We need stronger evidence for (or against) hepatocellular carcinoma surveillance

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Summary

Current guidelines from EASL recommend that most patients with cirrhosis are offered surveillance for hepatocellular carcinoma (HCC), but fewer than expected patients actually receive it. The recommendation is based on observational studies and simulations, not randomized trials. In this opinion piece we argue that a randomized trial of HCC surveillance vs. no surveillance is necessary and feasible, and we believe that clinician and patient participation in HCC surveillance would be better if it were based on trial results demonstrating its value.

Introduction

I (PJ) clearly remember my meeting with John, a 57-year old man, in the outpatient clinic. He had been diagnosed with alcohol-related cirrhosis five years earlier and was doing very poorly back then, but he had managed to quit alcohol and live a stable life, and his ascites was now a thing of the past. I would have discharged him from our outpatient clinic, had he not said that he was losing weight despite maintaining his usual diet. His wife confirmed this, and so we agreed to do an ultrasound examination to "make sure that nothing was amiss". Of course, he had a hepatocellular carcinoma (HCC). It turned out to be multifocal, not amenable to any treatment with curative intent. I talked to the couple again, and they were understandably frustrated that we had been following him for years without noticing this cancer that was now going to kill him. Oh yes, I remember this conversation. And I am convinced that many of you reading this remember similar conversations from your practice. I am equally convinced that you do not remember quite so well the many patients you have seen whose ultrasound examination did *not* show an HCC, just as you forget the times when the ultrasound showed something that required additional CT scans before the patient was cleared of cancer suspicion. Studies from behavioral psychology have shown that we overestimate the occurrence of events that come easily to mind, such as an HCC that we might have diagnosed earlier.[1] This pattern may explain why many hepatologists are in favor of HCC surveillance, and equally why hepatologists may be poorly positioned to judge the value of HCC surveillance.

Current guidelines from EASL recommend that patients with cirrhosis are offered surveillance for HCC, with some exceptions.[2] It is well recognized that this recommendation rests on observational studies and simulations, not randomized trials. Fewer than expected cirrhosis patients actually receive surveillance.[3] One solution has been to develop models to predict the individual patient's

HCC, expecting that low-risk patients can be exempted from surveillance. We believe that there is a need for a randomized trial of HCC surveillance for the reasons we expound in this opinion piece.

The purpose of HCC surveillance

HCC surveillance aims to prolong survival by reducing deaths from HCC whilst simultaneously improving (or at least not decreasing) quality of life; it is hoped that surveillance allows an earlier HCC diagnosis and curative treatment. Yet, a United States study found that 27.5% of cirrhosis patients experienced harms during 3 years of HCC survival.[4] While none of them died from those harms, they may have suffered a decrement in their quality of life.

Leaving aside quality of life and focusing on survival, HCC surveillance will provide the greatest benefit to those whose rate of HCC development (rate 1→2 in Figure 1) is high compared with their rate of death without HCC (rate 1→4), such as a 50-year-old man with compensated cirrhosis due to hepatitis C who is otherwise healthy. By extension, HCC surveillance provides the least benefit to those who are most likely to die without having developed HCC. They are the patients whose rate of death without HCC is much higher than their rate of HCC development, or whose rate of death from other causes after HCC diagnosis (rate 2→4) far outweighs their rate of death from HCC (rate 2→3). This view is recognized by the EASL guidelines which state that patients' life expectancy and ability to tolerate curative-intent treatment should be taken into consideration when offering surveillance.[2]

Problems with current evidence for HCC surveillance

We rely on observational studies

A well-conducted randomized trial provides an unbiased and unconfounded estimate of the average effect that we can expect from offering HCC surveillance to our patients. As a rule, regulatory bodies insist that clinical interventions are shown to be net beneficial in at least one well-conducted randomized clinical trial before they are adopted into clinical practice. HCC surveillance comes with benefits, harms, and costs—just like any other intervention. We are wrong to think that HCC surveillance is the default, and that the burden of proof is on those who question the benefits of surveillance.[5,6] Studies without randomization are prone to bias and uncontrolled confounding.[7,8] Fortunately, randomized trials typically reach the same conclusions as the observational studies that have gone before them, but there have been notable examples where a medical practice established without a randomized trial was stopped or even reversed when a randomized trial was finally conducted.[9]

We trust the '1.5% risk per year' limit, but are not sure what it means

Current guidelines for HCC surveillance and many review articles state that HCC surveillance is cost-effective if the HCC risk exceeds 1.5% per year.[2,10,11] This conclusion can be traced to a simulation study from 1996,[12] but we find the statement problematic for two reasons. First, the 1.5% per year statement been repeated so many times that its perceived validity is much higher than its true validity; studies that find an HCC risk above 1.5% per year often claim that HCC surveillance is therefore beneficial in their population.[13-16] Second, we have not been able to determine from the 1996 simulation study or its references whether simulations assumed an HCC *risk* of 1.5% per year or an HCC *rate* of 1.5 per 100 person-years. The latter is often presented as a "rate of 1.5%", and because many authors use "rate" and "risk" interchangeably,[11] the true meaning

is often lost. It is of crucial importance whether researchers mean "rate" (events per person-years of observation) or "risk" (probability of experiencing event), as the risk of HCC depends on the rate of HCC development *and* the rate of death without HCC (Figure 1).[17]

Table 1 uses simulations to shows how the risk of HCC varies in response to changes in the rate of death without HCC when the HCC rate is held constant at 1.5 per 100 person-years.[18] The rate of death without HCC among cirrhosis patients was between 10 and 18 per 100 person-years in studies from the United States, England, and Sweden.[19-21] We are wrong to think that an HCC rate of 1.5 per 100 person-years therefore means that the risk of HCC is 1.5% after 1 year, 5*1.5% = 7.5% after five years, etc. We must incorporate the rate of death without HCC into our computation of HCC risk, particularly when the rate of death without HCC is high (Table 1). The solution is simple: be accurate when it comes to rate or risk, do not express a rate as a percentage, and use the cumulative incidence function to compute HCC risk—not the Kaplan-Meier function.[22]

We do not know how HCC surveillance affects quality of life

It is possible that HCC surveillance reduces patients' quality of life. Maybe those surveilled are burdened by the frequent reminders of a looming cancer, by the need to travel to the hospital, by false-positive screening tests, or by futile screening examinations offered to patients who would not benefit from an early HCC diagnosis. Alternatively, maybe they feel reassured by the screening examinations, and maybe the biannual hospital visits are a welcome opportunity to get help with non-HCC health issues. At present though we do not know how HCC surveillance affects quality of life, and the decision to recommend HCC surveillance should be based on the effects on survival and on quality of life.[23] A randomized trial could tell us both and indeed is being attempted in another situation that is similar to HCC surveillance, namely Barrett's oesophagus.[24]

We have given up on randomization on the basis of a single patient survey

It has been argued that patients would not be willing to participate in a randomized trial because they insist on undergoing surveillance.[11] This argument rests on a survey of 205 Australian patients with Child-Pugh class A or B cirrhosis.[25] The participants in this study were given verbal information and a written decision aid to guide their decision to participate in a trial of HCC surveillance vs. no surveillance. As many as 204 (99.5%) said they would not participate, the vast majority because they preferred surveillance. We have two concerns. First, the decision aid was biased in favor of HCC surveillance. There is no mention of harm except that a figure on the second-last page mentions the possibility of "inconvenience of clinical visits, ultrasounds and other tests every six months" and of "anxiety from false positive result" (without explaining what a "false positive result" is). The figure is preceded by pages stating, in our view, that a survival benefit from HCC surveillance is plausible although not guaranteed.[25] The content of information leaflets has been hotly debated in other screening programs.[26] Second, as a field, we must do better than giving up on a randomized trial of HCC surveillance on the basis of a single survey.

Prediction models do not address the core question and can be hard to interpret

Several studies have developed prediction models that stratify cirrhosis patients by their HCC risk,[13,27-30] but they cannot answer the question whether the resulting high-risk group (or the low-risk group) benefits from HCC surveillance. Of course the studies have value nonetheless, and they are indispensable in the planning stages of a randomized trial.

Prediction models have identified several correlates of cirrhosis severity as risk factors for HCC, along with male gender and increasing age. However, most of the studies used Cox regression to identify risk factors, so they have in fact identified predictors of the *rate* of HCC development,[13,27-29] not the *risk*.[31] What matters for decisions about HCC surveillance is the *risk* of HCC

development. Again, this risk depends on the rate of HCC development *and* the rate of death without HCC, and prediction studies must consider both rates in their analysis.[17,22,32-34] The ideal patients for HCC surveillance are those who possess a characteristic with a strong positive effect on the rate of HCC development and a negative or small effect on the rate of death without HCC. Male gender is such a characteristic.

Table 2 shows results of simulation studies illustrating the effects of hypothetical risk factors on the rates of HCC development and on the rate of death without HCC.[18] One of those risk factors (#1) could be male gender, with its roughly 3-fold increase in HCC rate and null effect on death without HCC,[27-29] others resemble increasing age or decompensation with their increasing effects on both the rate of HCC and the rate of death without HCC. Clearly, the effect of an HCC risk factor on the risk of HCC depends on the factor's effects on *both* possible outcomes (HCC and death without HCC). One suggestion to facilitate the interpretation of prediction models is to use Fine & Gray regression instead of Cox regression.[32]

We need a randomized trial of HCC surveillance

It is likely that some patients with cirrhosis can expect substantial benefit from HCC surveillance, while others can expect substantial harm; we just don't know which patients fall into which group. Clinical equipoise exists somewhere between those two extremes, i.e., there are patients whom we would expect to have a fifty-fifty chance of experiencing net harm or net benefit. It is our hope that we can reach a consensus on who these equipoised patients are in terms of, e.g., underlying chronic liver disease, severity of cirrhosis, gender, age, comorbidities, and frailty. Then we should include these patients in a randomized trial of HCC surveillance vs. no surveillance. Such a trial could give us all the information we need about benefits, harms, and costs so that an informed decision can be made by patients, clinicians and policy makers whether or not to take up, deliver or invest in a

surveillance program. It would also avoid the complexities of rates and risks and competing outcomes, as we would simply be comparing all-cause mortality between those under surveillance and those not. There are, however, obstacles to such a trial.

Sample size

Recently, a randomized trial of CT-based surveillance for lung cancer in men aged 50 to 74 years with a smoking history found no effect on all-cause mortality: After 10 years of follow-up, the 13,195 participants randomized to surveillance vs. no surveillance had all-cause mortality rates of 13.93 vs. 13.76 per 1000 person-years, for a rate ratio of 1.01 (95% CI 0.92 to 1.11). The authors' conclusion, however, focused exclusively on the rate ratio for lung cancer-related mortality (0.76, 95% CI 0.61 to 0.94), which was the primary outcome.[35] A randomized trial of HCC surveillance must study all-cause mortality as the primary outcome; it is far more relevant to the patient than HCC-related mortality. Moreover, it can be difficult to determine whether a patient died from HCC or from cirrhosis. Algorithms to define HCC-related death exist,[36] but they could never be good enough for a trial with a possibly small effect of the intervention.

An HCC surveillance trial designed to compare all-cause mortality after, say, 5 years between patients randomized to HCC surveillance or no surveillance will need to include several thousand patients (Table 3). Note that if we argue that a trial would require an unrealistically large number of patients, we are at the same time arguing that the effect of surveillance will be very small.

Generalizability of trial results

In a randomized trial of HCC surveillance, the patients randomized to 'no surveillance' should receive the standard-of-care except HCC surveillance. That standard may differ between countries. For example, in some places those patients would be followed as outpatients, in others they would not. It will be important to have prespecified subgroup analyses by standard-of-care, because some

of the benefit of HCC surveillance may come from the outpatient visits that accompany ultrasound examinations, not from a reduction in HCC-related mortality.

Another source of regional variation is the access to liver transplantation. The benefit of HCC surveillance is likely greater if all patients with unresectable HCC within the Milan criteria can be offered a liver transplantation. That will not be possible in all countries,[37] and that is a threat to the generalizability of trial results. One solution is to conduct prespecified subgroup analyses by 'standard practice for liver transplantation for HCC'.

Screening tools

Abdominal ultrasound (with or without alpha-fetoprotein) is the standard screening tool and has been for many years. Newer imaging tools have been examined, but none are in widespread use and neither are biomarker panels. It has been argued that "the promise of HCC screening in reducing HCC-related mortality cannot be fulfilled with currently available tests."[5] It is true that more sensitive and specific screening tests could greatly increase the benefits and reduce the harms of HCC surveillance, but for now ultrasound is the standard that we think must be tried in a randomized trial.

Conclusion

Currently HCC surveillance lacks the evidence for it to be recommended practice. We believe that healthcare systems, clinicians, and patients would be much more likely to participate in HCC surveillance if it were based on randomized trial results showing it is of value.

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Table 1. Results of simulation studies to demonstrate how the incidence rate of death without HCC (Figure 1: rate 1→4) affects the risk of HCC, assuming a constant incidence rate of HCC (Figure 1: rate 1→2). Incidence rates are per 100 person-years. Note that the risk of HCC goes down as the incidence rate of death without HCC goes up. If we mistakenly assume that an incidence rate of 1.5 per 100 person-years equals a risk of 1.5% per year, so that the 5-year risk is 5*1.5% = 7.5% and the 10-year risk is 15%, we will overestimate the true risk substantially when the incidence rate of death without HCC is high.

		Cumulative risk of HCC		
Incidence rate of HCC	Incidence rate of death without HCC	After 1 year	After 5 years	After 10 years
1.5	0[†]	1.5%	7.3%	14.0%
1.5	1.5	1.5%	6.9%	13.0%
1.5	6	1.5%	6.3%	10.5%
1.5	15	1.4%	5.0%	7.2%
1.5	24	1.3%	4.2%	5.4%

[†] If we use the Kaplan-Meier method instead of the cumulative incidence function to compute the cumulative risk of HCC, we are by definition assuming that the incidence rate of death without HCC is zero.

Table 2. Results of simulation studies to illustrate the effects of hypothetical risk factors that affect the hazard ratio of both competing events, i.e., HCC development and death without HCC, on the cumulative 5- and 10-year risks of HCC. Risk factor #1 could be male gender, and risk factor #5 could be clinically significant portal hypertension. In these simulations the incidence rate of death without HCC is 10 per 100 person-years, and the incidence rate of HCC is 1 per 100 person-years. Note that the effect of a risk factor on the relative risk of HCC depends on that risk factor's effect on *both* competing events. The relative risks are only weakly affected by the incidence rate of HCC: If it is increased from 1 to 2 per 100 person-years, the 10-year relative risk for risk factor #5 increases from 1.28 to 1.30. They are more strongly affected by a change of the incidence rate of death without HCC: If that rate is increased from 10 to 20 per 100 person-years, the 10-year relative risk for risk factor #5 decreases from 1.28 to 1.08.

Hypothetical risk factor	Hazard ratio of HCC development for patients with vs. without risk factor	Hazard ratio of death without HCC for patients with vs. without risk factor	5-year relative risk of HCC for patients with vs. without risk factor	10-year relative risk of HCC for patients with vs. without risk factor
#1	3	1	2.79	2.72
#2	3	2	2.30	1.91
#3	3	3	1.88	1.42
#4	2	1	1.90	1.87
#5	2	2	1.51	1.28
#6	2	3	1.27	0.96

Table 3. Sample size estimations depending on all-cause mortality and its two components, HCC-related causes (Figure 1: state 3) and other causes (Figure 1: state 4), and the hypothesized effect of surveillance on deaths from HCC-related causes. The hypothetical trial has all-cause 5-year mortality as the primary outcome and employs 1:1 randomization, a power of 80%, a significance level of 5%, and a one-sided test of statistical significance (null hypothesis: surveillance has no effect or reduces survival; alternative hypothesis: surveillance improves survival).

Standard-of-care arm				Surveillance arm		N
All-cause 5-year mortality	Deaths from HCC, % of all deaths	5-year HCC-related mortality (Fig. 1: state 3)	5-year mortality from non-HCC causes (Fig. 1: state 4)	Proportion of deaths from HCC averted by HCC surveillance	All-cause 5-year mortality	Number of patients to randomize
30%	5%	1.5%	28.5%	50%	29.3%	90,730
40%	5%	2.0%	38.0%	50%	39.0%	57,878
50%	5%	2.5%	47.5%	50%	48.8%	38,074
40%	10%	4.0%	36.0%	50%	38.0%	14,418
40%	15%	6.0%	34.0%	50%	37.0%	6,386
50%	20%	10.0%	40.0%	50%	45.0%	2,390
40%	25%	10.0%	30.0%	50%	35.0%	2,282
30%	25%	7.5%	22.5%	50%	26.2%	3,530
30%	25%	7.5%	22.5%	25%	28.1%	14,368
40%	5%	2.0%	38.0%	25%	39.5%	231,912
40%	5%	2.0%	38.0%	75%	38.5%	25,678
40%	5%	2.0%	38.0%	100%	38.0%	14,418

Figure 1. Disease model for HCC surveillance. There are four states and four transitions between them indicated by arrows. The intensity with which a transition occurs is expressed as a rate, and the probability of making a specific transition is expressed as a risk. A transition from state 2 to state 1 is possible with curative treatment (or spontaneous regression of HCC), but it is not necessary for the discussion and therefore not in the figure.