EDITORIAL

Limitations of screening for hepatocellular carcinoma

"...not all patients who develop hepatocellular carcinoma while undergoing screening have a good outcome ... and a significant proportion of these patients will still die either from their hepatocellular carcinoma or from the underlying liver disease."

Morris Sherman*
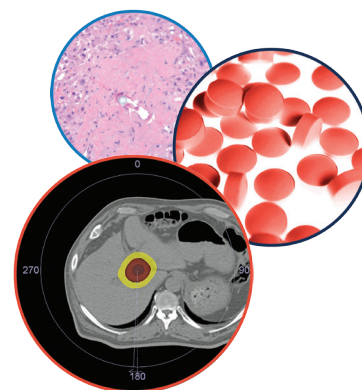
Hepatocellular carcinoma (HCC) screening has become common practice and has been shown to be highly successful in good hands. In Japan, more than 60% of all HCCs are discovered when they are smaller than 2 cm [1]. In Europe, one report indicates that 74% of screen-detected HCCs are smaller than 3 cm [2]. These are easily treated and can be cured. However, not all patients who develop HCC while undergoing screening have a good outcome. A significant proportion of these patients will still die either from their HCC or from the underlying liver disease.

Many authors have emphasized that screening consists of more than just tests. There should be a process that includes identification of the at-risk group(s), application of the test, appropriate recall procedures and a process in place to manage diseases discovered by screening. For best results screening should be carried out as a controlled program, rather than on an *ad hoc* basis.

Thus, failure of HCC screening can be looked at from the point of view of the program, or from the point of view of the individual who suffered a failure of screening.

Failure of screening in an individual patient essentially means failure of the screening tests to detect the HCC at a curable stage or failure to properly interpret the screening test results (recall procedures), or failure to apply the appropriate treatment for that stage of disease at a timely interval after detection.

Studies of resection and local ablation suggest that the likelihood of cure starts to diminish once the HCC is between 2 and 2.5 cm in diameter [3–5]. Therefore, the target size lesion that screening should detect is below approximately 2.5 cm. To be useful, a screening test should be able to find most lesions smaller than this size. Failure of the screening test to identify such a small cancer that is present and may be curable may be due to inadequate sensitivity of the screening test, too long an interval between screening tests, development of an aggressive cancer that exhibits microvascular invasion and/or metastasis even while still small, or to an infiltrative tumor that does not form a clearly identifiable lesion.

The serological screening tests are AFP concentration, des-γ-carboxy prothrombin and the L3 fraction of AFP. However,

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many studies have shown that these are insufficiently sensitive tests, picking up no more than approximately 60% of small HCCs [6–15]. As the HCC gets larger the likelihood of any of the tests being elevated increases, but even at a tumor size of >5 cm the sensitivity is less than optimal. AFP is the most commonly used, but is the least sensitive. Furthermore, all three of these tests also identify advanced HCC with a poor prognosis. A test that indicates advanced disease cannot also be a marker of early-stage disease.

The recommended screening test is ultrasound. The sensitivity of ultrasound in a noncirrhotic liver is better than 80% [16], but for small HCC the sensitivity falls to approximately 60%. There is some controversy as to whether the addition of biomarkers to ultrasound enhances detection. Studies in Japan using ultrasound and biomarkers have approximately the same detection rate as in Europe without biomarkers [1,2].

There are well-known factors that limit the sensitivity of ultrasound, most importantly, fatty liver, with or without obesity. The presence of fat attenuates the ultrasound beam, so that the beam is less able to penetrate the full substance of the liver. Typically, the parts of the liver most distant from the probe – that is, posteriorly and superiorly – are not well seen. Cirrhosis, with the presence of multiple nodules, also makes it difficult to determine whether any of the nodules are suspicious for HCC.

Finally, good ultrasound is technically demanding. Cursory examination will miss important lesions. Poor technique is probably the most important cause of failure of ultrasound to detect the presence of a significant nodule. However, CT scan or MRI is not the answer. Although these are more sensitive than ultrasound and do not suffer from the problems of fat or cirrhosis, they are not suitable for HCC screening. CT scan without contrast is probably not more sensitive than ultrasound, and may even be less sensitive. If only arterial or venous phase imaging is performed important diagnostic lesion characteristics will be missed. For best sensitivity and specificity a four-phase CT scan is required [17]. Thus, screening would entail essentially four CT scan runs twice a year, possibly for many years. The radiation dose would be significant. We worry less about the radiation dose in patients who have HCC, but in patients not known to have HCC and who may never get HCC it is questionable whether the radiation dose is justified. MRI does not involve radiation.

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More recently, MRI hepatobiliary phase imaging contrast agents have been used for HCC diagnosis. The value of these agents as screening tests has not been evaluated. However, both CT scan and MRI are very costly, with a very high incremental cost–efficacy ratio, making them economically unfeasible [18].

Irregular screening is another cause of failure to detect small HCC. The ideal interval between screening tests is not known. The interval depends on the time it takes for a tumor to grow from being undetectable to being incurable. Since growth rates vary, and neither curability of small lesions, nor incurability of larger lesions are 100% predictable, identification of the appropriate screening interval for an individual patient is not possible. However, studies have suggested that a 6-month interval is the most appropriate balance between too many false positives and too many missed opportunities for cure.

Another reason for failure of screening at a personal level is failure to adequately investigate screen-detected lesions. This surprisingly common. Physicians may not immediately investigate screen-detected lesions, preferring to monitor progress. Decision analysis, however, has indicated that this is the least effective option [19]. The analysis found that a delay in the investigation of screen-detected lesions increased the risk of diagnosis at a stage associated with less than optimal cure rates.

The final reason for failure of HCC screening at an individual level is failure to offer appropriate treatment. This is uncommon with small HCC, which approximately responds equally well to local ablation, resection or transplantation. However, detection of HCC at a later stage (e.g., >2 cm) is less forgiving if the wrong treatment is offered. Local ablation is less effective at these tumor sizes, and resection or transplantation might offer better survival. However, local ablation, usually radiofrequency ablation, continues to be offered to such patients.

Screening programs fail when the population being screened does not have a risk high enough to warrant screening. Although groups at risk for HCC have been defined, the majority of people in those groups will not develop HCC. More recently, risk scores have been developed that allow identification of those at lower risk within the larger at-risk groups, who can be withdrawn from screening programs.

Screening programs will also fail if overdiagnosis is prevalent – that is, the diagnosis of a

lesion as cancer when it is unlikely to cause the patient's death. Overdiagnosis is an inevitable consequence of screening, but it is likely that overdiagnosis plays only a small role in HCC screening. Furthermore, the algorithm described in the American Association for the Study of Liver Diseases guidelines [20], and which has been validated [21–23], minimizes the likelihood of overdiagnosis by requiring either histology or classical radiological appearances of HCC for confirmation of the diagnosis.

Therefore, it can be seen that screening for HCC may fail on several levels. It is easy to understand failure of screening of an individual patient, but factors leading to failure of a screening program are less well recognized, but equally as important.

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