Role of Surveillance in Prevention of Hepatocellular Carcinoma

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Hepatocellular carcinoma is a common malignancy and one of the important public health problems in India. The surveillance of hepatocellular carcinoma (HCC) is an established approach to detect early cancers in patients with defined risks. However, there are still controversies and issues to be addressed regarding the optimal surveillance methods and interval. The current level of awareness among physicians in India about surveillance is low and the need and most cost effective surveillance strategy in developing country like ours is unclear. This article has tried to discuss these issues in their appropriate perspective. To address this complicated issue, a multicenter randomized prospective study however may be required. (J Clin Exp Hepatol 2014;4:S43–S49)

Hepatocellular carcinoma (HCC) is the fifth commonest cancer worldwide and third commonest cause of cancer related mortality.[1] In India, the mean incidence of HCC as per four population-based registries was 2.77% for males and 1.38% for females. The prevalence of HCC in India varies from 0.2% to 1.6%.[2,3] It is interesting to note that the consolidated data from cancer registries of India do not reflect HCC as an important malignancy.[4]

Risk of HCC development is high in patients with liver cirrhosis of any etiology, particularly with chronic hepatitis B virus (HBV) or hepatitis C virus (HCV) infection.[5] Since India has a high prevalence of HBV infection (4% of population, i.e about 40 million Indians)[6] as well as HCV infection (0.3–1.5%) it could contribute to the high incidence of HCC.[7] Other risk factors for HCC like high prevalence of Nonalcoholic Fatty Liver Disease (NAFLD) obesity, diabetes, alcohol consumption among males are also present in India.

Nonalcoholic Fatty Liver Disease (NAFLD) particularly its more aggressive form, nonalcoholic steatohepatitis (NASH) is an important factor which can lead to cirrhosis and HCC. It is estimated that nearly two-thirds of obese people have some form of fatty liver, ranging from steatosis to NASH. NASH can progress to liver cirrhosis in 3%–15% and subsequently to liver cancer.[8] A study by Prasad et al showed that age-standardized prevalence rates of metabolic syndrome were 33.5% overall, 24.9% in males and 42.3% in females in India. Authors concluded that metabolic syndrome is a significant public health problem even in one of the poorest states of India.[9] Hence NASH is particularly important in countries like India where metabolic syndrome is on the rise.

It is important to note that in the absence of an effective screening program and only 7% of population being covered by cancer registries, under reporting cannot be ruled out.[10] A recent study in which 130 trained physicians independently assigned causes to 122429 deaths, which occurred in 1·1 million homes in 6671 small areas that were randomly selected to be representative of all of India, based on a structured nonmedical surveyor's field report has put the liver cancer as the 4th commonest cause of death in male and 8th commonest cause of death in female.[11]

Survival in HCC directly correlates with the stage of the disease. In early stage patients who receive potentially curative therapy, a considerable improvement in survival has been observed (5-year survival ranges between 40% and 70%) as compared to the patients who present late (5-year survival less than 5%). However, the treatments are received by only a small number of patients. Data from developed country like United States based on population-based studies indicate that only approximately 10% of patients with HCC receive these treatments.[12] Against this background, surveillance plays a key role. HCC surveillance has been advocated to detect HCC at an early stage, when critical treatment can be applied and hence higher survival can be expected.

A successful surveillance strategy if in place will be able to detect and prevent premature deaths from HCC. In a study from Japan, 81% of HCC detected by surveillance

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Abbreviations: AFP: alpha-fetoprotein; CI: confidence interval; CLD: chronic liver disease; DCP: des-γ-carboxy-prothrombin; HBV: hepatitis B virus; HCC: hepatocellular carcinoma; HCV: hepatitis C virus; NAFLD: Nonalcoholic Fatty Liver Disease; NASH: nonalcoholic steatohepatitis; QI: quality improvement; RCT: randomized controlled trial; TPCT: triple phase CT scan; US: ultrasound; USG: ultrasonography; USG: ultra sonogram

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Prevention

(n = 391) were considered suitable for curative resection compared with 46% of symptomatic HCC (n = 1251).[13] The overall 5-year survival rate was 51% for asymptomatic tumors compared to 5–21% for symptomatic disease. But cost-effectiveness of surveillance still remained a controversial issue in resource poor developing countries like India.

There is no randomized controlled trial for HCC surveillance although this was previously attempted. In a study to test the feasibility of conducting a randomized controlled trial (RCT) of HCC surveillance in patients with cirrhosis authors concluded that although an RCT is theoretically ideal for determining the efficacy, efficiency, and cost-effectiveness of HCC screening, informed patients prefer surveillance. A randomized study of HCC screening is not feasible when informed consent is imparted.[14] Hence it would be important for a study to be planned addressing various challenges which would help to understand importance of HCC surveillance.

The aim of this article is to discuss—

- Surveillance and its role in HCC
- Current level of awareness about surveillance among physicians managing CLD patients
- Role of dedicated HCC surveillance program: evidences from different countries
- A cost effective and feasible surveillance strategy in Indian context
- Role of surveillance in post surgery HCC patients.

SURVEILLANCE

Surveillance consists of periodic application of a diagnostic test (screening test) to subjects at risk for developing a given disease. Screening is traditionally defined as one-time application of a diagnostic test amongst asymptomatic individuals, in order to identify unrecognized early disease or precursors of disease. Several criteria need to be met, for a surveillance program such as 1) disease or condition must be fairly prevalent in the general population/subpopulation, 2) must be an important public health problem, 3) the surveillance test should be safe, free of serious adverse effects, and acceptable to the population being served, 4) the test should be able to diagnose the disease at a stage in which treatment is still possible and which is much more effective than when diagnosed in the non-surveillance population, 5) benefits gained should reflect in the population level not in the individual level.

The major rationale behind surveillance program for HCC is that patients diagnosed with HCC during surveillance have smaller tumors which are more often amenable to treatment and they can live longer than patients diagnosed with HCC during routine clinical care.[15] Surveillance is also possible because of existence of a well defined high risk group.

The tests most commonly used for surveillance of HCC are measurement of tumor marker alfa-fetoprotein (AFP) and or ultrasonography (USG), both of which are widely acceptable in general population. Ultrasound may play an important role in HCC surveillance. A study was conducted by Singal et al (2009) to determine the performance characteristics of surveillance with ultrasound for the detection of HCC, particularly early HCC as defined by the Milan criteria. Based on the literature review, authors concluded that the surveillance ultrasound detected the majority of tumours before they presented clinically, with a pooled sensitivity of 94%. However, ultrasound was less effective for detecting early HCC with a sensitivity of 63%. Alpha-fetoprotein provided no additional benefit to ultrasound. Although surveillance with ultrasound demonstrates limited sensitivity for early HCC, this may be improved by testing at 6-month intervals.[16] However this study did not address the effectiveness in clinical situation. A study was conducted to evaluate the effectiveness of a surveillance program with ultrasound and alpha-fetoprotein (AFP) in clinical practice to detect early HCCs. In this prospective study conducted in 446 patients with Child A/B cirrhosis, surveillance ultrasound and AFP had sensitivities of 44% and 66% and specificities of 92% and 91%, respectively, for the detection of HCCs. Sensitivity significantly improved to 90%, with minimal loss in specificity (83%) when these tests were used in combination.[17]

In a prospective study conducted in India at All India Institute of Medical Sciences, New Delhi, 194 patients with liver cirrhosis of varied etiology with no detectable HCC were followed up for a mean period of 34.9 months. Serum AFP measurement, abdominal ultra sonogram (USG) was done every 6 months, and triple phase CT scan (TPCT) every year. The authors found that in most patients, liver cirrhosis was related to HBV infection, HCV infection or both (36.6%, 27.8% and 6.2%, respectively). During a cumulative follow-up of 563.4 person-years, HCC was detected in 9 subjects, having an incidence rate of 1.60 (95% confidence interval 0.55–2.64) per person-year. All had infection with HBV, HCV or both (4, 4 and 1, respectively).[18]

A limiting factor for such surveillance programs is the failures and they potentially contribute to late-stage tumors in one-third of cases. The most common reason for finding HCC at a late stage was an absence of detection, suggesting better surveillance strategies are needed. Various studies show significant variation in the effectiveness of surveillance programmes. Variations in physician- and system-level factors are more important than patient-level factors in determining surveillance rates and they may contribute to late stage tumor presentation.[19]

There are several other novel biomarkers which are currently being assessed. Marrero et al, 2009 evaluated des-γ-carboxy-prothrombin (DCP) and lectin-bound AFP (AFP-L3%) as potential surveillance tests for HCC. They compared these two biomarkers with AFP and concluded