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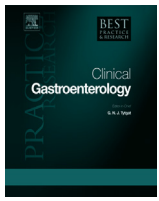

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Cost-effectiveness of liver cancer screening

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A B S T R A C T

Screening for primary liver cancer means surveillance for hepatocellular carcinoma (HCC), which is one of the most common cancers worldwide. Detection of HCC for curative treatment is increased by surveillance, but target population, optimal periodicity and cost-effectiveness aspects are still debated issues. The aim of surveillance is to obtain a reduction in HCC-related mortality and this is usually achieved through an early diagnosis that increases both applicability and cost-effectiveness of curative treatments. The aim of the present review is to analyse economic aspects of HCC surveillance. Articles that assessed cost-effectiveness of surveillance for HCC, published between 1996 and February 2013, were reviewed in order to verify the cost-effectiveness of surveillance, its optimal periodicity, the target population and the role of alternative surveillance strategies. International guidelines are currently based on the results of such cost-effectiveness analyses, highlighting the importance of the release of cost-effectiveness-guided guidelines for HCC management.

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Liver cancer screening aims to detect tumours before symptom appearance. As for any other cancer, it is cost-effective to screen people considered at risk for the specific cancer, and a suitable risk profile, able to accomplish this requisite, is only available for hepatocellular carcinoma (HCC). Thus, screening for primary liver cancer means screening for HCC. Hepatocellular carcinoma is the fifth most common cancer in men and the seventh in women, with an increasing incidence in Western countries [1]. Each year, HCC is diagnosed in more than half a million people worldwide, including approximately 20,000 new cases in the United States, arising in about 90% of cases in patients with chronic liver disease caused by hepatitis B (HBV) and C virus (HCV) infection [1,2]. Other risk factors include alcoholic liver disease, haemochromatosis, non-alcoholic fatty liver disease (NAFLD) and primary biliary cirrhosis in advanced stages [3–7]. Cirrhosis is the most important risk factor for HCC, regardless of its aetiology, and the annual risk of developing HCC among cirrhotic subjects is estimated to range between 1% and 6% [1,3]. Importantly, HCC is the main cause of mortality of these patients [1].

It is important to distinguish screening from surveillance, as the two terms describe different strategies of early diagnosis. Screening is a cross-sectional use of a screening test to detect prevalent cancer in a population, while surveillance relies on the repetition of the test at scheduled intervals to identify incident cancers. At present, screening programs for primary liver cancer do not exist; conversely, surveillance for HCC is largely adopted in most countries. This review will address the results of surveillance for the early detection of HCC, highlighting cost-effectiveness aspects.

A prerequisite for implementing surveillance is based on the possibility of identifying patients at high risk. This is the case for HCC, considering subjects with known HBV or HCV infection and all patients with cirrhosis. An early diagnosis of HCC, through surveillance, can enable the application of potentially curative treatments [8–10]. Thus, to improve the prognosis of HCC, patients 'at-risk' should be included in surveillance programs. Instead, most patients presenting with HCC were not included in these programs because of the lack of knowledge of their risk status, an inadequate physician awareness of the oncologic risk or poor patient compliance with the offered surveillance [10–12]. Surveillance for HCC is currently recommended by international guidelines [13–15] even if the strength of the evidence supporting its efficacy is modest [1], depending on the unfeasibility of randomized controlled studies [16]. A key point in defining the cost-effectiveness (CE) of surveillance programs is an analysis of its rationale and the available clinical results.

Rationale

Surveillance for HCC has become widely applied even though strong evidence of any benefit is lacking. Two randomized controlled trials have been published on HCC surveillance, both carried out in China. The first one is a population-based study that recruited nearly 19,000 HBV-infected patients regardless of the presence of cirrhosis, and compared semiannual US + alpha-fetoprotein (AFP) surveillance against no surveillance [17]. Although the adherence to surveillance was less than 60%, the HCC-related mortality was reduced by 37% in the surveyed subjects as a result of an increased resection rate of the detected lesions. The second study, dealing with AFP-based surveillance in high-risk HBV positive individuals, did not show differences in overall survival between surveyed and non-surveyed patients, probably because those who were diagnosed with early HCC did not undergo appropriate treatment [18]. Rather than a surveillance failure, this latter study demonstrated the futility of surveillance if patients are undertreated at the time of HCC diagnosis. Additional randomized controlled trials should be performed to validate these results in other geographical areas, especially in Western countries, but they are probably unfeasible when patients are correctly informed on the risk-benefit of surveillance [16].

The ideal interval of surveillance for HCC was initially suggested based on the rate of tumour growth up to the limit of its detectability by imaging procedures. The available data based on tumour growth models suggested that the time lapse between an undetectable lesion and growth to 2 cm is about 4–12 months, and according to the volume doubling time of small HCCs, which is around six months and with an aim of detecting tumours below 3 cm in diameter, the suggested interval for surveillance in patients with cirrhosis was set at six months [19,20]. A shorter three-month interval has been proposed by Japanese guidelines [21], but in the only available RCT, comparing cirrhotic patients submitted to three versus six-month US surveillance, no difference in HCC incidence or in prevalence of small