Clinical Imaging 40 (2016) 311–314

Contents lists available at ScienceDirect

Clinical Imaging

journal homepage: http://www.clinicalimaging.org

Screening for hepatocellular carcinoma in high-risk populations☆

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ARTICLE INFO

Article history:
Received 15 October 2015
Accepted 5 November 2015

Keywords:
Hepatocellular carcinoma screening
Liver cancer screening
Hepatitis B
Hepatitis C
Cirrhosis

ABSTRACT

Screening for hepatocellular carcinoma (HCC) should be implemented in the high-risk population. High-risk population includes patients with cirrhosis of any etiology, patients with chronic hepatitis B virus with or without cirrhosis, and patients with chronic hepatitis C virus with cirrhosis. A randomized controlled trial of over 18,000 high-risk individuals demonstrated that biannual screening reduced HCC-related mortality by 37%. The screening test of choice is ultrasound imaging with an interval of 6 months.

1. Introduction

Hepatocellular carcinoma (HCC) is the fourth most common cancer worldwide [1]. In the United States, there are approximately 35,660 new cases of HCC diagnosed each year with 24,550 deaths attributable to HCC [2]. The incidence among Chinese American men is especially high at 21.6 per 100,000 [3]. The most common risk factors for HCC are chronic hepatitis B virus (HBV) and hepatitis C virus (HCV) infections, which account for 30–40% of HCC in the United States. In areas of Asia and Africa where HBV is endemic, the additional exposure to aflatoxins in the normal diet is a cofactor that increases the rate of development of HCC. Men are more than twice as likely as women to develop HCC. Additional factors that may be associated with greater incidence of HCC include older age and diabetes mellitus [4]. For patients with cirrhosis, the 5-year risk of developing HCC is 5–30%. Cirrhosis may develop due to chronic hepatitis virus infection as well as alcohol abuse and obesity [5]. Other causes of cirrhosis include metabolic disorders such as hemochromatosis and alpha-1-antitrypsin deficiency.

2. Review of the evidence for HCC screening

2.1. Clinical studies

As surgical resection, transplantation and ablation are recommended for smaller tumors, finding an effective way to detect HCC at an earlier stage appears advantageous. Screening for HCC in high-risk individuals has been conducted for decades. In China, for example, data have been gathered at least as far back as 1972 [6]. Published studies based on the data from loosely organized surveillance programs suggest that screening detects HCC at an earlier stage and improves survival [7–9]. However, many studies have been subject to both lead time bias and length bias. Only two randomized controlled trials have been conducted with the purpose of determining the efficacy of screening high-risk patients in reducing the mortality of HCC [10,11]. These studies, conducted in the 1980s to the 1990s, were both performed in China where there is a high incidence of HCC.

2.2. Effect of screening on HCC-related mortality in high-risk individuals, a randomized controlled trial in Shanghai, China (Zhang et al.) [11]

The largest randomized controlled trial of 18,816 subjects was conducted in Shanghai by Zhang et al. to evaluate the effect of screening on HCC-related mortality in high-risk patients [11]. From 1993 to 1997, patients with HBV infection or a history of chronic hepatitis (age: 35–59 years old) were randomized to the screening group ($n=9373$) or the control group ($n=9443$). Screening consisted of serum AFP testing and abdominal ultrasound every 6 months. Subjects were considered *positive* during screening if AFP≥20 μg/l or the ultrasound detected a solid lesion in the liver. Fifty-two cases of stage I HCC were detected in the screening group. Not a single case of stage I HCC was diagnosed in the control group. The 5-year survival rate was 46.4% in the screening group and 0% in the control group. The 5-year survival rate for stage I cancers was 67.8% (see Table 1). Overall there was a significant survival advantage for patients diagnosed with HCC in the screening group. With a mortality rate ratio in the screening vs. control group of 0.63 (see Table 2), this large study showed that screening resulted in a 37% reduction in HCC mortality in high-risk subjects.

☆ None of the authors have a conflict of interest.

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http://dx.doi.org/10.1016/j.clinimag.2015.11.010
0899-7071/

Table 1
Effect of screening on HCC detection in randomized controlled trials

Study	Screening method	Study arm	No. of subjects	% stage I Ca detected	% stage II Ca detected	% stage III detected
Chen et al., 2003 [10]	AFP, ALT	Screened	3712	27.9	50.8	21.3
		Control	1869	3.7	52.8	43.5
Zhang et al., 2004 [11]	AFP, ultrasound	Screened	9373	60.5	13.9	25.6
		Control	9443	0	37.3	62.7

2.3. Effect of screening on HCC-related mortality in high-risk males, a randomized controlled trial in Qidong, China (Chen et al.) [10]

There is a smaller randomized controlled trial by Chen et al. that was designed to evaluate the effect of screening (AFP and ALT only, no ultrasound) on HCC-related mortality in high-risk males Qidong, China [10]. Hepatitis-B-positive males from ages 30–59 years old were randomly assigned to the screening group ($n=3712$) or to the control group ($n=1869$). The screening group was scheduled for biannual laboratory testing using AFP and ALT. Subjects were considered *positive* during screening if AFP≥20 μg/l or ALT≥40 U. One- and three-year survival rates were significantly increased in the screening group (23.5% and 6.8%, respectively) compared to the control group (9.6% and 3.9%). However, 5-year survival rates remained essentially the same at 3.8% in the screening group and 3.9% in the control group, with no overall statistically significant difference in mortality between the screening and control groups (see Table 2). The authors concluded that although screening can detect smaller, earlier stage cancers, the only advantage is lead time gain.

In contrast to the patients in the Zhang et al. study, only a small percentage of the HCC patients in the Chen et al. study were eligible for resection. In the study by Zhang et al., 75% of patients received radical treatment for HCC. Furthermore, the Zhang et al. study used ultrasound imaging in addition to AFP for screening whereas Chen et al. study did not use ultrasound. The differences in screening methods as well as the differences in eligibility for resection may explain the disparate findings in mortality benefit in the two studies.

3. HCC screening recommendations

Practice guidelines from the American Association of the Study of Liver Diseases (AASLD) and the European Association for the Study of the Liver (EASL) have recommended HCC screening for patients at high risk [6,12]. High-risk population is defined as patients with cirrhosis of any etiology, patients with chronic HBV (with or without cirrhosis), or patients with chronic HCV (with cirrhosis). The recommended screening interval is 6 months, based on the doubling time of HCC, estimated at 80–117 days [6,12].

The AASLD deems screening and surveillance cost effective if the expected risk of HCC is greater than 1.5% per year in HCV-positive patients and 0.2% in HBV-positive patients [12]. These values for cost effectiveness are based on ability to receive therapy and increase life expectancy at an acceptable rate (acceptable cost per quality-adjusted life year of approximately US$50,000) [13].

3.1. How to perform HCC screening

Although earlier guidelines recommended both AFP and ultrasound for initial screening, the AASLD and EASL now recommend ultrasound imaging alone as primary screening method for HCC. Elevation of AFP occurs not only in patients with HCC but also in those with chronic liver disease without HCC [12]. The sensitivity of ultrasound alone ranges from 65% to 80% with a specificity of above 90%, making ultrasound a more sensitive and specific test for HCC [12]. While combination screening with AFP and ultrasound increases the detection rate of the disease (by approximately 6–8%), the false-positive rate is also increased (5% false positive with AFP alone, 2.9% with ultrasound, combination: 7.9%) [6]. According to EASL guidelines, combination screening results in an increase in cost of approximately 80% per each HCC diagnosed. Due to increased sensitivity and specificity, lower false-positive rate, and cost effectiveness, screening with ultrasound alone is advised. However, as AFP measurement is easily obtained and historically recognized as a screening tool, it persists as a screening marker in clinical practice.

HCC has a variable appearance on ultrasound. HCC is often seen in the setting of a cirrhotic, nodular liver (see Fig. 1). Small HCC tumors are typically hypoechoic in comparison with background liver parenchyma (see Fig. 2). If hyperechoic, they may retain an isoechoic to a hypoechoic halo. Lesions may also be heterogeneous in appearance, depending on the presence of fibrosis, fatty changes, and/or necrosis (see Fig. 3).

3.2. Recall strategy

When screening ultrasound is abnormal, diagnostic tests should be initiated, either quadruple-phase contrast-enhanced computed tomography (CT) or dynamic contrast-enhanced magnetic resonance imaging (MRI). HCC usually demonstrates arterial enhancement with washout in the portal venous phase. EASL guidelines divide masses into three categories based on size, <1 cm, 1–2 cm, and >2 cm. AASLD guidelines divide masses into those <1 cm and >1 cm in size. The associations are in agreement with that a mass <1 cm should be followed up with imaging approximately every 3–4 months and if growth is demonstrated, it should be treated as HCC (or further investigated with radiologic testing based on size). For nodules greater than 1 cm, if one or both CT and MRI demonstrate typical HCC radiological findings, the lesion can be treated as HCC. If neither study demonstrates typical findings, tissue biopsy may be performed. For lesions greater than 2 cm, EASL requires only one positive radiological examination for HCC diagnosis.

Table 2
Effect of screening on HCC-related mortality in randomized controlled trials

Study	Screening method	Study arm	% 1-year survival	% 3-year survival	% 5-year survival	Mortality rate/100,000	Rate ratio of mortality of screened vs. controlled
Chen et al., 2003 [10]	AFP, ALT	Screened	23.5	6.8	3.8	1138.1	1.02
		Control	9.6	3.9	3.9	1113.9	
Zhang et al., 2004 [11]	AFP, ultrasound	Screened	65.9	52.6	46.4	83.2	0.63
		Control	31.2	7.2	0	131.5	