP was via enzyme-linked immunosorbent assay (Architect reagent kit, Abbott). For the analysis of AFP, we used AFP level at the time of earliest "positive ultrasonography" in Group A–C, to investigate the associations between patterns of AFP elevation and ultrasonography positivity; and AFP at the time upon definite diagnosis of HCC in Group D since the ultrasonography had been negative. Once a patient had been found to have an abnormally high AFP level (above 20 ng/ml), we traced his AFP level retrospectively to check when their AFP began to rise. To classify the pattern of AFP elevation, "abrupt elevation" was defined if one had high AFP at diagnosis but the last value within 6 months was normal; whereas "insidious elevation" referred to the AFP having been high before diagnosis and the time from initial rise to diagnosis were recorded.

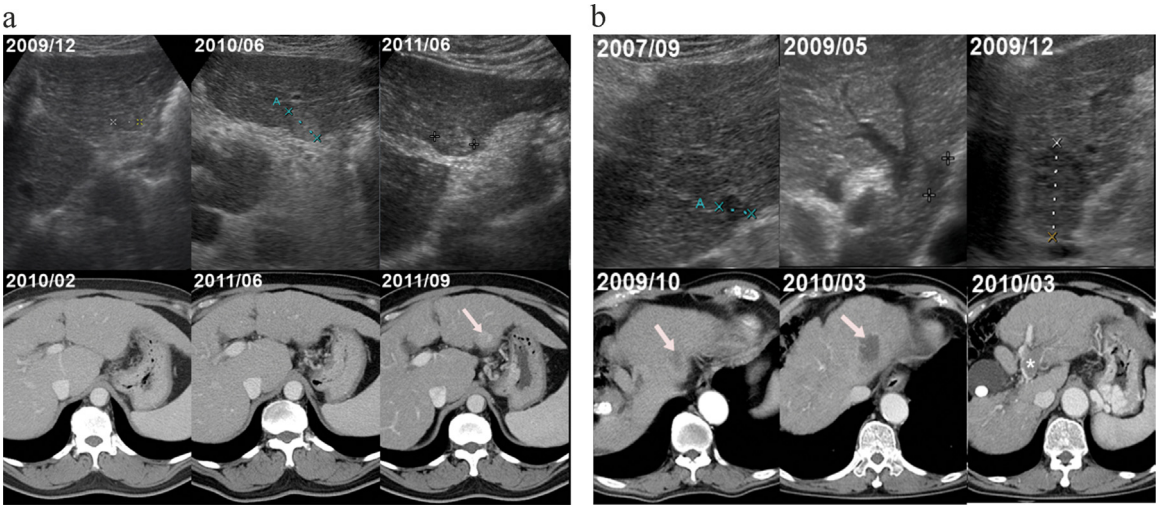

Fig. 1. (a) This patient had a new 1.7 cm liver nodule found at segment 2 by ultrasonography surveillance in 2009/12, however computerized tomography (CT) in 2010/02 and 2011/06 failed to show any enhancing nodule. While stationary nodule size had been noted by subsequent ultrasonography; an early enhancing and wash-out pattern (white arrow) was demonstrated by follow-up CT after 22 months. (b) Another patient had a new 1.7 cm liver nodule found in 2007/09, and CT at the same time showed atypically enhancing pattern (white arrow). Serial aspiration biopsy had also been negative. However, rapid tumor progression with suspicious portal vein thrombosis was found in 2009/12 ultrasonography. Repeat biopsy suggested poorly differentiate carcinoma and CT scan in 2010/03 confirmed 5 cm tumor with early contrast washout and left portal vein thrombosis (asterisk).