Factors That Affect Efficacy of Ultrasound Surveillance for Early Stage Hepatocellular Carcinoma in Patients With Cirrhosis

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BACKGROUND & AIMS: **Ultrasound surveillance does not detect early stage hepatocellular carcinomas (HCCs) in some patients with cirrhosis, although the reasons for this have not been well studied. We assessed the rate at which ultrasound fails to detect early stage HCCs and factors that affect its performance.**

METHODS: **We collected information on 1170 consecutive patients included in the Italian Liver Cancer (ITA.LI.CA) database who had Child–Pugh A or B cirrhosis and were diagnosed with HCC during semiannual or annual ultrasound surveillance, from January 1987 through December 2008. Etiologies included hepatitis C virus infection (59.3%), alcohol abuse (11.3%), hepatitis B virus infection (9%), a combination of factors (15.6%), and other factors (4.7%). Surveillance was considered to be a failure when patients were diagnosed with HCC at a stage beyond the Milan criteria (1 nodule ≤5 cm or ≤3 nodules each ≤3 cm).**

RESULTS: **Ultrasound surveillance failed to detect HCC in 34.3% of patients and more often in the annual program than in the semiannual one (41.3% vs 32.2%; $P < .01$). Nearly half of surveillance failures were associated with at least one indicator of aggressive HCC (levels of AFP >1000 ng/mL, infiltrating tumors, or vascular invasion and metastases). Semiannual surveillance, female sex, Child–Pugh class A, and α-fetoprotein levels of 200 ng/mL or less were associated independently with successful ultrasound screening for HCC.**

CONCLUSIONS: **Based on our analysis of surveillance for HCC in patients with cirrhosis, the efficacy of ultrasound-based screening is acceptable. Ultrasound was least effective in identifying aggressive HCC, and at surveillance intervals of more than 6 months.**

Keywords: Liver Cancer; Early Detection; Fibrosis; Survival.

Hepatocellular carcinoma (HCC) is the fifth most common tumor worldwide and the main cause of mortality of cirrhotic patients.[1] Despite continuous therapeutic advances its prognosis remains poor because the majority of these tumors are identified at a late stage. Several cohort and one randomized control study have shown that regular ultrasound surveillance in high-risk populations can achieve this goal and increase survival.[2–6] For this reason, all international guidelines recommend implementation of regular ultrasound surveillance in these patients.[1,7]

In the surveillance setting, ultrasound has been found to have an excellent specificity (>90%), but low sensitivity.[3,8] Namely, a meta-analysis of 13 studies performed

Abbreviations used in this paper: **AFP, α-fetoprotein; BMI, body mass index; CI, confidence interval; CT, computed tomography; HALT-C, _____; HCC, hepatocellular carcinoma; MRI, magnetic resonance imaging; OR, odds ratio.**

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in tertiary care centers indicated that ultrasound sensitivity in detecting early stage HCC may be as low as 63%, and that the addition of α-fetoprotein (AFP) measurement adds marginal benefit.[9] The majority of these studies, however, were performed in the 1990s, when ultrasound examinations were performed with old technology equipment. After the year 2000, newer probes with higher-density crystals, together with compound and harmonic imaging, have improved the chance of identifying small liver nodules. Ultrasound nonetheless had several limitations: first, it fails to detect infiltrative tumors; second, its sensitivity remarkably decreases in cirrhotic livers with coarse echo texture, in obese patients, in those with abdominal gas, or those not compliant with the breath-hold command; third, it is highly operator-dependent and requires expertise, so that ultrasound examinations performed in real-life settings may have a lower yield.[10]

An analysis of the causes of surveillance failure to detect early HCC could lead to a better use of the ultrasound technique or highlight the need for alternative methods of surveillance in some cases. The aims of our study were to assess the failure rate of regular ultrasound surveillance in detecting an early HCC in a large population of cirrhotic patients recruited at several medical institutions, including both tertiary and primary care hospitals, and to identify the factors responsible for ultrasound failure.

Patients and Methods

Patients

We retrospectively analyzed the data from the ITA.LI.CA database, including 3027 consecutive patients diagnosed with HCC from January 1987 through December 2008 at 11 Italian medical institutions (6 academic tertiary care centers and 5 hepatology/gastroenterology units located in general hospitals). The data were collected prospectively and updated every 2 years. Among the initial 3027 patients, we selected the 1170 Child–Pugh A or B cirrhotic patients diagnosed with HCC during semiannual or annual ultrasound surveillance. Child–Pugh C patients were excluded because practical guidelines do not recommend surveillance for these patients.[1] AFP determinations were available only at the time of HCC diagnosis.

The macroscopic HCC features of all Child–Pugh A and B patients of the ITA.LI.CA database are described in Supplementary Table 1. Cirrhosis was diagnosed histologically in 446 cases and by clinical, endoscopic, or ultrasound evaluation in the remaining cases.

The criteria used for the classification of the etiology of cirrhosis, diagnosis, and staging of HCC are reported in the Supplementary Materials and Methods section. HCC was classified as biologically aggressive if, at the time of diagnosis, it showed at least one of the following: AFP level greater than 1000 ng/mL, diffuse involvement of the liver on imaging, vascular invasion, or distant metastases.

To be included in the study patients had to be diagnosed with HCC during ultrasound surveillance. We conventionally accepted that this was shown by the availability of an ultrasound examination negative for HCC, and performed in the 12 months preceding HCC diagnosis. If the last negative ultrasound was performed more than 1 year before the examination suggesting the HCC presence, the patient was excluded from the analysis because his/her surveillance was considered inconsistent.

According to the surveillance interval, patients were divided into 2 groups, as follows.

Group A contained patients with an ultrasound examination performed between 1 and 6 months before tumor diagnosis. Because most of the examinations were performed between 4 and 6 months before tumor diagnosis, we considered this group to have semiannual surveillance.

Group B contained patients with an ultrasound examination performed between 7 and 12 months before HCC diagnosis. Because most of the examinations were performed between 7 and 12 months before tumor diagnosis, we considered this group to have annual surveillance.

Surveillance failure was defined as follows: (1) the detection of a tumor beyond the Milan criteria after HCC staging had been completed; (2) the detection of HCC after a negative ultrasound by computed tomography (CT) or magnetic resonance imaging (MRI), which were prompted by insufficient ultrasound quality or an increase of AFP level to greater than 50 ng/mL. Surveillance failure was determined in 2 calendar periods (1987–1999 and 2000–2008), with the cut-off point set at the end of the 20th century because, at that time, the new compound and harmonic imaging were introduced in the ultrasound equipment.

Statistical Analysis

Continuous data are expressed as medians and ranges or means ± standard deviations in case of non-normal or normal data distribution, respectively. The Mann–Whitney *U* test was used to compare continuous data, and chi-square analysis or the Fisher exact test were used to compare discrete variables. The Pearson product moment was used to study correlations between continuous variables.

Factors available in at least 90% of patients at the time of HCC diagnosis and potentially affecting ultrasound surveillance were investigated by univariate analysis. Factors associated with surveillance failure with a *P* value of .10 or less were tested by multiple logistic regression analysis with stepwise backward elimination of nonsignificant variables. The odds ratio (OR) and 95% confidence interval (95% CI) were reported. The Med Calc statistical package was used for these analyses. For