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Overdiagnosis: An Understudied Issue in Hepatocellular Carcinoma Surveillance

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Abstract

Overdiagnosis, the detection of clinically insignificant disease that would not otherwise impact the patient's lifespan, is a phenomenon that has been described in several solid tumors such as prostate, breast, thyroid, and lung cancers. Population-based efforts to reduce hepatocellular carcinoma (HCC) mortality in cirrhosis patients by screening and early detection may result in the overdiagnosis of HCC. One of the harms of overdiagnosis is subsequent overtreatment, which can result in increased costs, as well as physical side effects, psychological harms, and poorer quality-of-life. In this review, we explore the potential for overdiagnosis in HCC.

Keywords

Overdiagnosis; overtreatment; harms; surveillance; screening; HCC

Introduction

Hepatocellular carcinoma (HCC) is the third leading cause of cancer-related death worldwide, and its incidence is increasing in the United States[1, 2]. The prognosis for HCC is typically poor, largely related to most patients being diagnosed at late stages when curative therapies are not available. Therefore, professional societies in Western countries, including the American Association for the Study of Liver Diseases (AASLD) and European Association for the Study of the Liver (EASL), recommend routine biannual surveillance with ultrasound, with or without serum alpha-fetoprotein (AFP), in patients with cirrhosis with the goal of detecting HCC at an early stage[3, 4]. More intensive surveillance guidelines from Eastern professional societies reflect the higher prevalence of HCC in the East compared to Western countries, predominately due to high rates of endemic viral hepatitis.

The value of any cancer screening program is determined by a balance of screening benefits and screening harms. The goal of HCC screening and primary measure of benefit is a reduction in cancer-specific and all-cause mortality. These benefits must be weighed against

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potential physical, financial, and psychological harms including radiologic or invasive tests performed for indeterminate or false positive results. Additionally, screening carries a risk of overdiagnosis, i.e. detection of tumors that would not have caused symptoms or death had they not been detected. Overdiagnosis has been described and quantified for other malignancies, including prostate, breast, and lung; however, there are few studies evaluating overdiagnosis in patients with HCC[5]. The aim of this review is to discuss the potential for overdiagnosis in patients with HCC and its clinical significance.

Benefits of HCC surveillance

The goal of HCC surveillance is to detect tumors at an early stage, when curative treatment is possible, thereby reducing HCC-related mortality. HCC surveillance was shown to significantly increase early tumor detection and reduce HCC-related mortality in a large randomized controlled trial among patients with chronic hepatitis B[6]. There is currently no Level I evidence to support a similar survival benefit of HCC surveillance in patients with cirrhosis; however, a meta-analysis of available cohort studies found an association between HCC surveillance and increased early HCC detection (OR 2.08, 95% CI 1.80–2.37), increased curative treatment receipt (OR 2.24, 95% CI 1.99–2.52), and improved 3-year survival (OR 1.90, 95% 1.6702.17)[7], which remained significant in the subset of studies adjusting for lead-time bias. Additionally, a recent analysis of data from the prospective French ANRS cohort found adherence to semiannual ultrasound surveillance was associated with improvement in lead-time adjusted survival[8]. Lead-time bias is the perception of improved survival due to finding a tumor earlier in its course and following it for longer periods of time, without changing overall survival. Length time bias, another inherent bias of non-randomized data, relates to an increased likelihood of detecting indolent tumors than aggressive tumors. Although some studies have attempted to adjust for lead-time bias, they have assumed a wide range of tumor doubling times, and no studies to date have adjusted for length time bias. Despite these limitations, currently available data suggest HCC surveillance is likely associated with increased early tumor detection and improved overall survival. Several cohort studies of demonstrate underuse of HCC surveillance in patients with cirrhosis, likely contributing to the high rates of advanced stage presentation and poor survival observed in clinical practice.[9–11]

Harms of HCC surveillance

The benefits of HCC surveillance must be considered in light of screening-related physical, financial, and psychological harms. Screening physical harm can include direct complications of screening tests as well as subsequent diagnostic testing, whether invasive or non-invasive. Although ultrasound and alpha fetoprotein (AFP) have minimal direct physical harms, they can lead to high rates of diagnostic imaging for false positive or indeterminate lesions. Imaging studies including CT and/or MRI are associated with contrast injury, radiation exposure, and cost. Liver biopsy may be required for liver lesions not characterized by CT or MRI and can be associated with risk of bleeding, tumor seeding, and/or injury to nearby organs[12, 13]. In a retrospective cohort study of 680 cirrhosis patients undergoing HCC surveillance, Atiq and colleagues found 27.5% experienced downstream surveillance-related physical harms over a 3-year period, with a higher proportion of ultrasound-related

harm than AFP-related harm[14]. In another single-center study among 999 patients with cirrhosis followed for 2.2 years, HCC surveillance resulted in 2.7-times more surveillance-related harms than benefits[15]. In a Markov model of cirrhosis patients undergoing surveillance, Taylor and colleagues found surveillance was associated with 13 (95%CI 12–14) fewer deaths for every 1000 patients followed over a 5-year period, equivalent to a number needed to treat of 77 to prevent one death from HCC. However, the authors noted 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 65 cross-sectional imaging (CT/MRI) studies and 39 liver biopsies.[16] Although psychological harms, e.g. anxiety and depression, have been described for other cancer screening programs, including lung cancer and colon cancer, no studies to date have characterized this aspect for HCC surveillance. Together, these data highlight the potential for HCC surveillance-related harms and the need for further studies.

Overdiagnosis in Cancer Screening

In addition to screening-related harms discussed above, overdiagnosis is a potential pitfall of any screening program. Overdiagnosis should be suspected when a rise in incidence for a disease is observed without a concomitant rise in mortality. Of note, overdiagnosis is distinct from low specificity and false-positive findings. For example, a false positive finding in HCC surveillance would include a regenerative nodule detected on surveillance ultrasound that led to subsequent biopsy; however, this would not be categorized as overdiagnosis. Several scenarios can lead to overdiagnosis; 1) detection of pre-malignant lesions; 2) detection of indolent tumors that slowly progress; or 3) detection of a tumor in a patient with high competing risk of mortality.

Overdiagnosis of premalignant lesions

Overdiagnosis of small, premalignant lesions has been described in other cancer screening programs including breast cancer screening. In an analysis of Surveillance, Epidemiology, and End Results (SEER) data from 1975 to 2012, Welch and colleagues found a shift in the size of detected lesions with increasing use of screening mammography. The proportion of small (<2 cm) breast tumors increased from 36% to 68%. However, the authors noted a significant increase in small tumor detection (162 more cases per 100,000 women) without a significant decrease in large tumor detection (30 fewer per 100,000 women), suggesting a significant number of tumors were overdiagnosed[17]. While breast cancer mortality has declined over time, the degree to which screening mammography is responsible remains controversial[18]. A large multicenter, randomized screening trial performed in Canada found annual mammograms in women aged 40–59 did not reduce breast cancer mortality, and nearly one-fourth (22%) of tumors were classified as overdiagnosis[19]. Improvement in imaging techniques has also led to frequent incidental detection of small, asymptomatic pancreatic cysts, which may occur in up to 13% of adults[20]. Despite a lack of data supporting pancreatic cancer screening, prolonged surveillance of these lesions with CT/MRI, invasive testing, and surgical resection is often performed. This practice may cause harm in patients with low-risk lesions, such as small side-branch intraductal papillary

mucinous neoplasms (IPMNs), in which rates of malignant transformation are relatively low[21].

For HCC, the potential for overdiagnosis due to detection of pre-malignant lesions is driven by surveillance intensity, including surveillance intervals and test choice. Prior trials comparing HCC surveillance intervals have found more frequent surveillance intervals (e.g. 4 months vs. 12 months) identified a larger proportion of early stage tumors, resulting in more patients receiving curative therapies but no difference in overall survival[22, 23]. Similarly, Trinchet and colleagues found 3 vs. 6 month intervals for HCC surveillance identified a higher proportion of small liver lesions, but there was no difference in HCC detection or overall survival between the two groups[22].

HCC diagnosis is typically made based solely on radiographic criteria (using dynamic CT/MRI), and does not necessarily require histologic confirmation, however biopsy plays an important role if atypical imaging features are present. In recent years, diagnostic imaging modalities for HCC have improved significantly, resulting in increased sensitivity and more frequent detection of small liver nodules in patients with cirrhosis, increasing the potential for overdiagnosis. Based on current Western societal guidelines (AASLD and EASL), the diagnosis of HCC may only be confirmed in lesions ≥1 cm in size. Lesions <1 cm are less likely to be HCC, and CT/MRI traditionally have low accuracy for characterization of subcentimeter HCCs[24, 2526]. Current guidelines recommend close observation of lesions <1 cm using ultrasound every 3 months for up to 2 years, reserving diagnostic imaging with CT or MRI for lesions that enlarge[3]. However, CT/MRI is often used in cases with subcentimeter lesions in clinical practice, despite guideline recommendations, contributing to the burden of overdiagnosis.

The LI-RADS (Liver Imaging Reporting and Data) system, proposed in 2011 to standardize classification of liver nodules identified on CT or MRI, categorizes nodules on a scale of 1–5 ranging from LR-1 (definitely benign) to LR-5 (definitely HCC)[27]. Indeterminate lesions may be characterized as LR-2, LR-3, or LR-4. Limitations of the LI-RADS criteria include some discordance with other systems and guidelines (e.g. AASLD and OPTN) and there is a lack of head-to-head comparisons between LI-RADS and other criteria, which may result in unnecessary downstream testing for indeterminate, but benign nodules. Further, the LI-RADS system is dynamic and there is a need for prospective validation of the respective LR 1–5 categories with regard to likelihood of HCC to mitigate the risk of overdiagnosis. Of particular concern with regard to overdiagnosis is the case of a subcentimeter lesion with arterial enhancement and washout, which is classified as LR-4 (suspicious for HCC). This classification may prompt providers to pursue further testing with frequent CT/MRI and even biopsy; however, the lesion is more likely to be benign than HCC at this small size. In fact, prior studies have shown less than 20% of subcentimeter tumors are HCC, whereas the rest are more likely dysplastic or regenerative nodules[22]. Overall, the natural history of subcentimeter lesions has not been clearly determined. Several benign hepatic lesions may mimic HCC, and continued monitoring of these lesions may result in harms including radiation exposure, contrast exposure, and complications from biopsy or other invasive procedures.

Increasing use of gadoxetate-enhanced MRI, particularly in the East, may compound the issue of overdiagnosis, both for subcentimeter lesions as well as larger pre-malignant lesions. Prior studies suggest this test lacks perfect specificity and a proportion of high-grade dysplastic nodules will have overlapping features with early HCC[26]. Finally, the suboptimal performance of ultrasound in subgroups of patients, including the morbidly obese and those with nonalcoholic steatohepatitis, may also lead to increased use of CT/MRI as primary screening tests, further increasing the likelihood of overdiagnosed lesions and subsequent harms[28].

Overdiagnosis due to Detection of Indolent Tumors

The success of a cancer screening program is contingent upon the assumption that the tumor has a gradual, predictable growth pattern. Cancer screening is less likely to be effective for aggressive tumors with rapid growth patterns due to a lower likelihood of detecting these patients at an earlier stage and lower effectiveness of treatments. Likewise, screening is likely of low benefit in patients with slow growing tumors, although for different reasons. Screening is highly likely to detect these patients at an earlier stage and facilitate treatment (commonly known as length time bias), thereby often regarded as a success. However, the natural history of these patients without cancer detection and treatment could have been similar given the indolent nature of these tumors. If these patients suffer treatment-related complications or significant adverse events, cancer screening could have actually decreased survival and/or quality of life.

Overdiagnosis of indolent tumors has been observed in other malignancies, most notably prostate cancer. Use of prostate specific antigen (PSA) for prostate cancer screening has led to a significant burden of overdiagnosed, asymptomatic tumors which likely would not have impacted patient survival or quality of life. In the U.S. Prostate, Lung, Colorectal, and Ovarian Cancer (PLCO) trial of 77,000 men randomized to either annual PSA and digital rectal exam vs. no PSA screening, investigators observed a 22% increased detection of prostate cancer in the screening group but no difference in overall mortality[29]. However, the European Randomized Study of Screening for Prostate Cancer found PSA screening resulted in a mortality benefit with reduction of 0.71 prostate-cancer deaths per 1000 men aged 55–69 screened[30]. At 11-year and 13-year follow-up, further reduction in mortality was noted in the PSA-screened group, and the number needed to screen to prevent one prostate cancer death decreased to 1,055 and 781 men, respectively[31, 32]. The conflicting results from these two large multicenter RCTs led to significant controversy regarding PSA screening, resulting in discordant recommendations from professional societies, and in 2012 the U.S. Preventative Services Task Force (USPSTF) issued a recommendation *against* prostate cancer screening in men of all ages[33]. These guidelines were a departure from 2008 USPSTF guidelines that recommended against PSA screening only in men ≥ 75 years, and American Urological Association guidelines recommending shared-decision making regarding PSA screening in men between 55–69 years of age[34, 35]. These various guidelines have led to significant confusion amongst both patients and health-care providers regarding the merits and harms of PSA testing, including the impact of overdiagnosis. In long-term follow-up data from the Prostate Cancer Intervention versus Observation Trial (PIVOT), Wilt and colleagues reported that in 731 men with localized prostate cancer randomized to

radical prostatectomy vs. observation alone, surgery was not associated with all-cause or cancer-specific mortality benefit. Additionally, surgical intervention was associated with more frequent adverse events lasting up to 10 years later, including treatment-related limitations in activities of daily living (ADLs), urinary incontinence, and erectile dysfunction[36]. Consequently, overdiagnosis of prostate cancer may lead to unnecessary treatment with associated harms and no impact on survival.

Traditionally, HCC has been considered an aggressive tumor and rarely viewed as indolent, with 5-year survival rate of <15%[37]. An indicator of the malignant potential, or "aggressiveness", of a tumor is the tumor volume doubling time (TVDT), which reflects the intrinsic growth rate of a tumor; however, TVDT may be highly variable given the biologic heterogeneity of HCC. Villa and colleagues found tumor doubling times ranged widely from 30–621 days (median 83 days) with median survival significantly lower in those with TVDT in the 1st quartile (<53 days) compared to the three quartiles (11 vs. 41–47 months respectively, $p<0.0001$).[38] Other studies of HCC growth rates have similarly found heterogeneous TVDT[39–42], and HCC tumors may even spontaneously regress[43] TVDT may vary based on liver disease etiology (i.e. hepatitis B-associated HCC has faster TVDT than HCV-related HCC) which may partially explain observed differences in prognosis[44].Of note, studies assessing TVDT are limited by small sample sizes and potential for misclassification given most studies lack histologic diagnosis, and further studies are needed. Additionally, there is a lack of data supporting a constant tumor growth rate, and it remains unclear whether indolent lesions will remain slow growing or may develop a more rapid growth rate over time. Further studies evaluating TVDT are needed to determine if overdiagnosis related to detection of indolent tumors is of potential concern.

Overdiagnosis due to Detection of HCC in Patients with Competing Mortality Risk

Whether a tumor is indolent or aggressive, it would be classified as overdiagnosed if it occurs in a patient with multiple comorbid conditions and associated competing risk of mortality. These patients would be more likely to die from a non-cancer related cause, so the HCC would unlikely result in morbidity or mortality.

This phenomenon of overdiagnosis due to competing mortality risk has been well-described in colorectal cancer (CRC) screening. While the elderly are disproportionately affected by CRC, routine screening with colonoscopy may be inappropriate in some patients with advanced age and underlying comorbid conditions that might otherwise significantly limit their life expectancy. CRC screening in the elderly (age > 75 years) is controversial and not specifically addressed in societal guidelines[45, 46]. Nonetheless, some studies have found utilization of CRC screening to be highest in the elderly, particularly those covered by Medicare, as well as those with multiple comorbidities given their more frequent contact with the healthcare system[47, 48]. Though the yield of colonoscopy is likely higher in the elderly than younger populations, they are also more likely to have comorbid conditions and more vulnerable to procedural complications.

Examples of overdiagnosis due to competing mortality risk have also been noted in breast, lung, and prostate cancer screening programs. In a cross-sectional analysis of data from the National Health Interview Survey (NHIS), Deshpande and colleagues found a greater

number of chronic conditions was associated with increased adherence to screening mammography[49]. Similar findings have also been noted in lung cancer, where a substantial number of screening-detected cases are likely overdiagnosed due to a high all-cause mortality rate in smokers. This was noted in the Mayo Lung Project, a randomized trial designed to evaluate an intense lung cancer screening program using chest X-ray and sputum cytology compared to routine clinical care, which found no mortality benefit for patients in the intervention arm, even after extended follow-up[50]. In a longitudinal multicenter study of 11,521 men treated with radical prostatectomy, those with histologically-confirmed Gleason score ≤ 6 had a 20-year prostate cancer-specific mortality rate of only 1.2%. Further, irrespective of age at diagnosis, prostate cancer-specific mortality risk was significantly lower than the risk of mortality from competing causes[51].

For HCC surveillance, approximately 80–90% of HCC patients in the United States have underlying cirrhosis, which may range from asymptomatic compensated cirrhosis to decompensated liver disease, which carries a high risk of associated morbidity and mortality[37]. Unlike other malignancies, HCC is unique in that prognosis and treatment options depend not only on tumor stage, but also on underlying liver function, as evidenced by the inclusion of the Child Pugh score in the Barcelona Clinic Liver Cancer (BCLC) staging system[52]. Given the high 1-year mortality rate of patients with advanced (Child Pugh C) cirrhosis, the competing risk of liver-related mortality renders HCC surveillance ineffective in this subset of patients. In a multicenter Italian study of 1051 patients, Trevisani and colleagues demonstrated HCC surveillance had the largest survival benefit in patients with Child Pugh A cirrhosis, marginal benefit in patients with Child B cirrhosis, and no benefit in those with Child Pugh class C outside of liver transplantation[53]. At the present time, there is widespread underuse of recommended HCC surveillance in the United States among patients with cirrhosis, particularly among those with subclinical cirrhosis, racial/ethnic minorities, and the underinsured[10, 54]. It is possible that ongoing efforts to increase adherence to HCC surveillance programs may result in a greater proportion of overdiagnosed lesions in the future, highlighting the need for appropriate implementation of HCC surveillance in clinical practice[55].

The issue of overscreening in patients with advanced cirrhosis who are not acceptable liver transplant candidates is potentially avoidable. However, due to providers' under-recognition of subclinical or compensated cirrhosis, patients with decompensated, symptomatic cirrhosis may actually be more likely to receive HCC surveillance[3]. In a U.S. study of surveillance-related harms, Atiq and colleagues found 13.1% of cirrhosis patients receiving surveillance in a safety-net hospital system had decompensated cirrhosis (Child Pugh C) and over one-fourth (29.2%) of these patients experienced physical harms, defined as the receipt of diagnostic evaluation related to false positive surveillance tests[14]. Patients with Child Pugh C cirrhosis may be particularly prone to complications of diagnostic evaluation (e.g. contrast nephropathy or post-biopsy bleeding). Further, Child Pugh C patients who are not candidates for liver transplantation are also unable to undergo HCC-directed therapy due to risk of further hepatic decompensation, and thus can only be harmed by additional investigation of overdiagnosed lesions. It is also important to note that an individual patient's competing risk of cirrhosis-related mortality is dynamic, and the need for ongoing HCC surveillance should be continually reassessed to minimize potential for overdiagnosis.

To date, there are few studies assessing overdiagnosis in HCC related to competing risk of non-liver mortality, and longitudinal data on the natural history of HCC is sparse. A population-based Danish study of 8482 patients with alcoholic cirrhosis found 5-year cumulative HCC risk was 1.0% (95% CI 0.8–1.3%). Although the 5-year cumulative mortality in these patients was high at 43.7% (95%CI 42.6–44.7%), only 1.8% of deaths were related to HCC[56]. These data suggest high competing risk of mortality in these patients and the possibility of HCC overdiagnosis; however, further studies are needed, particularly in patients with NASH who have high rates of non-liver mortality.

Why is Overdiagnosis Important?

Although early detection of HCC and delivery of curative treatment is the mediating pathway to improving survival, these outcomes are not equivalent. By definition, a patient with an overdiagnosed lesion will not receive any benefit from treatment, and can only be harmed. Some of the harms associated with overdiagnosis include not only adverse physical harms of downstream diagnostic testing and procedures, but also psychological and financial harms. Screening tests and a resultant cancer diagnosis can have adverse psychological effects, including resultant depression and anxiety, previously described in patients undergoing PSA testing or mammography[57, 58]. In HCC, false positive testing may result in physical harms but psychological harms have not been quantified. Additionally, the patient may experience adverse psychological consequences from being “labeled” as a cancer patient. Further, overdiagnosis does not reduce disease-specific mortality for the individual. Rather, it can lead to overtreatment, which is costly and carries its own risks. For example, most (>90%) men in the United States with screen-detected prostate tumors received aggressive treatment, and Welch and colleagues estimated PSA screening has resulted in >1 million additional men receiving prostate cancer treatment in the U.S.[29, 59, 60].

In HCC, overdiagnosis has several potential implications, including harm to the individual patient, negative effects on quality of life (QOL), and increased financial burden. Many HCC tumors are diagnosed at an asymptomatic stage; however, treatment for a small, screen-detected HCC can result in significant morbidity and mortality. Curative and palliative treatments can result in prolonged survival in well-selected patients but may result in complications and debility, resulting in poorer QOL without a concomitant increase in survival, in poorly selected patients and those with overdiagnosed tumor. For example, surgical resection has a perioperative mortality of approximately 5–10%[61]. Similarly, transarterial chemoembolization (TACE) may result in post-embolization syndrome, contrast-induced nephropathy, liver decompensation, as well as other complications[62].

On a larger, societal scale, overdiagnosis leads to misleading and incorrect information about screening tests. For instance, overdiagnosis not only overestimates disease incidence and inflates survival statistics, but also the sensitivity, specificity, and positive predictive value of a particular screening test, as it misclassifies “healthy” patients as “disease-affected”. These miscalculations can thus hinder efforts to accurately assess the benefit of a screening test or novel therapeutic interventions.

Addressing overdiagnosis in HCC

It is clear the potential for overdiagnosis is largely dependent on surveillance recommendations and how surveillance programs are implemented in clinical practice. The intensity of HCC surveillance programs should not only take into account the incidence of HCC in the at-risk population but also patient-level risk factors, competing mortality risk, and availability of effective treatment options. There are currently significant differences in professional society guideline recommendations for HCC surveillance between Eastern and Western countries, likely resulting in differential risk of overdiagnosis. Eastern society guidelines (e.g. JSH and KLCSG) suggest more aggressive surveillance strategies, including biannual CT/MRI and follow-up of lesions with gadoxetate-enhanced MRI, and tend to err on the side of overdiagnosis. These recommendations likely reflect the higher incidence of HCC in Eastern populations compared to the West[63, 64]. As previously described, Western professional society guidelines (AASLD and EASL) have attempted to minimize the propensity for overdiagnosis through measures such as serial ultrasound monitoring for small lesions. Further, underuse of HCC surveillance in cirrhosis patients remains a significant issue in Western countries, so overdiagnosis of HCC may increase as surveillance programs are more widely implemented in the future.

The best way to evaluate to evaluate the impact of overdiagnosis in cancer screening programs is by conducting a randomized controlled trial (RCT), where one can determine if screening results in improved overall survival. While some patients with HCC will die despite early diagnosis and treatment, others will have a good outcome despite lack of screening. An RCT would also account for confounders inherent to observational studies including differences in age, comorbidity degree of liver dysfunction and performance status. Although a prior study suggests a RCT for HCC surveillance is unfeasible based on patient preference, and some believe it may be unethical, it should be noted these data are important to not only quantify screening benefits but also harms and overdiagnosis[65]. The importance of this approach has been highlighted by our experiences with breast and prostate cancer screening, where the potential for overdiagnosis and harms is being increasingly recognized.

In the absence of RCT data, modeling studies, including cost effectiveness analyses, can be conducted to evaluate the impact of cancer screening programs and overdiagnosis. These have been conducted for several other cancers including breast and lung cancer screening programs. However, the quality of any modeling study is dependent upon data inputs, including information on the natural histories of HCC with and without screening, which are inadequately characterized. Further, these studies often underestimate competing mortality risk and therefore underestimate the impact of overdiagnosis.

Unfortunately, it can be difficult to quantify the effect of overdiagnosis due to lack of long-term natural history studies on patients with untreated lesions. The extent of overdiagnosis in HCC is difficult to quantify, as it is not feasible to perform a trial in which all liver nodules are biopsied and followed off therapy to determine the natural history of such lesions. The precise magnitude of HCC overdiagnosis is inherently difficult to quantify as the only definitive proof occurs when untreated patients die of unrelated causes. Further,

overdiagnosis of indolent lesions can be difficult to diagnose and quantify as abnormal lesions are almost always treated. However, given the rising incidence of HCC and improvement in imaging studies, patients and providers must be aware of the propensity for overdiagnosis.

In HCC, tumor size itself may be a less important determinant of HCC prognosis than the underlying biologic characteristics of the tumor. A limitation of currently available imaging-based screening exams (e.g. ultrasound, CT) is that they assess tumor size rather than molecular/biologic characteristics. Future studies that aim to better characterize tumor growth patterns and predict HCC natural history (e.g. tumor growth rate estimation) are needed. Prognostic biomarkers, including those that can characterize a tumor's natural history, may also help distinguish indolent vs. aggressive tumors in the future; however, none with sufficient accuracy are currently available.

Conclusion

Cancer overdiagnosis is an inevitable consequence of screening programs, and has been described in other malignancies including breast, prostate, and lung cancers. Recent efforts to reduce HCC mortality with biannual ultrasound to detect tumors at an early stage likely has benefits but may also result in screening-related harms including overdiagnosis. Overdiagnosis in HCC surveillance can be related to detection of indolent tumors, detection of "pre-malignant" tumors, and detection of HCC in patients with high competing risk of mortality. Overdiagnosis can exacerbate screening-related harms, including downstream diagnostic testing and treatment, which results in increased costs, the potential for procedural complications, and poor quality-of-life. However, overdiagnosis has been poorly quantified and characterized in HCC screening programs to date. Further investigation is needed to determine optimal surveillance strategies and target populations for screening, with the goal of mitigating overdiagnosis risk.

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Abbreviations:

AASLD	American Association for the Study of Liver Diseases
AFP	alpha fetoprotein
BCLC	Barcelona Clinic Liver Cancer
EASL	European Association for the Study of the Liver
HCC	Hepatocellular carcinoma
JSH	Japan Society of Hepatology
KLCSG	Korean Liver Cancer Study Group

PLCO	Prostate, Lung, Colorectal, and Ovarian Cancer
PSA	prostate specific antigen
QOL	quality of life
RCT	Randomized controlled trial
SEER	Surveillance, Epidemiology, and End Results
TACE	transarterial chemoembolization
TVDT	Tumor volume doubling time
USPSTF	U.S. Preventative Services Task Force

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