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Modelling the benefits and harms of surveillance for hepatocellular carcinoma: information to support informed choices

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Abstract

Surveillance by ultrasonography for hepatocellular carcinoma (HCC) for individuals with cirrhosis is recommended. There is debate regarding the effectiveness of surveillance in reducing mortality and there is little information on the harms available to patients considering surveillance. The aim of this study was to provide estimates of both the benefit and harms of surveillance. A Markov model was built to simulate outcomes of individuals entering surveillance. Following identification of a focal lesion by ultrasound surveillance further investigations were defined by the EASL-EORTC recall policy. Benefit and harm outcomes are expressed per 1000 patients over 5 years. For every 1000 patients in surveillance over 5 years there are 13 fewer deaths (95% confidence interval 12-14) compared with no surveillance, equating to a number needed to screen to prevent one death from HCC of 77. In comparison, many more individuals experienced harm through surveillance. For every 1000 patients, 150 (95% confidence interval 146-154) had one or more false positive tests equating to a number needed to harm from surveillance of 7. As a consequence of a false positive test, 65 individuals required at least one additional unnecessary CT scan or MRI and 39 required an unnecessary liver biopsy according to the recall policy. Surveillance benefits were sensitive to the incidence of HCC and the mortality benefit achieved by treatment. Harms were sensitive to the rates of false positive testing and the frequency of liver biopsy. **Conclusion.** There is a balance between the small absolute mortality benefit to surveillance for HCC and the numerically more frequent harms resulting from false positive testing. Implementation of the recently revised AASLD recommendations is predicted to reduce harms from unnecessary liver biopsy.

Introduction

Individuals with cirrhosis are at risk of developing hepatocellular carcinoma (HCC) at a rate of approximately 3% per annum.(1, 2) This complication is often fatal, particularly if HCC is diagnosed at late stage. Treatment with curative intent can be considered providing cancer is diagnosed at early stage and liver function is sufficient. These observations have led to the recommendation that patients with cirrhosis undergo routine 6-monthly ultrasound surveillance for the development of HCC.(3-5)

The benefits of surveillance have not been demonstrated in a randomised trial including only patients with cirrhosis. There are however a large number of non-randomised case-control studies that suggest a survival benefit of diagnosing HCC in surveillance. These studies have been summarised in two systematic reviews that concluded surveillance was likely to lead to earlier diagnosis of HCC but diverged when an effect on mortality was considered. Singal and colleagues concluded that there was a significant improvement in survival with surveillance amongst patients with HCC(6) while Kansagara and co-workers were more circumspect in their conclusions.(7) Since the publication of those two reviews further case-control studies have been published, each indicating that there is a survival advantage for patients with HCC diagnosed in surveillance.(8, 9) Importantly, the analyses from the meta-analysis of survival outcomes have been used to support the recommendation for surveillance in the recently published AASLD guideline on the management of HCC.(10)

The published case-control studies provide limited information to patients considering entering surveillance since they only contain patients who have developed HCC rather than a population with cirrhosis as a whole and consequently these studies will inevitably overestimate the magnitude of the benefit of surveillance. In the absence of a relevant randomised controlled trial the absolute benefit of surveillance is unknown. Similarly, information on the harms of surveillance are scarce though a

recent report has suggested that the burden of additional testing may be significant with the authors suggesting that mechanisms to reduce the harms of surveillance were required(11) Since the majority of patients entering surveillance will not develop HCC it is of critical importance that the possible harms of surveillance are assessed and presented to patients at the outset so that these individuals may give informed consent.

It is accepted by many of the leaders in the field of HCC surveillance that a randomised controlled trial is impossible and previous attempts to assess the feasibility of such a trial have failed.(2-4) Modelling studies to assess the case for surveillance to date have considered the cost-benefit of surveillance as a whole without explicit assessment of the potential benefits and harms to the individual.(12) Furthermore, these models often simulate ideal treatment decision making and end after the first treatment for HCC.(12) This does not reflect clinical practice where recurrence after potentially curative treatment is frequent.

The aim of this study was to model the likely benefits and harms of surveillance from an individual patient perspective using contemporaneous diagnostic algorithms and treatment outcomes to inform the development of decision tools to support individualised choices in surveillance. We show that the absolute benefit to a patient entering surveillance is low and that harm results from surveillance at a greater frequency principally through false positive testing.

Methods

A Markov process model was built for two 1000 patient cohorts: one cohort undergoing regular 6-monthly HCC surveillance using ultrasound and the other cohort receiving no specific surveillance. The cohorts were simulated using patients aged 50 years with well compensated Child-Pugh class A cirrhosis at entry. Patients were followed for 5 years or until death using a cycle length of 6-months. A probabilistic analysis using Monte Carlo simulation was done recognising the uncertainty around the estimates of the benefits and harms of surveillance. For this analysis values were randomly sampled from the gamma distribution of each of the variables included in the model.

Patients in whom a suspicious nodule was identified were investigated according to the EASL–EORTC endorsed recall policy that until very recently was also endorsed by AASLD.(5, 10, 13) Briefly, for nodules <1cm in diameter early follow-up with ultrasound at 4 months is recommended and this continues until there is a change in the size of the nodule at which point further investigation is planned according to the new size. For nodules 1-2cm in diameter further dynamic imaging is scheduled either by 4-phase computed tomography (CT) or by contrast enhanced magnetic resonance imaging (CE-MRI). In experienced centres, as is assumed in this study, if either of these techniques displays the radiological hallmarks of HCC then the diagnosis is confirmed. If the nodule remains indeterminate then biopsy is recommended. For nodules >2cm a single imaging modality (4-phase CT or CE-MRI) displaying the radiological hallmark of HCC is sufficient for diagnosis. Specific treatment modalities were not included in the model. Instead the overall mortality of patients diagnosed with HCC from recently published studies examining the effectiveness of surveillance was modelled to give a clear indication of the likely mortality benefits of surveillance in current clinical practice. An overview of the model is provided in **Figure 1**.

Model parameters

Transition probabilities were estimated from the literature and are summarised in **Table 1**. The incidence of HCC was defined in two large prospective studies at 2.5% per annum.(14, 15) The base case model assumed that the incidence of HCC was identical in both the surveillance and no surveillance cohorts. There are no good data to estimate possible additional HCC diagnoses amongst patients undergoing surveillance and the risk of "overdiagnosis" of HCC amongst patients with compensated cirrhosis is felt to be small.(3)

Application of the EASL-EORTC endorsed recall policy was assessed using the studies that have underpinned adoption of that policy.(16-18) The false positive rate of the index ultrasound scan was extracted from a prospective randomised study of 3- versus 6-month surveillance using data form the 6-month arm.(14) The size of the first focal non-HCC lesion recorded in that study was used to define follow-up testing. That testing was defined by the recall policy and nodules between 1 and 2 cm in diameter were assessed by 4-phase CT or CE-MRI. During that evaluation 27% of identified nodules were characterised as definitely non-malignant, as described in a recent evaluation of a large number of patients undergoing ultrasound based surveillance.(19, 20) The impact of the removal of this recall policy from the most recent iteration of the AASLD guideline(10) was assessed in sensitivity analyses. The frequency of the use of either 4-phase CT and CE-MRI or both in combination was not modelled since there is limited published data on the frequencies with which each modality is used in the evaluation of a patient after an abnormal surveillance ultrasound. In addition the use of contrast enhanced ultrasound was not specifically modelled since this is not included in the diagnostic algorithm in either the EASL-EORTC or AASLD guidelines.(5, 10)

Mortality estimates were made using the DEALE method(21) from survival data from those studies accounting for lead time bias included in a systematic review of non-randomised studies of surveillance for individuals with cirrhosis.(6) Specifically the survival modelled at 3 years after diagnosis was 39% in individuals undergoing surveillance and 29% in individuals not in surveillance, an absolute risk reduction of 10%. These outcomes were supported using data from both modelling studies of the impact of lead time bias as well as more recent published non-randomised studies.(8, 9, 22) For the purposes of sensitivity analyses the absolute risk reduction in mortality was varied between 5 and 25% by varying survival in those individuals allocated to surveillance.

Model outcomes

The primary outcome measure in the model for benefit was the absolute change in overall mortality. This absolute change in mortality was then used to calculate the number needed to screen (NNS) to prevent one death over 5 years. This outcome was chosen since it reflects the most critical patient relevant endpoint for an individual with cirrhosis. Diagnosis of HCC at early stage is a surrogate outcome measure and is susceptible to biases including lead-time bias. As a consequence, whilst desirable, early stage diagnosis of HCC is not suitable to gauge the benefit of surveillance to the individual. The primary outcome measures for harm were the absolute number of patients undergoing unnecessary additional imaging investigations (i.e. those that did not ultimately result in the diagnosis of HCC) and the number of patients undergoing unnecessary invasive procedures. The absolute change in the proportion of individuals experiencing these harms was used to calculate the number needed to harm (NNH) over 5 years. The greatest harm was counted for each individual entering the model in a hierarchy where liver biopsy was considered greater than at least one unnecessary 4-phase CT or CE-MRI, which in turn was considered greater than a false alarm with intensified ultrasound-based follow-up. Several other measures have been suggested as indicators of harm in screening

programmes including rates of overdiagnosis and negative psychosocial consequences,(23) but in the absence of data from randomised controlled trials there is insufficient data to model these with any accuracy.

Sensitivity analyses

Model parameters were varied across plausible ranges in deterministic sensitivity analyses. Several scenario-based sensitivity analyses were done to examine specific aspects of surveillance where there are few data. Specifically, a scenario encompassing low rates of biopsy in indeterminate lesions were modelled since it is apparent that some centres do not adhere to the endorsed recall policy. A specific model where individuals at risk of HCC but not at risk of progressive liver disease was also assessed to understand the benefits and harms of surveillance in individuals such as those with hepatitis B virus (HBV) infection that is controlled on antiviral treatment or those with sustained virological response (SVR) following treatment for hepatitis C virus (HCV) infection.

Results

Benefit of surveillance

Over the 5-year horizon of the no surveillance model a total of 110 individuals developed HCC and there were 82 deaths attributable to HCC. In addition, there were 82 deaths unrelated to HCC. In the 1000 individuals undergoing routine ultrasound-based HCC surveillance for 5 years, there are 13 fewer deaths (95% confidence interval 12-14) with surveillance achieved through a reduction in HCC specific mortality (**Table 2**). This 1.3% absolute mortality reduction equates to a number needed to screen (NNS) of 77 to prevent one death from HCC over a five-year period.

Sensitivity analyses for benefit

The magnitude of the benefit estimated in this model is based on published case-control series where a significant proportion of HCC is diagnosed beyond traditional curative criteria. For instance, in the most recent studies the proportion with very early, or early HCC varies from 27% to 61%.(8, 9) In the prospective studies used to define the harms of surveillance the rates of early diagnosis are in excess of 70% suggesting that the survival benefit of surveillance may be greater under conditions that can be achieved in prospective trials. To reflect this in the deterministic sensitivity analyses we increased the proportion of individuals surviving after HCC diagnosis in surveillance to 54% at 3 years (an absolute mortality reduction of 25%) in line with previous modelling study estimates.(24) Under those conditions there were 30 fewer deaths in the surveillance group, equating to a NNS of 33 to prevent one death from HCC (**Figure 2**). Equally however, there is uncertainty in the estimates of benefits in surveillance and many authors identify a threshold of lead time bias beyond which surveillance for HCC is ineffective. Modelling reduced efficacy of surveillance (where the absolute mortality reduction with surveillance was 5%) negated much of the benefit of surveillance such that there were only 6 fewer deaths under those circumstances.

The incidence of HCC has consistently been shown to impact on the cost-effectiveness of surveillance. When this parameter was varied between 1% and 5% there was a significant impact on the benefits of surveillance. The absolute number of fewer deaths ranged from 5 to 23, equating to NNS from 200 to 43 respectively. Variation in the rates of mortality from competing mortality, both liver failure and death from co-morbid medical conditions had minimal impact on mortality reductions. Consequently, combining these parameters in a scenario where there was ongoing significant risk of HCC development (2.5% per annum) but low competing mortality risk (0.5% per annum), as may be seen in patients with HCV related cirrhosis and SVR, did not impact on the benefit of surveillance for HCC although predictably overall mortality declined in both groups. In parallel with the base case model, increased benefit of surveillance was only seen when the survival estimate with surveillance was increased.

Harm of surveillance

The harms calculated in the model were estimated from the number of additional imaging tests and the number of liver biopsies done (**Table 2**). Those tests and procedures that did not diagnose HCC were deemed unnecessary since they were the result of false positive testing. In surveillance 150 (95% confidence interval 147-155) individuals had a false alarm leading to additional investigation over the 5-year horizon giving a number needed to harm (NNH) of 7. This included 65 individuals (95% confidence interval 63-67) undergoing at least one unnecessary 4-phase CT or CE-MRI whilst the remainder had intensified ultrasound based follow-up. In that model, there were 39 individuals (95% confidence interval 38-40) who underwent unnecessary liver biopsy following the identification of an indeterminate lesion on 4-phase CT or CE-MRI according to the endorsed recall policy. The associated number needed to harm (NNH) for 4-phase CT or CE-MRI was 15, and for biopsy it was 26.

Sensitivity analyses for harm

In deterministic sensitivity analyses the rates of additional testing were increased if the rate of false positive ultrasonography is increased. Increasing the false positive rate to 6% per annum increased the total number of individuals undergoing at least one additional unnecessary cross-sectional imaging investigation, i.e. 4-phase CT or MRI, to 93 (with a NNH of 11) and the number undergoing liver biopsy to 64 (NNH 16) over 5 years. In contrast reducing the rate of false positive diagnosis reduced the number of individuals undergoing additional unnecessary cross-sectional imaging to 50 and the number undergoing unnecessary liver biopsy to 35.

Recognising the removal of the recall policy from the updated AASLD guideline(10) we modelled continued imaging surveillance for change of indeterminate nodules rather than exposing individuals to biopsy as a matter of routine. This strategy maintains the number of individuals undergoing unnecessary imaging investigations but reduces the number of unnecessary invasive procedures to 6 over 5 years. This is in line with a recent report of the harms of surveillance.(11) In that study, additional CT and MRI scans were also done where the exclusion value of the surveillance ultrasound was low and where nodules <1cm were identified, in contrast to recommendations in the EASL-EORTC endorsed recall policy. In models of these scenarios the number of individuals undergoing additional unnecessary cross-sectional imaging was increased. For instance, assuming a rate of 10% for non-diagnostic ultrasound and that half of those individuals were then investigated by 4-phase CT or MRI the number of individuals undergoing unnecessary imaging was increased to 315, equating to a NNH of 3. Additionally, in a scenario where half of individuals with a <1cm lesion on surveillance underwent 4-phase CT or MRI the NNH decreased to 9 over the 5-year horizon. These values illustrate the likely harms of surveillance and the additional burden of testing that is placed on an individual entering a surveillance program where a defined recall policy is not in place.

Visualising the benefit and harm of surveillance

The model outputs were combined into a graphical summary to provide patient relevant information in an accessible format (**Figure 3**). This summary is based on published examples from the literature of population screening for cancer and highlights the relative benefits and harms of surveillance for HCC.

Discussion

Prospective evidence that supports surveillance for HCC in individuals with cirrhosis is weak and there is uncertainty over both the benefits and harms of implementation. It is widely stated that a randomised controlled trial comparing surveillance with no surveillance is not possible and to better understand the benefits and harms of surveillance a modelling approach was required. Using these methods we show that the absolute benefit of surveillance is small with 13 fewer deaths amongst 1000 individuals (a 1.3% increase in patients surviving) after 5 years surveillance. Furthermore, we highlight the likely harms of surveillance, particularly with regard to the proportion of individuals who undergo at least one unnecessary 4-phase CT or CE-MRI (6.5%) or an unnecessary liver biopsy (3.9%) according to the EASL-EORTC endorsed recall policy. These estimates are of critical importance when considering the net benefits of surveillance and they can readily be incorporated into clinical decision making and material for participant consent for surveillance using the summary illustrated in **Figure 3** that extends previously developed decision aids.(25) The use of such decision aids such as this is advocated by many bodies with roles in improving healthcare(26, 27) and their use in increasing patient knowledge and in stimulating an active role in decision-making is supported by a recent Cochrane evidence synthesis.(28)

The models presented incorporate contemporaneous measures of rates of early HCC diagnosis and false positive testing through well organised surveillance programs enacted in a randomised clinical trial. Additionally, the models include recent estimates of the likelihood of benefit, through reductions in overall mortality amongst patients diagnosed with HCC. Critically, these are combined in cohorts of individuals with cirrhosis to give patient relevant estimates of the likely outcomes of surveillance. In contrast to previous modelling studies the resulting estimates give a real-world perspective of the

outcomes of surveillance rather than more optimistic models where assumptions including those regarding treatment allocation may overestimate the likely benefits of surveillance.(24, 29, 30)

The absolute increase in overall survival indicated in the base case model (1.3%) is approximately 10-fold less than that suggested by the published non-randomised studies where the benefit of surveillance is estimated to be at least a 10% absolute overall mortality reduction over 3 years.(6, 10) The discrepancy between this estimate and the output from the model is explained by the design of those prior studies.(6, 8, 9, 22) These were case-control studies that included only patients diagnosed with HCC and therefore did not include the majority of patients with cirrhosis who undergo surveillance but do not develop HCC. This majority dilutes the overall benefit of surveillance that is seen in those studies and identifies a significant group of individuals who do not directly benefit from surveillance and are exposed to the consequent risks and harms. However, there remains uncertainty regarding the magnitude of the benefit of surveillance in individuals with cirrhosis due to the absence of a relevant randomised controlled trial. This uncertainty was addressed in sensitivity analyses that increased 5-year survival to 54% in the surveillance cohort as suggested by a modelling study.(24) With this there was an increase in the survival benefit of surveillance to 3.0% at 5 years. There are a several lines of evidence that question whether this degree of benefit can be achieved in clinical practice. Firstly, the rates of curative treatment in surveillance studies are lower than the rates of diagnosis of early stage HCC likely due to the presence of advanced liver disease and/or non-liver co-morbidity. For instance, in the randomised trial of surveillance intervals the proportion of individuals diagnosed with disease within the Milan criteria was in excess of 70% yet 58% were exposed to treatment with curative intent. Secondly, HCC recurrence is a major concern after both liver resection and ablative treatments limiting the overall benefits of these treatments.(2) Lastly, there is the ongoing risk of the development of liver failure with progressive liver disease and whilst there is now treatment available that will largely prevent that progression in individuals with viral hepatitis that risk is still present for

many other patients. Ultimately this progression will limit the absolute benefit of any surveillance program where death from liver disease is very likely without transplantation.

The likely harms of surveillance identified here are significant, both in terms of additional cross-sectional imaging by 4-phase CT or CE-MRI and also the probability of an invasive liver biopsy. The endorsed recall policy that is included in the EASL-EORTC guidelines is recommended to increase the rates of early detection of HCC, particularly of lesions <2cm in diameter since it is at this size that surgical resection and ablative treatments are most effective and models have predicted that utilising biopsy in this way benefits patients.(31) The recent removal of the recall policy from the AASLD guideline highlights concerns around the utility of liver biopsy from small lesions and there is a recognition that utilisation of the recall policy may result in a number of unnecessary biopsies.(32) The impact of liver biopsy in a cohort of individuals undergoing surveillance has not however previously been assessed. In the only other study to assess the likely harms of surveillance there was a very low rate of biopsy(11), suggesting that the recall policy had not been widely adopted in the United States in any case.

The other critical aim of the recall policy is to protect patients from unnecessary investigations where the risk of HCC is low, particularly in those individuals with very small (<1cm) focal lesions. In the study from Atiq and colleagues(11) the rate of additional and unnecessary cross-sectional imaging investigations was higher than that seen in our base case model, largely due to imaging of both individuals with very small focal lesions and those individuals undergoing ultrasonography where the exclusion value was felt to be low. In sensitivity analyses these scenarios were readily recreated and the large numbers of individuals undergoing additional unnecessary imaging investigations were remarkable. For instance, if 50% of individuals with sub-centimetre nodules had additional cross-sectional imaging this would mean more than 1 in 9 individuals in a surveillance program would

undergo such testing in a 5-year period. Indeed, if the data from the study from Atiq and colleagues were extrapolated to these models, more than one third of these individuals would undergo more than one additional unnecessary 4-phase CT or CE-MRI investigation. Removal of the recall policy from the updated AASLD guideline has the potential therefore both to reduce the rate of diagnosis of HCC <2cm in diameter and perhaps more importantly to increase the imaging harms of surveillance albeit with the understandable aim of protecting patients from the risks of liver biopsy. There are no prospective data that confirm the benefits of the recall policy on mortality outcomes and these observations argue strongly for comparative prospective evaluation of recall policies to standardise surveillance programs and to define which strategies are optimal in early diagnosis and in the protection of patients from unnecessary imaging investigations.

The harms of surveillance are not limited to the consequences of false positive testing. It can be argued that there is harm associated with false negative testing and consequent late diagnosis of HCC. In high quality prospective studies of surveillance, the rate of diagnosis beyond the Milan criteria is between 20 and 30%.(14, 15) The rate of false negative testing in surveillance is unknown but it seems likely these individuals had a false positive ultrasound test, or perhaps more likely multiple false negative tests before diagnosis. In addition, there is the issue of psychosocial harms that are associated with other forms of cancer screening. There are no data on the psychosocial consequences of HCC surveillance and there are features of surveillance that suggest that this may be significant. Surveillance is done frequently and in the case of a positive test there is additional testing before diagnosis. Furthermore, after a potentially false positive ultrasound there is intensified testing, either by ultrasound or cross-sectional imaging, with the spectre of cancer constantly present. This additional testing likely increases any negative psychological consequences of surveillance as well as increasing the opportunity costs to the patient. This important aspect of the impact of surveillance on the patient has not been measured and it is critical that this issue is addressed to help support patients enrolled

in surveillance where psychosocial morbidity associated with cirrhosis is already prevalent and concerns regarding the risk of HCC are relevant.(33, 34)

This study aimed to identify the relevant benefits and harms of surveillance for HCC in individuals with cirrhosis. The relative paucity of data on both the benefits of surveillance in individuals with cirrhosis and the harms of surveillance necessitated a modelling approach. This is not intended to replace prospective evaluations of the harms of surveillance but is rather a starting point identifying areas where the evidence base is weak and to support clinician and patient decision making until that evidence is available.

There are a number of limitations to this study due to the relative lack of prospective data and the potential for additional biases in non-randomised studies of surveillance. For instance, there are few data on length-time bias whereby slower growing tumours are more likely detected in surveillance. Additionally, it is likely that the adjustments that are typically made for lead-time bias are imperfect. Each of these factors would act to overestimate the impact of surveillance in clinical practice. It might also be argued that because the populations used to derive the estimates of the benefits and harms of surveillance are not the same the results of the models cannot necessarily be combined. There are differences in the study populations used and there are no data on survival outcomes for patients developing HCC in the study from Trinchet and colleagues.(14) Similarly, there are no data on harms that accompany the studies of survival benefit synthesised by Singal and colleagues.(6) There is however consistency between the proportion of patients treated with curative intent in the study used to define the rate of false positive testing (at 58%)(14) and those that were used to define the benefits of surveillance that range from 41% to 76%(6, 8, 22) suggesting that the mortality outcomes are likely to be similar. Finally, the models employed in this study deliberately use outcome data rather than modelled treatment allocation and clinical trial outcome data to give an assessment of the likely

benefits and harms of surveillance in current clinical practice. They are therefore subject to variations in that clinical practice. While this is clearly a limitation of the approach and may reflect suboptimal clinical approaches to surveillance it provides a real-world estimate that is directly relevant to clinicians and patients considering surveillance.

In summary, this study identifies a small absolute benefit to surveillance for HCC in individuals with cirrhosis. There are numerically many more individuals who experience harm from surveillance through both unnecessary imaging investigations as well as liver biopsy. Whilst these harms may be considered less clinically significant their frequency is important and may alter the acceptability of surveillance to some patients. The potential impact of both the benefits and harms of surveillance has been summarised in forms that could be readily incorporated into patient decision aids to inform individualised decision-making regarding participation in surveillance. Adherence to the current EASL-EORTC endorsed recall policy drives much of the additional invasive testing but conversely it may protect patients from inappropriate testing where the probability of diagnosing HCC is low. Implementation of an altered recall policy could provide a solution to concerns about the harms of liver biopsy as well as preventing the increase in unnecessary imaging investigations predicted in the absence of a defined recall policy. Comparative prospective studies to define optimal follow-up testing are required in populations of patients with cirrhosis.

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Figure and Table Legends

Figure 1. Model overview. Dotted lines indicate from which group the benefit and harm outcomes were calculated.

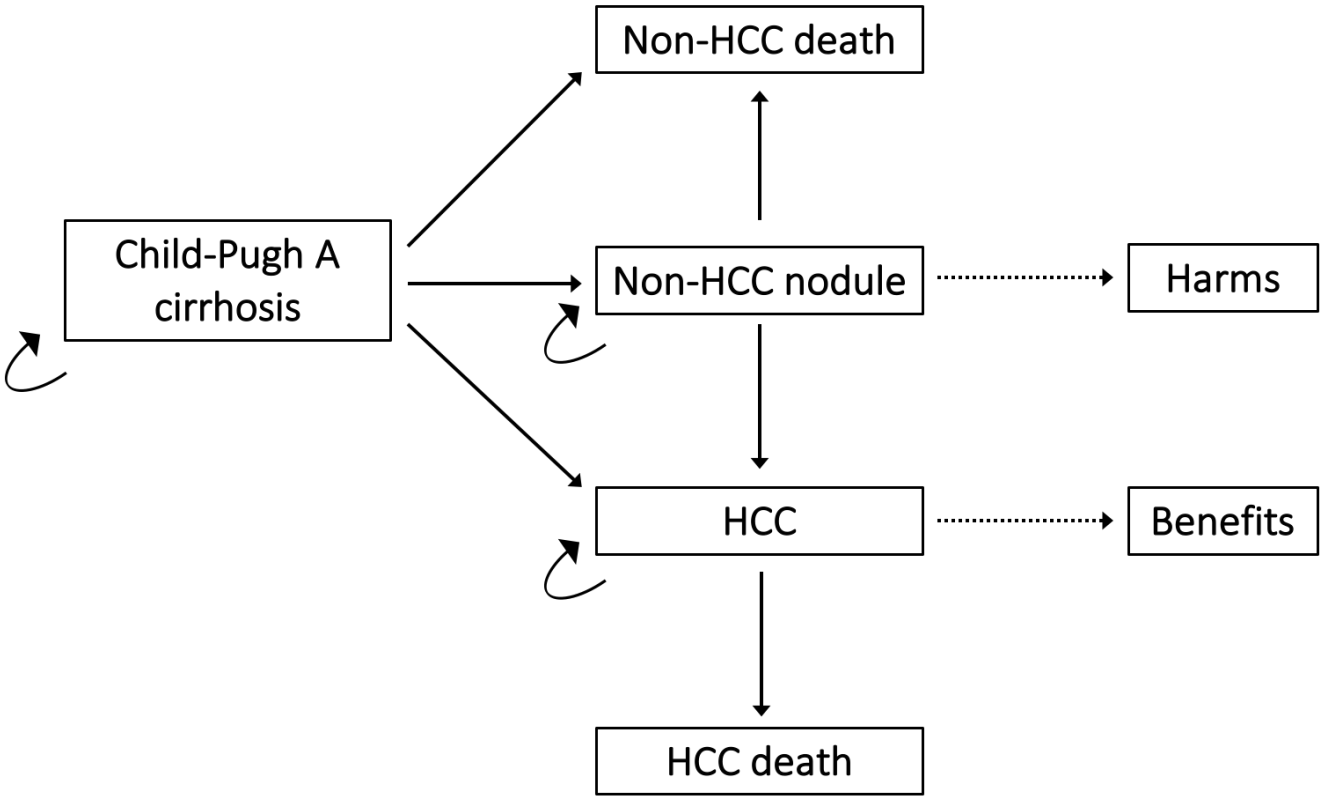

Figure 2. Sensitivity analyses of the benefits of surveillance. Each of the parameters was varied within the plausible ranges stated in Table 1. The dotted line indicates the base case estimate of the number of deaths prevented by surveillance.

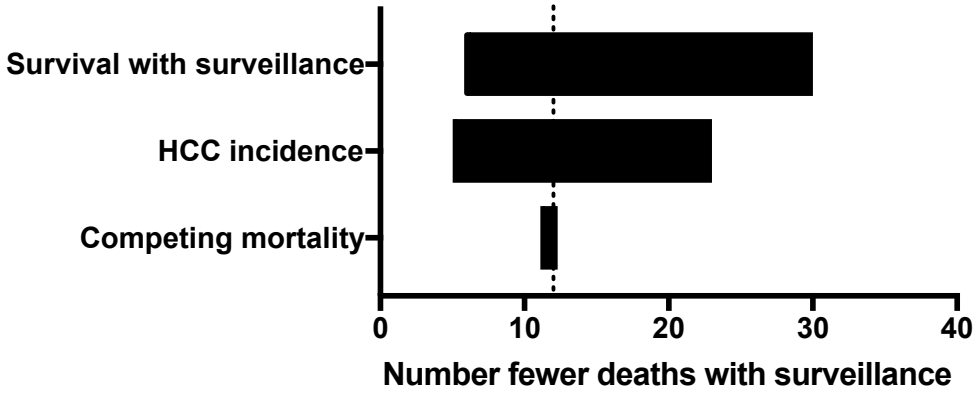

Figure 3. Estimates of the benefits and harms of surveillance for HCC among 1000 individuals with cirrhosis over five years.

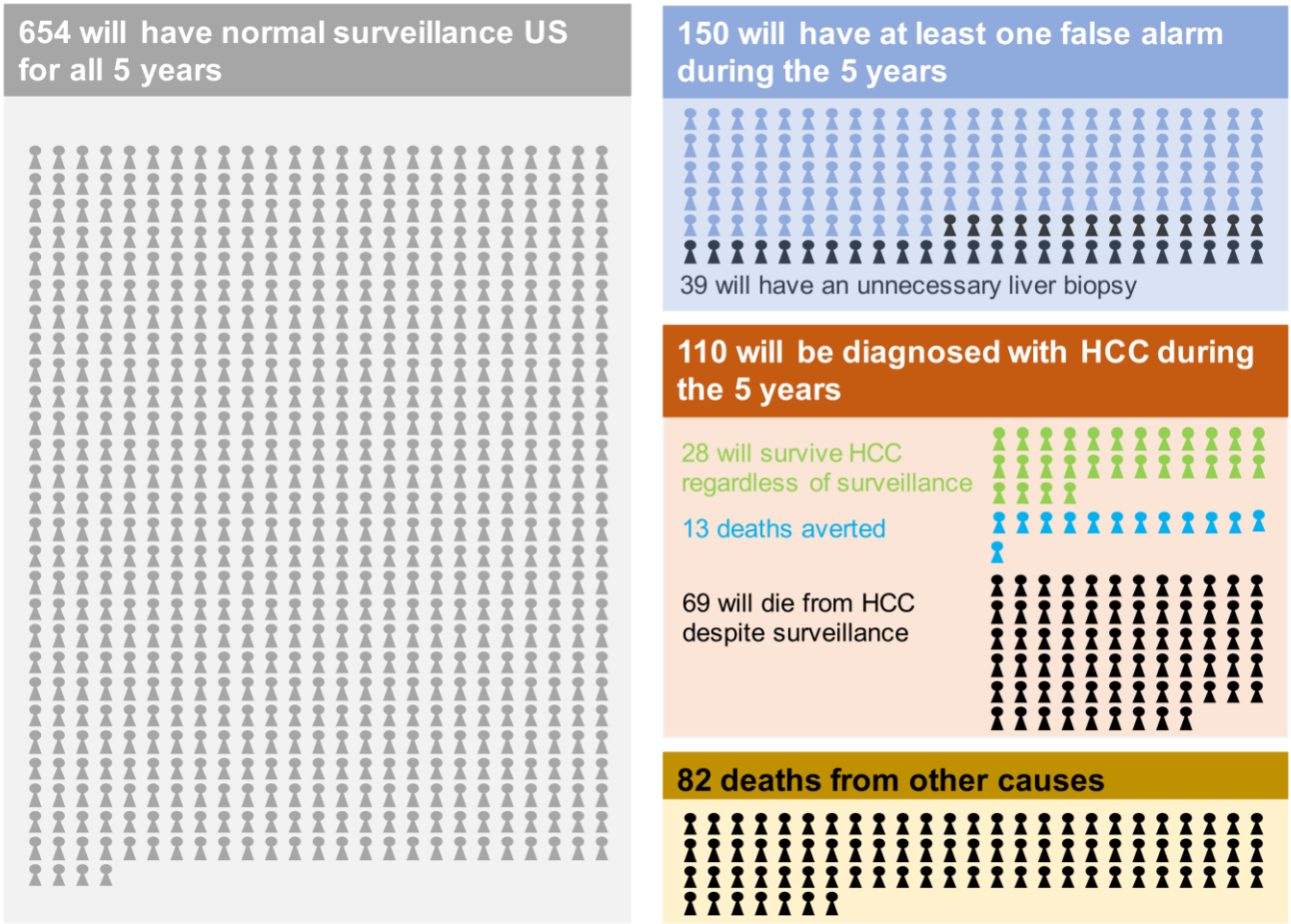

Table 1. **Model input parameters**.

Parameter	Annual probability	Range	Reference
HCC incidence	0.025	0.01 – 0.05	(13, 14)
Non-HCC focal lesion incidence	0.04	0.03 – 0.05	(13, 14)
<1cm	0.022	-*	
1-2cm	0.016	-*	
>2cm	0.002	-*	
1-2cm non-HCC focal lesions definitively benign on CT/MRI	0.27	0.20 – 0.30	(18, 19)
Competing mortality	0.018	0.005 – 0.05	(13, 14)

*Varied proportionally with non-HCC focal lesion incidence

Table 2. **Summary estimates of the benefits and harms of surveillance among 1000 individuals over 5 years**.

Event	No surveillance (n=1000)	Surveillance (n=1000)
Diagnosis of HCC	110	110
Benefits of surveillance		
Deaths from HCC	82	69
Deaths from other causes	82	82
Total number of deaths	164	151
Harms from surveillance		
Individuals without cancer having	-	
A false alarm	-	150
Intensified ultrasound follow-up	-	85
Additional CT/MRI	-	65
Liver biopsy	-	39