Best Practice & Research Clinical Gastroenterology 28 (2014) 783–793

Contents lists available at ScienceDirect

Best Practice & Research Clinical Gastroenterology

3

Surveillance for hepatocellular carcinoma

Morris Sherman, MB BCh PhD, FRCP(C), Professor of Medicine *

University of Toronto, University Health Network, Toronto General Hospital, 200 Elizabeth Street, Toronto, ON M5G 2C4, Canada

Keywords:
Hepatocellular carcinoma
Cancer screening
Ultrasonography
Alpha fetoprotein
Desgamma carboxy prothrombin

A B S T R A C T

When hepatocellular carcinoma presents with symptoms cure is seldom possible and death usually follows within months. However, it is possible to detect HCC early, at which stage it is curable. This requires a surveillance program. The components of such a program include: identification of the at risk population, provision of appropriate surveillance tests, and an appropriate method of determining whether the abnormalities found on screening are cancer or not. Surveillance for liver cancer meets all these criteria. Unfortunately high quality evidence showing benefit of liver cancer surveillance is lacking, but lesser quality evidence is plentiful, including several cost efficacy analyses that all show that surveillance does decrease mortality. Therefore all the continental liver disease societies and all national liver disease societies have recommended that surveillance should be undertaken.

Introduction

Hepatocellular carcinoma (HCC) has a well-deserved reputation as a rapidly progressive cancer that is almost invariably fatal. This is because in the absence of procedures to ensure early diagnosis HCC presents with symptoms, usually those of liver failure. By this stage the cancer is usually large, and untreatable. Tumour progression is apparently rapid, with the interval from diagnosis to death being about three–six months. This is the pattern of disease that existed everywhere before the development of ultrasound and CT scan, and is still the pattern of presentation where these techniques are either not available or not applied.

* Tel.: +1 416 340 4756; fax: +1 416 591 2107.
E-mail address: morris.sherman@uhn.on.ca.

http://dx.doi.org/10.1016/j.bpg.2014.08.008
1521-6918/

However, HCC has a prolonged subclinical growth period [1–4], during which, if discovered, interventions are often possible, and cure can be achieved. This raises the possibility that surveillance could detect sub-clinical lesions that might be amenable to curative treatment. In this chapter we will examine the recommended HCC surveillance techniques and the controversy surrounding them. We will also see how the recommendations about surveillance rest not only on clinical evidence, but also on modelling studies using cost-efficacy techniques.

Principles of cancer surveillance

The objective of a cancer surveillance program is to decrease mortality from the disease. It is important to make the distinction between mortality (number of deaths/unit time) and survival (duration of life following diagnosis). Mortality is the only absolute proof of efficacy of a surveillance program. Survival is a surrogate endpoint because it is subject to several sources of bias that do not influence mortality. These include lead-time bias and length bias. Lead-time bias is the apparent increase in survival that comes exclusively from diagnosis at an earlier stage of disease. The duration of survival from diagnosis to death is increased, even if no intervention is applied. Length bias arises from the fact that surveillance is more likely to detect slow growing cancers than rapidly growing cancers, which might go from undetectable to death within the surveillance interval.

There are a number of surrogate endpoints in addition to survival that have been evaluated in attempts to prove efficacy of surveillance. Stage migration is the ability of surveillance to find earlier stage disease compared to a population that does not undergo surveillance. Stage migration is a necessary outcome of screening programs but cannot be used to prove efficacy because stage migration paradoxically improves survival in both populations (Fig. 1). Furthermore, simply finding early stage disease is not sufficient. The early stage disease has to be curable with high frequency, or the effect on mortality will not be detected.

Proof of cancer surveillance efficacy

There is at present very little evidence to prove that HCC surveillance decreases mortality. The best evidence for the efficacy of surveillance has to come from randomized controlled trials. However, the study design is crucial. There have been several large-scale randomized trials, in China, each of which had faults in the design, or the execution or in the interpretation [5–7]. Furthermore, these were conducted years ago, using technology that is no longer up-to-date, and using clinical criteria that would be considered inadequate today.

The ideal randomized controlled study would compare a group of at-risk subjects undergoing surveillance to a group that does not undergo surveillance. In order to increase efficiency of recruitment and study conduct only the patients with the highest risk of HCC should be included. Those in the arm undergoing surveillance should receive ultrasound every six months. The quality of ultrasound should be such that lesions up to 2–2.5 cm can be detected, even in a cirrhotic liver. Patients who have nodules on the liver should be investigated according to standard algorithms, such as those proposed by the guidelines from the American Association for Study of Liver Disease or the European Association for study of the Liver [8–10]. Once the diagnosis has been confirmed patients should be staged and undergo treatment according to recommendations from the same organizations.

The first randomized HCC surveillance study to be published compared surveillance with alpha-fetoprotein (AFP) to no surveillance [5]. Subjects with AFP >200 g/mL were subject to ultrasound. As expected, in the group undergoing surveillance there were more tumours found and more that were found at an early stage. However, there was no survival benefit. The major criticisms of this study included that patients with diagnosed HCC did not necessarily get the required treatment, and that it is not clear that the proportion of all cancers defined as early stage were early stage as defined today (BCLC stage 0 or A). Even by the definitions used in the study only 27% of HCC's were diagnosed at an 'early' stage. In a second study, also in China, AFP and ultrasound was compared to no surveillance [6]. This study showed a survival benefit, and 76% of cases were early stage. However, the duration of the study was rather short, and only 38 out of more than 8000 subjects in the surveillance arm developed HCC. Finally, another study, also in China used a cluster randomization process and randomized