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HEPATIC CANCER (N PARIKH, SECTION EDITOR)

Harms of Hepatocellular Carcinoma Surveillance

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Abstract

Purpose of Review Hepatocellular carcinoma (HCC) surveillance in patients with cirrhosis is associated with decreased mortality by enabling early tumor detection. However, the benefits of any cancer screening program must be considered in light of potential physical, financial, and psychological harms, as well as the risk of overdiagnosis. Herein, we summarize the potential harms of HCC surveillance.

Recent Findings To date, two retrospective studies have addressed physical harms of HCC surveillance. Based on these data, 15% to 28% of patients undergoing HCC surveillance experience physical harm including additional cross-sectional imaging or liver biopsy. Although psychological and financial harms have been reported for other cancers, there are currently limited data specific to HCC. An ongoing multi-center prospective study assessing all four types of harms should provide data in the near future.

Summary HCC screening may improve survival by diagnosing tumors at an early stage, but limited sensitivity and specificity of screening tests can result in unintended harms. There is a need for further quality data evaluating both the benefits and harms of HCC surveillance.

Keywords Hepatocellular cancer · Screening · Risks · Overdiagnosis

Abbreviations

AASLD	American Association for the Study of Liver Diseases
AFP	Alpha-fetoprotein
CT	Computed tomography
HCC	Hepatocellular carcinoma
EASL	European Association for the Study of the Liver
MRI	Magnetic resonance imaging
NASH	Nonalcoholic steatohepatitis
NCCN	National Comprehensive Cancer Network

Introduction

Hepatocellular carcinoma (HCC) is a deadly cancer and projected to become the third leading cause of cancer-related death in the USA by 2030 [1, 2]. Potentially curative options such as surgical resection and liver transplantation are only available for patients diagnosed with HCC at an early stage [3]. Data from two randomized controlled trials performed in patients with chronic hepatitis B [4, 5] and several cohort studies in patients with cirrhosis have demonstrated the benefits of HCC surveillance; it significantly improves early detection of HCC, curative treatment receipt, and overall survival [6]. In accordance with this, the American Association for the Study of Liver Diseases (AASLD), National Comprehensive Cancer Network (NCCN) and European Association for the Study of the Liver (EASL) guidelines recommend biannual surveillance using ultrasound, with or without serum alpha-fetoprotein (AFP), in patients with cirrhosis and select groups of patients with chronic hepatitis B infection [7–9]. Despite these recommendations, uptake of surveillance remains low in the USA, with less than 20% of patients with cirrhosis receiving guideline-concordant surveillance [10], and thus only a small percentage of HCC are detected at an early stage [11].

The benefits of any cancer screening program must be balanced in light of potential pitfalls, including the risk of overdiagnosis [12] and screening-related harms. This critical assessment is of significant importance as expert guideline panels aim to develop pragmatic recommendations and best

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practices regarding screening [13]. As with many other cancers [14], there are limited data on harms of HCC surveillance compared with those regarding its benefits. In this review, we sought to summarize the current data on the physical, psychological, and financial harms associated with HCC surveillance.

Harms Related to HCC Surveillance

The potential negative consequences of HCC surveillance include physical, psychosocial, and financial harms and risk of overdiagnosis (Table 1).

Table 1 Domains of potential harms of HCC surveillance (adapted from [12, 15])

Domain	Description	Examples
Physical	• Temporary or permanent pain, injury, illness or impairment	• Pain from venipuncture • Contrast-induced nephropathy following CT • Bleeding after liver biopsy from false positive ultrasound
Psychological	• Negative emotions, mood symptoms, or psychiatric disorder • Disruption of relationships, altered social identity or status owing to a medical condition	• Fear that screening test will be positive • Anxiety following positive ultrasound while awaiting CT/MRI results • Depression about cancer diagnosis and "labeling" as a cancer patient
Financial	• Patient-level: Monetary costs, including treatment expenses, nonmedical expenses incurred while obtaining treatment and indirect costs due to loss of productivity • Society-level: Costs to healthcare system	• Direct cost of screening test and downstream testing after a positive test • Opportunity cost related to missed work during follow-up testing
Overdiagnosis	• Detection of pre-malignant lesion • Detection of indolent cancer • Detection of cancer in patient with high competing mortality risk	• Biopsy of lesion detected by screening reveals dysplastic nodule • Small HCC detected with slow tumor doubling time in a patient that eventually dies with, not from HCC • HCC detected in a patient with decompensated cirrhosis that is not a candidate for locoregional therapy due to poor liver function; patient dies of sepsis

Physical Harm

Potential physical harms may result from initial screening tests as well as subsequent diagnostic testing for positive results, both invasive and non-invasive. These harms may range from relatively minor in severity (eg., patient discomfort with venipuncture) to moderate (eg., radiation exposure, minor bleeding) to severe (eg., requiring hospitalization, or resulting in permanent disability or death).

Physical Harm Caused by Imperfect Surveillance Specificity

Although HCC surveillance using ultrasound and AFP causes minimal discomfort and few direct physical harms, its specificity is limited (about 70–90%) [16], resulting in a significant proportion of false positive findings leading to potential downstream harms associated with diagnostic evaluation protocols. A positive result prompts further diagnostic evaluation with dynamic contrast-enhanced cross-sectional imaging with computed tomography (CT) or magnetic resonance imaging (MRI), and in cases of indeterminate imaging findings, a liver biopsy [8]. CT and MRI are associated with radiation exposure, risk of contrast injury and costs to both the patient and healthcare system. The risk of contrast-induced nephropathy (CIN) has been reported as high as 25% in hospitalized patients with cirrhosis undergoing CT [17]. Though the risk of renal toxicity is lower with gadolinium-based contrast agents compared with iodinated contrast [18], patients undergoing MRI may still experience other physical harms such as pain related to intravenous access, contrast extravasation [19], claustrophobia during the exam [20], or rarely, nephrogenic systemic fibrosis (NSF) in patients with renal impairment [21]. Further, there are recent data reporting concern about gadolinium accumulation in the brain tissues, which remains of uncertain clinical significance [22]. The detection of indeterminate lesions on cross-sectional imaging often results in multiple subsequent CT/MRI scans, and may ultimately lead to biopsy. While percutaneous liver biopsy is generally regarded as a safe procedure, up to 80% of patients experience some pain [23]; further, there are small (but potentially serious) risks of bleeding, infection, pneumothorax, visceral perforation, and even death [24, 25]. The incidence of needle tract seeding the abdominal wall following biopsy of an HCC is lower than previously thought, but not zero [26, 27]. False positive AFP levels are common, and occur more often in patients with elevated liver enzymes, active inflammation, and viral hepatitis [28, 29].

To date, two retrospective studies have addressed the prevalence of physical harms of HCC surveillance in patients with cirrhosis. Atiq et al. found over 25% of patients with cirrhosis undergoing surveillance over a 3-year period experienced physical harm attributed to false positives and indeterminate results, ranging from mild (single or multiple cross-sectional

imaging scans) to severe (liver biopsy, angiogram) [30]. There was higher proportion of harms attributed to ultrasound than AFP (22.8% vs 11.4%, $p < 0.001$) and harms occurred more often in certain subgroups, including patients with nodular liver on ultrasound, portal hypertension, elevated ALT, and those receiving hepatology subspecialty care. In a second study of 999 cirrhosis patients enrolled in an HCC surveillance program for over 2 years, > 15% of patients were found to have a suspicious nodule that required further evaluation and was later determined to be either benign or remained indeterminate [31]. Among the subset of patients who had further evaluation with CT/MRI, 17% experienced severe harm, defined as ≥ 4 cross-sectional imaging exams or liver biopsy. Eleven (0.5% of the total cohort) patients underwent liver biopsy, of whom 5 had benign histology. Overall, surveillance resulted in 2.7 times more harms than benefits in this study. Correlates of surveillance harm included normal serum albumin level, lack of baseline thrombocytopenia, and nodule size < 2 cm. Risk-stratification tools are needed to better assess indeterminate nodules detected during HCC surveillance and obviate the need for unnecessary imaging tests and/or biopsies.

In a Markov modeling study by Taylor et al., HCC surveillance was associated with 13 fewer deaths for every 1000 patients with compensated cirrhosis followed over a 5-year period, equivalent to a number needed to screen of 77 patients to prevent one death from HCC [32]. However, significantly more patients were harmed by surveillance, with 150 (95% CI 146–154) of the 1000 patients having at least one false-positive surveillance test, leading to CT or MRI studies in 65 patients (6.5%) and 39 (3.9%) liver biopsies. Notably, the proportion of patients predicted to undergo biopsy for diagnosis of HCC was significantly higher than the proportion biopsied in the Atiq and Konerman studies (0.02% and 0.5%, respectively) [30, 31]. These differences are likely attributable to differential approach to indeterminate lesions in the USA and in Europe, as the modeling parameters included the EASL-EORTC recall policy allowing for routine biopsy of 1–2 cm indeterminate nodules found on cross-sectional imaging, rather than serial observation [33]. The recently revised AASLD guidelines specifically recommend against routine biopsy of every indeterminate nodule to reduce harms from unnecessary procedures [8]. When Taylor and colleagues modeled the recall strategy of continued imaging surveillance rather than exposing individuals to routine biopsy, they predicted a reduced rate of unnecessary biopsies from 3.9 to 0.6% over 5 years.

A recent prospective cohort study performed by Singal and colleagues has evaluated the benefits and harms of HCC surveillance in patients with cirrhosis at a single safety-net health care system [34]. Among 613 cirrhosis patients with ≥ 1 surveillance ultrasound or AFP, an abnormal result was observed in 207 (33.8%). Surveillance ultrasound/AFP led to HCC diagnosis in 15 patients, with 12 patients requiring only one CT or MRI to establish HCC diagnosis and 3 patients requiring 2 to 4 imaging studies. Of the remaining patients, 130 were monitored with continued surveillance and 62 (10.1%) patients underwent diagnostic imaging, all without subsequent HCC diagnosis; 49 patients had one CT or MRI, 11 had two studies and 2 had three studies. No patients underwent liver biopsy or other invasive procedures. Although one-third of patients in this prospective cohort had a false positive surveillance result, there were minimal surveillance harms (and no patients experienced severe harms).

Overall, the current data are mixed on the incidence of physical harms related to HCC surveillance. A prospective, multicenter randomized controlled trial is ongoing to assess screening-related benefits and harms among a cohort of > 2800 cirrhosis patients over a 4-year period is expected to be completed in 2023 (NCT 03756051).

Physical Harm Caused by the Limited Benefits of Surveillance

Although physical harms of surveillance are generally understood as harms caused by false positive screening results warranting further investigation, harm also results from false negative findings on surveillance tests [35]. False negative tests can lead to delayed (or missed) cancer diagnoses which, in turn, may delay necessary treatment, resulting in poorer outcomes and significant psychological distress.

With regard to HCC surveillance, ultrasound has been shown to be less sensitive in patients with obesity (76% in patients with BMI > 30 compared with 87% in patients with BMI < 30) and nonalcoholic steatohepatitis (NASH) compared with those with other etiologies of cirrhosis (59% vs 84%, respectively) [36]. In a study by Simmons et al., up to 20% of all ultrasounds performed for surveillance were deemed inadequate to exclude HCC and, further, were inadequate in more than one-third of patients with NASH-related cirrhosis, Child Pugh C cirrhosis, and BMI > 35 [37].

The limited sensitivity of surveillance ultrasound for HCC in patients with obesity or fatty liver disease is related to altered visualization due to the presence of subcutaneous fat, in addition to hepatic steatosis. Consequently, this leads to under recognition of small or early stage HCC tumors [36]. While the AASLD practice guidelines acknowledge limited US reliability in patients with truncal obesity or marked parenchymal heterogeneity, CT or MRI is not recommended as the primary imaging technique for HCC surveillance due to risks related to radiation and nephrotoxicity and, in case of MRI, due to cost and low accessibility [8]. This is contrary to the conclusions of the American College of Radiology expert panel which recommends that due to the severe limitation of ultrasound utility in patients with obesity, NASH, and nodular cirrhotic livers, consideration should be made for surveillance of HCC with either MRI or multiphase CT in these patients [38]. However, the predicted transfer of up to 20% of patients from

ultrasound-based to CT/MRI-based surveillance as a consequence of inadequate ultrasound assessment would have significant resource and financial impact, given the relative limited capacity of these modalities compared with ultrasound in most populations [39]. In addition, the performance of CT and MRI for HCC surveillance in patients prone to ultrasound failure, such as those with obesity, is unknown. Larger, prospective studies are expected to evaluate this dilemma in the future.

Psychological Harms

Cancer screening may result in psychological harms at any point along the screening "cascade" and have deleterious effects on patients' quality of life [40]. For instance, a patient may experience harm prior to the screening test (due to anxiety about a potential positive result), while awaiting test results, after a positive screening test result while awaiting diagnostic testing, after a diagnosis of cancer is made, during cancer treatment, and following cancer cure (due to concern about recurrence). Psychological harms may range in severity from mild anxiety to severe depression, or even suicide.

Psychological harms of screening tests have not been extensively evaluated or quantified in most cancers [41], including HCC. However, there are some data from cancers such as breast and prostate, demonstrating that screening tests and false positive results can have both short- and long-term adverse psychological effects, including resultant depression, anxiety and diminished quality of life [42, 43]. For example, in a study of women undergoing mammography, those with false positive results still reported negative psychological consequences up to 3 years after being declared cancer-free [44]. In addition, receiving a cancer diagnosis is a stressful event, and patients may experience adverse psychological consequences from being labeled as a "cancer patient" [45]. In a population-based study of SEER data, Fang et al. found an increased risk of death from cardiovascular causes and suicide in men in the first year following prostate cancer diagnosis compared with the general US male population [46]. Patients with false negative screening tests may experience significant psychological distress after an eventual (delayed) cancer diagnosis is made. Further, patients with false-positive screening tests may be less likely to participate in subsequent cancer screening [47]. Prospective studies are ongoing to evaluate the psychological impact of HCC surveillance in patients with cirrhosis (NCT 03756051).

Financial Harms

Cancer screening may result in financial harms impacting both the individual patient and society. Potential harms to the individual include not only the direct costs of screening tests and downstream diagnostic testing, but also travel costs and opportunity costs related to missed work for follow-up appointments.

Little is known about the financial consequences of false positive results arising from HCC surveillance. However, the financial toxicity of screening has been evaluated for other cancers. For example, of 1087 participants in the Prostate, Lung, Colorectal and Ovarian Cancer Screening Trial, 43% had at least one false positive cancer screen; this group had significantly higher rates of follow-up testing, translating into an adjusted increase in mean medical expenditures of > $1000/year compared with those who did not have false positive tests [48]. The design of a surveillance program, including its screening modality and intervals, has a significant impact on its cost-effectiveness. This has been demonstrated in modeling studies showing that follow-up algorithms for management of lung nodules significantly impact the cost-effectiveness (and performance) of lung cancer screening [49]. Furthermore, the cost-effectiveness of a cancer screening program is dependent upon the incidence of the cancer in a given population. Generally, HCC surveillance is considered cost-effective in patients with cirrhosis when the incidence exceeds the threshold of 1.5% per year (or greater than 0.2% per year in patients with chronic HBV and no cirrhosis) [33].

It is important to note that studies modeling cost-effectiveness are generally assessing the situation from the societal perspective; costs to the individual patient may result in burdensome financial toxicity. In fact, financial concerns of patients may be one of the causes of underuse of HCC surveillance in the USA. In a recent survey study by Singal et al., patients reported several barriers to HCC surveillance, including cost and transportation difficulties, with > 40% expressing worry about their ability to pay medical bills [50].

Overdiagnosis

Even when a surveillance program succeeds in detecting a tumor at an early stage, there is still the potential for overdiagnosis. The concept of overdiagnosis, or the detection of tumors that would otherwise not cause symptoms or death had they not been detected, has been described in various solid tumors, including HCC. There are three potential models for overdiagnosis: (1) detection of premalignant lesions (i.e., dysplastic nodule), (2) detection of indolent HCC, and (3) detection of HCC in a patient with high competing risk of mortality [12].

In a typical clinical scenario, a patient is found to have a subcentimeter lesion on ultrasound. Though AASLD guidelines recommend close observation with short-term follow-up ultrasound in 3 months [8], CT/MRI is often used in clinical practice to further characterize these lesions, despite the low diagnostic accuracy of CT/MRI for lesions < 1 cm [51]. In fact, this lesion is far more likely to be benign, as less than 20% of subcentimeter liver lesions are eventually determined

to be HCC and much more likely to be regenerative or dysplastic nodules [52]. Further, high-grade dysplastic nodules may exhibit radiologic features similar to an early HCC [51]. Targeted biopsy of a liver mass may lead to a false-negative result in up to 7% of cases, particularly in patients with lesions <1 cm [53, 54]. The natural history of subcentimeter lesions is unclear; however, continued monitoring and/or treatment of these benign lesions can certainly result in unintended harms without any benefit to the patient. The study by Atiq et al. reported a high degree of utilization of diagnostic CT and MRI in patients with subcentimeter lesions, despite guidelines recommending repeat short-interval ultrasound in this scenario given the low risk of HCC [30].

Second, though HCC is generally regarded as an aggressive tumor, based on its dismal prognosis with overall 5-year survival rates of 15%, up to one-third of HCC exhibit indolent tumor growth patterns [55]. The tumor doubling time (TDT), a surrogate of tumor "aggressiveness," may vary significantly among patients resulting in heterogenous HCC growth patterns. In a contemporary multicenter cohort of patients with cirrhosis and untreated HCC, Rich et al. reported the median TDT was 229 days (IQR 89–627 days); indolent growth (defined as TDT > 365 days) was more common in non-viral than viral cirrhosis, particularly in patients with T1 HCC lesions (OR 3.41, 95%CI 1.08–10.80) [55]. Patients with very indolent tumors, particularly those with decompensated cirrhosis, may receive little benefit from aggressive HCC treatment and rather, experience treatment-related harm.

Lastly, overdiagnosis may occur in a patient found to have HCC that is more likely to die from a non-cancer related cause, such decompensated cirrhosis or another life-limiting comorbid condition. Surveillance is not recommended in patients with cirrhosis and advanced liver dysfunction (Child Pugh class C) who are not liver transplant candidates, given the risk of further hepatic decompensation with HCC-directed therapy and competing risk of mortality due to end-stage liver disease itself [8]. Despite these guideline recommendations, patients with decompensated cirrhosis may actually be more likely to receive surveillance, as they are more likely to be linked to subspecialty care, and a proportion of patients with early or compensated cirrhosis may be undiagnosed [56, 57]. Compounding this issue, patients with decompensated cirrhosis are susceptible to harm from further downstream diagnostic and therapeutic procedures, such as liver biopsy (due to coagulopathy), cross-sectional imaging (i.e., contrast-induced nephropathy), and locoregional therapy (at risk for further hepatic decompensation). In the study by Atiq et al., there was an excess of over-screening as 13% of patients had Child Pugh class C cirrhosis, with 29% of these patients experiencing physical harm [30]. These data suggest that some physical harms of screening may be preventable with provider education regarding guideline-concordant care.

Conclusion

HCC surveillance programs are associated with improved early tumor detection, curative treatment receipt and decreased short-term mortality; however, these benefits must be weighed against potential physical, psychological, and financial harms and the risk of overdiagnosis. Up to one-fourth of patients participating in HCC surveillance experienced physical harms including cross-sectional imaging or liver biopsy, while data on psychological and financial harms are limited. Further high-quality data is needed to determine optimal HCC surveillance strategies and target populations for screening to maximize benefits and mitigate unintended harms.

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Nicole E. Rich: Concept and design, drafting of the manuscript
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Compliance with Ethical Standards

Conflict of Interest Amit Singal has been on advisory boards and served as a consultant for Wako Diagnostics, Roche, Exact Sciences, Glycotest, Bayer, Eisai, BMS, and Exelixis.
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